METHADONE TREATMENT WORKS:

A Compendium For Methadone Maintenance Treatment

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A Monograph of The Chemical Dependency Research Working Group
The New York State Office of Alcoholism and Substance Abuse Services

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MONOGRAPH POLICY

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A Word From The Commissioner
by
Marguerite Saunders

The primary purpose of the Chemical Dependency Research Working Group (CDRWG) is to encourage collaborative research by institutions and to bring together professionals from diverse disciplines including researchers, clinicians, policy makers, community groups, methadone patients and consumers of drug related services. The CDRWG, formerly the Cocaine/Crack Research Working Group was initially conceptualized to address the growing problems associated with the use of cocaine and crack. However, in 1993 the scope of the project was expanded to include all chemical dependency-related issues. An important mission of the CDRWG is to not only enhance treatment, but to find better and more effective strategies and solutions to the drug-related problems that are negatively impacting our communities and reduce the quality of life for all. Presently the CDRWG has undertaken over twenty-five symposia and published timely materials to address the many difficult issues and problems that have become associated with drug use. A final change is the monograph format for publications with articles that focus on a single topic, instead of the previous newsletters.

The recently formed Bureau of Methadone Planning and Policy is dedicated to the many issues and concerns that effect the quality of methadone treatment. It is the purpose of the Bureau to assist programs and thus enhance the recovery of methadone patients and their integration into society. To reduce the stigma and provide effective treatment it has become the responsibility of OASAS to make information regarding methadone treatment available and accurate.

This compendium was developed as a resource for researchers, providers, clinicians, policy makers and patients. It may also serve as an educational tool for communities, and the family and friends of methadone patients. The New York State Office of Alcoholism and Substance Abuse Services (OASAS) has been committed to providing effective methadone treatment and to ensure that former chemically dependent individuals will become contributing citizens of their communities. For this purpose OASAS works to provide accurate information about methadone treatment and in dispelling the many misconceptions and myths about it that hinder quality treatment and the progress of methadone patients. We at OASAS regard methadone maintenance as an important treatment to ensure recovery from heroin addiction.

The information presented in this publication is based on thirty years of scientific research which forms the medical basis of methadone treatment. With the emergence of exceptionally pure heroin it is important that people associated with drug treatment and prevention and AIDS outreach understand the basic scientific principles upon which methadone maintenance has been developed. An anticipated forthcoming compendium (Part II) will focus on social issues that impact on the functioning of programs and the subsequent adjustment of methadone patients.

Welcome From The Chair
by
Herman Joseph, Chair, CDRWG

During the past year, the Cocaine/Crack Research Working Group (C/CRWG) changed its name to the Chemical Dependency Research Working Group (CDRWG) of the New York State Office of Alcoholism and Substance Abuse Services (OASAS). The CDRWG is now part of the OASAS Bureau of Methadone Planning and Policy which has allowed us to enlarge the scope of our interests. The CDRWG is funded by the Aaron Diamond Foundation through a grant to Medical and Health Research Association of New York City, Inc. (MHRA). With such diversified support the CDRWG will continue publishing timely information and organizing symposia around medical and social issues related to chemical dependency.

This compendium is devoted to scientific and selected clinical issues involved in methadone maintenance treatment. Although methadone maintenance was developed thirty years ago at The Rockefeller University, it remains a controversial and misunderstood approach to the treatment of heroin addiction. This compendium presents information to help persons involved with the treatment of addiction and policy decisions to understand some of the complicated, yet important scientific concepts that have evolved over the past thirty years.

Articles in the first section of the compendium focus on recent neuroscience discoveries and their relationship to the biological theory of addiction. The section begins with two articles by Joycelyn Woods that introduce the reader to a variety of difficult scientific topics including pharmacology, neuroscience and the endogenous opiate receptor-ligand system. The introductory material is followed by Dr. Vincent P. Dole's article, Implications of Methadone Maintenance for Theories of Narcotic Addiction which has been reprinted with the permission of the Journal of the American Medical Association (JAMA). This paper presents a summary of research issues involved in addiction theory and methadone maintenance treatment and was written for JAMA by Dr. Dole when he received the Lasker Award for Clinical Medical Research in 1988. Following the article by Dr. Dole is a Comparison Chart of Illicit Heroin Addiction and Stabilized Methadone Maintenance that compares the profound differences between illicit heroin addiction and methadone maintenance. The chart was developed by CDRWG staff as a response to the oft quoted criticism of methadone maintenance as "just substituting one addiction for another." In reality methadone maintenance has been a thoroughly researched and, when implemented correctly, the most effective treatment for heroin addiction. This section ends with Defining an Addiction which is reprinted from the Diagnostic and Statistical Manual of Mental Disorders.

The second section by this writer summarizes the basic information necessary to understand the rationale behind methadone maintenance treatment Topics included are history, methadone dosage, medical safety, adjustment of patients in treatment, review of follow up studies, AIDS and pregnancy. The information in this section is arranged so the compendium can be used as a resource manual and reference guide.

The third section presents special topics written especially for this compendium. The first article, written by Drs. J. Thomas Payte, Elizabeth Khuri and the CDRWG staff discusses the prescribing of pain medication to methadone patients and provides several clinical procedures. The second paper, by Dr. Norman Gordon, Functional Potential of the Methadone Maintained Patient, demonstrates that methadone patients function within the normal range in tests that measure ability, intelligence and coordination. The final paper by Dr. Ann Rosenberg, Selective Attention in Opiate Dependent Individuals: A Pilot Study Investigating the Effects of Endorphin Levels on Attention, shows that there are similar trends on performance tasks of selective attention in methadone patients and persons who do not use opiates.

It is our hope that this compendium will begin to break through many of the stereotypes and mythologies that are directed towards methadone programs and especially patients. In the final analysis it is the patients who are unjustly stigmatized by misinformation and a poor understanding of the complex issues involved in heroin addiction and methadone maintenance treatment. Communities are also adversely impacted by a lack of methadone treatment; properly administered programs have the potential to reduce drug-related crime, lessen the transmission of HIV and drug resistant TB, improve the patient's employment possibilities and assist patients in becoming contributing members of their community. Thus, the presence of well administered methadone programs improves the quality of life for all in the community.

A forthcoming and anticipated second compendium on methadone treatment will address poly drug use and social issues, including articles on cocaine/crack use, alcoholism, counseling, unemployment, vocational rehabilitation, homelessness, stigma and patient advocacy. The CDRWG will continue to publish articles on topics that are timely and of great concern. Through this monograph format, organizing articles around a specific issue, the CDRWG will be able to cover areas from various aspects and disciplines. The CDRWG will continue to present symposia and to facilitate the formation of committees to investigate and consider solutions to issues related to chemical dependency.

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Introduction to Neuroscience and Theories of Addiction

"A modern theory of narcotic addiction is that the compulsive (and quite specific) craving for narcotic drugs is a symptom of deficiency in function of the natural opiate-like substances in the brain. To be sure, sociological and psychological forces enter into the making of an addict, but these factors determine exposure - - - whether or not addictive drugs are available in the environment and whether a person chooses to experiment with them. In any person, with repeated exposure to a narcotic drug, the brain adapts and becomes pharmacologically dependent on a continuing input. In some susceptible persons - fortunately a minority of the population - the adaptation becomes fixed, and with repeated use a regular input of narcotic becomes a necessity. The experimenter has become an addict.

From this perspective methadone maintenance is replacement treatment, compensating for impairment in function of natural opiate-like substances."

Dr. Vincent P. Dole. Methadone maintenance: Optimizing dosage by estimating plasma level (Editorial). Journal of Addictive Diseases 1994 13(1): 1-4.

The Discovery of Endogenous Opiates
by
Joycelyn Sue Woods

For years it had been suspected that opiates had specific binding sites in the brain. There were several attempts to locate these sites, but the existing technologies were unable to distinguish between the non specific binding to tissue and the specific binding to receptors. It must be mentioned here that the first attempt to actually measure specific opiate binding was in the laboratory of Dr. Vincent Dole (Ingolia & Dole, 1970). Although the technology was not available at that time he laid the foundations for the discovery of opiate receptors.

By the early 1970s scientific technology had evolved to the point where the discovery of opiate binding sites seemed almost inevitable. The first to shake the scientific community was Solomon Snyder and his student, Candice Pert of John Hopkins University (Pert & Snyder, 1973). Using a technique developed by Avram Goldstein of Stanford University, Snyder and Pert located the elusive opiate receptor (Goldstein, Lowney & Pal, 1971). That same year, two other groups headed by Eric J. Simon of New York University (1973) and Lars Terenius in Uppsala, Sweden (1973) demonstrated specific opiate binding in nervous tissue. The treasure hunt had begun! "For why," Goldstein asked, "would God have made opiate receptors unless he had also made an endogenous morphine-like substance?"

In the mid-1960s, Choh Li of the University of California at Berkeley had isolated a pituitary hormone which he named B-Lipotropin (Li, 1964). He noted that one portion of this hormone had analgesic properties. One year after the discovery of the receptor sites, John Hughes at the laboratory of Hans Kosterlitz in Aberdeen, Scotland, reported the existence of an endogenous morphine-like substance which they later purified and named Enkephalin for 'in the head' (Hughes, 1975a; Hughes, 1975b; Kosterlitz, 1976) The Aberdeen group recognized that the peptide sequence of Enkephalin was contained within Li's B-Lipotropin. Li would later name the other endogenous morphine-like peptides, which also come from his pituitary hormone, Endorphin

for *morphine within*.

Today the term opioid is used for all endogenous morphine-like substances, including Dynorphin another brain opioid peptide system found by Avram Goldstein (Goldstein, Tachibana, Lowney, Hunkapiller & Hood, 1979). Other psychoactive peptides have been discovered and isolated using the techniques developed in these laboratories. In 1978, Solomon Snyder, John Hughes and Hans Kosterlitz shared the Lasker Award for their discoveries. Paralleling the discovery of Enkephalins, Endorphins and opiate receptors have been advances in the field of neuroscience. These advances have led to many exciting discoveries and generated a new interest in the functioning of the brain. We have entered a new era in our understanding of human behavior.

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Neuroscience Questions and Answers
by
Joycelyn Sue Woods

The intent of this article is to present a difficult and complex topic in terms that are understandable for those not familiar with neuroscience and pharmacology. The material is presented in question and answer format, followed by a Bibliography For Further Reading for those who may be interested in additional reading about the topic.

1. What are opiate receptors and what is their function?

   The discovery of specific receptors for opiate drugs was the first important finding that led to the discovery of endorphins and other active peptides. Receptors for various substances are located throughout the body such as the sex hormones, and are the way that the body communicates.

   In basic high school biology the "Lock and Key Model" has been used to describe how the sex hormones communicate within the body. In this model the sex hormone acts as the key and the receptor as the lock. When the key fits into the lock the communication has been made and the resultant effect is achieved. Usually a substance is either released, or its release is slowed (attenuated) or stopped (inhibited). Although receptors located in the brain are far more complex, the basic lock and key concept also fits for them to help conceptualize how they work.

   Neurons are specialized nerve cells whose main function is communication in the brain. Receptors are located along the outer membrane of the neuron. Neurons are arranged in chains which are called nerve tracts, or nerve pathways. However, the arrangement of a chain, one neuron to the next, is far too simple to explain how neurons communicate in the brain. Within each nerve tract there are many feed back loops and communication from other nuclei or systems in the brain.

2. Where are receptors located?

   Opiate receptors are located throughout the brain and nervous tissue. Within the mammalian brain the distribution of opiate receptors is differential. These areas include regions associated with pain transmission. Other receptor rich areas, which are not involved in pain transmission, are the limbic areas (emotional and motivational behaviors), including the hippocampus (memory), the septum (reward/pleasure), and amygdala (sex, in males penile erection, and aggression) and the hypothalamus (feeding, fright, flight and sex). The limbic system is probably the most important area of the brain involved in drug dependence and relapse. Opiate receptors are also found in peripheral nervous tissue, or nervous tissue not in the brain, especially throughout the intestines and reproductive organs.

3. How do receptors work and what are the receptors that methadone binds to?

   As previously mentioned receptors are the lock that a substance, either a neurotransmitter, a hormone, a peptide or a drug fits into and which opens the lock, or activates the function of the receptor. The endogenous substance that binds to a receptor is called a ligand, thus endorphins are the ligand for the opiate receptor. Sometimes the entire opiate system is referred to as the "Endogenous Opiate Receptor Ligand System."

   Receptors and their ligands, or any other substance that attaches to it 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, like other receptors throughout the brain and body can be broken down into several types. The three most important opiate receptors are the mu receptor named because morphine is preferential in binding to it, a kappa receptor and a sigma receptor. Although the endogenous opioids may prefer a certain receptor, they are not highly selective to any particular one, and therefore may bind to several types of opiate receptors.

   The most studied opiate receptor is the m receptor to which heroin, morphine and methadone bind. Almost all opioids have a significant affinity for the mu receptor causing many scientists to postulate that perhaps it could serve as an iso-receptor, or general receptor for all endogenous opioids. There is one very important point regarding the mu receptor and that is that methadone is highly selective for the mu receptor. This means that methadone is unlike most other opioids which usually bind to several types of opioid receptors (i.e., the mu, kappa and sigma). Methadone prefers the mu receptor.

   Like other receptors opiate receptors can be broken down further into sub types. The sub types are usually referred to as mu1, mu2 and so on. However, for these purposes it is not necessary to know the differences that constitute a receptor sub type.

   In methadone maintenance treatment narcotic blockade is achieved because of two properties of methadone. First, it is a long acting opiate and will last longer than other opioids which are short acting, such as heroin and morphine. And second, as discussed methadone has a greater affinity than heroin for the mu receptor. On an effective dose of methadone, 80-100 mg/day a large number of mu receptors will be filled and stay filled for 24 to 36 hours. Should heroin be administered it does not have the affinity to knock methadone out of the receptor. The resultant effect is that heroin can not activate the receptor and since it is a short acting narcotic it will be eliminated from the body with minimal effects. This is also how methadone, along with the phenomena of cross tolerance, protects patients from heroin overdose should they attempt to administer it.

4. What are endorphins and what is their function?

   The term endorphin is used to characterize a group of endogenous peptides whose pharmacological action mimics that of opium and its analogs. A peptide is a biologically active string of amino acids. The endogenous opioid system is complex with a multiplicity of functions within any given organism. There exists about two dozen known endogenous opioids which can be further broken down into three different endogenous opioid systems.

   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.

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

5. What are neurotransmitters and peptides?

   Neurotransmitters are biologically active substances in the brain that are constructed in neurons. There are presently nine substances that fit a strict criteria to qualify as a neurotransmitter, while there are many others which only partially fit the criteria. The nine known neurotransmitters are: Acetylcholine (ACh), Dopamine (DA), Norepinephrine (NE), Epinephrine (Epi), 5-Hydroxytryptophan (5-HT, or serotonin), g-Aminobutyric Acid (GABA), Histamine (His), Glycine (Gly) and Glutamate (Glu). You are probably most familiar with Norepinephrine and Epinephrine, as hormones in the body where they are called Noradrenaline and Adrenaline, respectively.

   Peptides are biologically active substances in the brain composed of amino acids that are produced in neurons. When peptides were discovered they did not meet all of the criteria for being a neurotransmitter. However, today peptides are considered to be a distinct and separate group of psychoactive substances. Certain features of their metabolism and their action differ markedly from those of the accepted transmitters, i.e. low molecular weight. Peptides can be formed only in the cell body because their synthesis requires RNA, in contrast to the low molecular weight neurotransmitters that are synthesized in the terminal of the neuron. Furthermore, there are differences in their action which could have profound consequences on the type and quality of information that is transmitted. This may be a result of two characteristic features of peptides: 1) peptides are effective at much lower concentrations than the classical neurotransmitters, and 2) there do not appear to be any specific or rapid mechanism available for terminating the action of peptides.

6. What is tolerance and dependence?

   The phenomena of tolerance and dependence are inextricably linked. Tolerance to opiates develops with chronic use of an opioid drug, or put another way; more of the drug is needed in order to get the original effect. As tolerance increases over time an individual will become dependent on the substance in order to function and feel normal. Without the substance the individual will undergo withdrawal which for opioids includes a specific set of symptoms called the abstinence syndrome.

7. What is an opioid?

   The preferred term, when referring to all the peptides with opiate properties is opioid peptide. These substances include opium and all drugs that come from the opium poppy (papaver somniferum) including the semisynthetic heroin (diacetylmorphine), codeine and morphine, the synthetic opiates such as methadone (dolophine) and meperidine (demerol) and the endogenous opiates such as endorphins, enkephalins and dynorphins. Thus, the term opioid is used to classify a family of substances whose biological action is similar to morphine. These substances produce a range of biological actions, including euphoria and the relief of pain. A common characteristic of opioids is cross tolerance, or if one is dependent on heroin then another opioid can be substituted, such as methadone to relieve the abstinence syndrome.

8. What is an antagonist?

   First lets begin with defining an agonist which is a substance that binds to the receptor and produces a response that is similar in effect to the natural ligand that would activate it. 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 other opioid overdose. This is achieved because 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.

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.

Narcotic antagonists have a unique pharmacological property that makes them have a stronger affinity to the opiate receptor than an agonist. This is how narcotic antagonists are able to actually "knock" an agonist out of the receptor as in the case of naloxone's use for emergency overdose treatment. Another important property of narcotic antagonists is that anyone dependent on any opiate, including methadone patients will be extremely sensitive to them. 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 their use is contra indicated because the patient 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 drugs used in obstetrics are Nubain and Stadol.

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Special Communications
Implications of Methadone Maintenance for Theories of Narcotic Addiction
by
Vincent P. Dole M.D.
On The Occasion of The Presentation of
The Albert Lasker Award for Clinical Medical Research

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This article is based on a lecture given at the presentation of the Albert Lasker Clinical Medicine Research Award on November 18, 1988, New York, NY. It was first published in the Journal of the American Medical Association, 1988, Volume 260, pages 3025-3029 and is published here with their gracious permission.

This article is dedicated to the memory of Marie Nyswander, M.D. who opened the modern era of treatment with her book The Drug Addict As A Patient (New York: Grune & Stratton, 1956). Her experience and compassion guided the development of methadone maintenance.

Abstract

Clinical success in rehabilitation of heroin addicts with maintenance treatment requires stability of the blood level in a pharmacologically effective range (optimally, 150 to 600 ng/mL) a phenomenon that emphasizes the central importance of narcotic receptor occupation. It is postulated that the high rate of relapse of addicts after detoxification from heroin use is due to persistent derangement of the endogenous ligand-narcotic receptor system and that methadone in an adequate daily dose compensates for this defect. Some patients with long histories of heroin use and subsequent rehabilitation on a maintenance program do well when the treatment is terminated. The majority, unfortunately, experience a return of symptoms after maintenance is stopped. The treatment, therefore, is corrective but not curative for severely addicted persons. A major challenge for future research is to identity the specific defect in receptor function and to repair it. Meanwhile, methadone maintenance provides a safe and effective way to normalize the function of otherwise intractable narcotic addicts. (JAMA 1988 260: 3025-3029)

The achievements of molecular biology in analyzing processes of cell function suggest that all diseases, including disorders of behavior, might ultimately be reduced to biochemical terms. The claim is extreme, but at least for narcotic addiction the optimism seems to be justified. Analysis of the clinical results of methadone maintenance treatment during the past 25 years, coupled with advances in the understanding of narcotic receptors and their ligands, support the view that compulsive use of narcotic stems from receptor dysfunction.

This is a departure from the traditional concept of addiction as misbehavior— a distinction of great practical consequence. As recently as four months ago the Supreme Court affirmed the denial of veteran's benefits to alcoholics on the ground that their condition is due to "willful misconduct" (Trayner v. Turnage, 1988), an opinion that seems to be at odds with the medical tradition of basing services on need rather than on fault. The ruling made explicit the widespread prejudice against addicts, one that if carried to logical limits would deny treatment to a skier with a broken leg or a sunbather with skin cancer. For the immediate future, the harshness of the ruling has stimulated corrective action in the legislature. In the longer term, scientific understanding should displace prejudice, and attitudes toward addictive behavior should become more consistent with medical tradition. At least so one may hope, provided that the scientific community can provide a basis for rational understanding of addictions as diseases.

Methadone Normalizes Function

This article, updating previous analyzes (Dole & Nyswander, 1968; Dole, 1970), is concerned mainly with the theoretical implications of methadone maintenance treatment and the direction of future work. The practical success of maintenance in rehabilitation of tens of thousands of addicts, now especially important as a measure of limiting the spread of acquired immunodeficiency syndrome, has been documented and need not be reviewed further (Dole & Joseph, 1978; Cooper, Altman, Brown et al, 1983; Newman, 1986; Kreek, 1987). The issue to be considered here is the basis of this success. The treatment is corrective, normalizing neurological and endocrinologic processes in patients whose endogenous ligand-receptor function has been deranged by long-term use of powerful narcotic drugs. Why some persons who are exposed to narcotics are more susceptible than others to this derangement and whether long-term addicts can recover normal function without maintenance therapy are questions for the future. At present, the most that can be said is that there seems to be a specific neurological basis for the compulsive use of heroin by addicts and that methadone taken in optimal doses can correct the disorder. When somatic function has been normalized, the ex-addict, supported by counseling and social service, can begin the long process of social rehabilitation.

The social rehabilitation of methadone maintenance patients and the normalization of endocrine function substantially exceed the expectation that Marie Nyswander, M.D., and I brought to the problem 25 years ago. Then, as now, it was clear that narcotic addiction could not be eliminated simply by prohibition, however severe the penalties. For a chronic user, the need for narcotic is inelastic. With tens of thousands of such persons as a market, limiting supply without reducing demand increases the price of illicit drugs to the point that black marketers are willing to take the necessary risks. The net result is a highly profitable business for the drug sellers, corruption of government officials, infiltration of legitimate business with laundered money, increase in crime committed by addicts to support their expensive habits, filling of jails, and deaths from injection of contaminated drugs of uncertain potency. The clear lesson to be learned from repeated failures of past policy is that demand must be reduced by effective treatment. The epidemic of narcotic use has not been extinguished by prohibition, civil commitment, jailing, or other punishments.

On the other hand, it must be conceded that attempts to treat addicts with narcotic maintenance 70 years ago were not successful. Indeed, leaders in the medical profession and the Public Health Service cooperated with enforcement agents in closing the experimental clinics, thus effectively transferring responsibility for control of addiction to the police (Musto, 1973). When Marie Nyswander and I began our work, the position of the Federal Bureau of Narcotics was that maintenance had been tried and had failed. The argument could not be denied, but it seemed self-serving. The failure of clinics that had been organized hastily in response to the panic that followed enactment of the Harrison Narcotic Act constituted the database. Not only

were physicians ill prepared to deal with the flood of desperate addicts, they had only two narcotic drugs, morphine and heroin, to prescribe. In retrospect, a major reason for their failure is clear: the physicians were using the wrong drug.

Our objective at the onset was simply to find a medication that would keep addicts content without causing medical harm and that would be safe and effective for use over long periods in relatively stable doses. The goal of social rehabilitation of addicts was not part of the original plan. Merely satisfying addicts, although not an ideal result, seemed better than the existing policy that forced incurable addicts into criminal activity.

Stability Essential

The initial studies, conducted at Rockefeller Hospital (New York) in collaboration with Mary Jeanne Kreek, M.D., examined the clinical effects of different narcotic drugs when given in various doses to long-term users of heroin. All drugs were of the opiate class that is, they were known to exhibit cross tolerance with morphine and all had been approved for human use as analgesics. The reason for failure of previous attempts to maintain addicts on morphine soon became apparent: the patients could not be stabilized on the drug. Despite frequent injections, their condition fluctuated between somnolence and agitation throughout each day, with tolerance increasing over consecutive days to the point that they were almost continuously agitated even when receiving huge doses of morphine. Similar results were obtained with heroin (which is essentially the same drug as morphine since it is rapidly converted to morphine in the body), hydromorphone, codeine, oxycodone, and meperidine. The prospect for maintenance treatment did not look promising at this point.

A remarkably different result was seen when, in the course of the scheduled testing, methadone was administered. The fluctuation in clinical state became less and then disappeared. Doses became stable. The patients seemed normal. Most remarkably, their interests shifted from the usual obsessive preoccupation with timing and dose of narcotic to more ordinary topics (Dole, Nyswander & Kreek, 1966). We had no explanation for this surprising result. Prior to our studies, methadone had been tested at the Public Health Hospital (Lexington, KY) and was found to be a typical opiate, distinguished from morphine only by greater oral effectiveness and a somewhat longer period of action (Eddy, Halbach & Breanden, 1957). However, because of the favorable response, we decided to continue administration of methadone beyond the original schedule and to observe longer-term effects. It was not until several years later that an explanation for the unusual result became apparent: the concentration of methadone in blood is stabilized by reversible absorption into tissues (Dole & Kreek, 1973), mainly the liver (Kreek, Oratz, Rothschild, 1978). The key factor is the reversibility of this absorption. Immediately after ingestion of the daily dose, 99% of the medication is bound to the tissues in equilibrium with the concentration in blood. It is released as the concentration falls, thus buffering the level. With a relatively steady concentration in blood, the narcotic receptors in critical cells remain continuously occupied and the patient becomes functionally normal. The essential feature in the treatment is the stability of receptor occupation, which permits interacting systems to function normally. The physiological and behavioral disturbances in heroin addiction apparently are consequences of the rapid changes in status of the endogenous narcotic receptor-ligand system. When the addict takes short acting narcotics, the system cycles between abstinence and narcosis several times a day. A stable state of adaptation is impossible.

Our work involved a fortunate accident that explains why the unique value of methadone for maintenance had not been discovered previously. The patients had just completed a long series of tests with other opiates and, as a consequence, had developed a high tolerance to narcotics. Therefore, methadone was administered in exceptionally high doses, about ten times greater than is needed for analgesic action in naive patients. Injected in a single, small dose to a nontolerant patient, methadone is a relatively short-acting drug. The bulk of the dose is quickly removed from blood and later is returned to circulation at a pharmacologically insignificant level. Only when large doses of methadone have been administered repeatedly do the nonspecific binding sites come into equilibrium with a pharmacologically effective concentration in circulating blood. When this condition is reached, all that is needed for buffering the concentration at a high enough level to ensure significant occupation of receptors is a single daily dose to replace the amount of drug that has been eliminated by metabolism. Moreover, because of efficient absorption from the gastrointestinal tract, the dose can be given orally, thus eliminating needle use.

Specificity

Studies of the original six patients on our metabolic ward demonstrated the absence of acute narcotic effect in methadone maintenance patients and provided an understanding of the importance of receptor occupation. Switching the daily dose to d-methadone in place of the usual racemic mixture of d- and l- methadone was followed by the gradual appearance of abstinence symptoms, as expected from the fact that the narcotic activity of methadone is limited to the l isomer. The patients, not noticing any difference in the taste or immediate effects of the daily dose, reported on the next day that they seemed to be "getting the flu." Only on the third day did they begin to suspect the medication and asked if "something had happened to the methadone." At this point they were returned to the usual racemic mixture. All symptoms cleared immediately. The patients had responded to the fall in concentration of l-methadone in blood and the resultant dissociation of this active isomer from critical receptors. When returned to medication containing l methadone, they again became functionally normal.

The acute effect of naloxone, an antagonist that displaces narcotic ligands from receptors, shows the extreme sensitivity of physically dependent patients to the degree of occupancy of their narcotic receptors. Within a few seconds after an intravenous injection of a minute dose of naloxone (1/20 the amount that might be used in treating a nontolerant patient with narcotic

overdose), a maintenance patient will be put into acute abstinence, with profound dysphoria. The subjective sensation apparently defies description in ordinary terms, being reported as a terrible feeling not like anything else. To an observer the patient appears to have been suddenly plunged into severe depression; he becomes immobile, sagging in posture, apparently grief-stricken.

Nontolerant patients are essentially unreactive to naloxone but are highly sensitive to narcotics. The classic studies of Houde et al (1960), quantitating the analgesia in pain patients following administration of a single dose of narcotic, showed a reproducible time course that depended on the dose and degree of tolerance induced by previous exposure. Subsequent studies by Berkowitz et al (1975) correlated this effect with the blood level of morphine, thus demonstrating a direct, moment-to-moment relation between analgesia and occupation of narcotic receptors. Studies by Inturrisi et al (1987) during the past 15 years have provided quantitative analyses of pain relief as a function of narcotic blood level. Clearly, the subjective experience of pain is inversely related to receptor occupation, given a constant input of sensory signals from injured tissue and dependent on the degree of narcotic tolerance.

Persistent Receptor Disorder

An interpretation of these phenomena is that the narcotic receptor-ligand system acts as a modulator, adjusting the intensity of suffering and the body's hormonal response to stress. In nontolerant patients, the reactions to tissue damage and related stresses are modulated by the natural ligands, the opioid peptides, while pain can be abolished therapeutically for a limited time by a dose of narcotic drug. However, repeated injections of narcotic lead to down-regulation of the modulating system and possibly also to suppression of endogenous ligands, thus contributing to narcotic tolerance and dependence and progressively diminishing the analgesic utility of narcotics.

This oversimplified analysis assumes a balance between activating and modulating processes. Under normal, unstimulated conditions, both processes are quiescent. When sensory stimuli activate neurological and humoral systems, the modulating processes react to protect against excessive response. With long-term administration of narcotics, the modulating system is down-regulated. The receptors become insensitive both to narcotic drugs and to their natural ligands. A new stability is achieved if methadone is given in an adequate daily dose, but at the price of continued dependence on the medication. Thus, a fundamental question in treatment of long-term users of narcotics is whether the modulating systems can return to normal function after termination of narcotic input. Ideally, methadone would be used as a stabilizing medication to provide immediate intervention, stopping the use of illicit narcotics and normalizing general metabolism. Later, after medical and social rehabilitation, the maintenance medicine would be withdrawn slowly and the patient would be totally cured.

Unfortunately, cure of chronic narcotic addiction is not that simple. Some patients do well after rehabilitation and termination of methadone maintenance, but the majority, although equally motivated, experience dysphoria, restlessness, irritability, and recurrent urges to use heroin again. The danger of relapse is great under these conditions. Objectively measurable physiological disturbances persist after detoxification from heroin or any other narcotic that has been used for a long time. These were noted by Himmelsbach (1968) in early studies of the abstinence syndrome at the Public Health Hospital. Observing signs of dependence (sympathetic nervous system hyperactivity) that persisted up to two years in prisoners serving long sentences, he surmised that the almost invariable relapse of prisoners after release was "abetted by what seem to be indelible effects of addiction on the nervous system" (Himmelsbach, 1968).

It had, of course, long been known that most long-term users of narcotics relapse after withdrawal of the drug. The Public Health Hospital was started in 1935 under the reasonable assumption that medically assisted detoxification with counseling, general medical care, and healthy living on a Kentucky farm would provide optimal conditions for cure. Nevertheless, more than 90% relapsed after return to New York City (Hunt & Odoroff, 1962). Although the hospital made major scientific contributions, using volunteers from the population of prisoners to test the addictive potential of new drugs and conducting fundamental studies of narcotic pharmacology, including the work of Wikler (1958) on conditioning, the initial goal "that of curing addicts" was never realized.

Persistent after effects of narcotic exposure also have been found in experimental animals. Physiological disturbances were demonstrated by Martin et al (1963) and Cochin and Kornetsky (1964) months after treatment of rats with morphine. Brase and associates (1976) have used a small priming injection of morphine followed by naloxone as a probe to unmask residual abnormalities in rats long after exposure to narcotic drugs. Surprisingly, little new clinical research has been directed to the phenomenon of protracted abstinence despite the fact that relapse after completion of treatment is the central problem of narcotic addiction. With the present availability of sensitive analytic techniques, including specific ligands for analysis of receptor binding, the problem seems ripe for renewed investigation. What is needed now are methods to assess the kind and degree of receptor derangement in addicts and a better understanding of the function of this modulating system in response to physiological stress. With a more detailed understanding of addiction in molecular terms, a fundamental cure may be possible. Indeed, progress may come from work on other conditions in which chronic exposure to powerful nonnarcotic drugs leads, in susceptible persons, to persistent derangement of neurological (Gunne & Barany, 1976; Gunne & Haggstrom, 1984) or endocrine (Williams, Dluhy & Thorn, 1980) function.

Practical Considerations

None of these theoretical speculations should divert attention from the fact that methadone maintenance is an available treatment for otherwise intractable addicts. It is effective under a wide variety of conditions provided that an adequate, constant daily dose is given. Like digitalis, methadone can be lifesaving. Although it is now possible to provide a theoretical explanation for their beneficial actions, in practical terms, the justification for use of either methadone or digitalis, and the details of how they should be used, stem from experience.

The comparison goes deeper. No one questions the need for efforts to prevent the cardiac damage that ultimately leads to congestive failure or the importance of protecting young people from exposure to narcotic drugs. Prevention is fundamental in limiting the prevalence of these conditions. In principle, there should be no conflict between prevention of a disease and treatment of an established disability, and in the case of heart disease there is none. But with drug addiction, a serious dilemma arises: limiting the supply of a dangerous drug, which is an essential part of prevention, can cause more damage to society than the addiction itself if extremes of enforcement promote criminal behavior. There is no simple answer to this dilemma. Obviously there should be a balance between enforcement and treatment, reducing both supply and demand proportionally. With heroin and related narcotics, methadone maintenance has by far the greatest immediate potential for reducing demand. It is therefore important that the medical profession understand its pharmacology, its indications, and its limitations.

The optimal daily dose of methadone for maintenance is the quantity that will hold the blood level in the 150 to 600 ng/mL range. This concentration range is consistent with binding to narcotic receptors when allowance is made for binding of methadone to plasma proteins and reduction in sensitivity of receptors with narcotic tolerance. As a general rule, 60 to 80 mg of oral d-methadone hydrochloride a day (reached by gradual increase over four to six weeks) is adequate and not excessive, although in exceptional cases substantially higher doses may be needed. If the activity of the hepatic microsomal enzyme oxidizing system has been increased by interaction with other medications being taken concurrently (Kreek, Garfield, Gutjahr et al, 1976; Tong, Pond, Kreek et al, 1981), or for unknown reasons (Tennant, 1987), the elimination of methadone will be accelerated. In extreme cases, even 100 mg/d may fail to hold the blood methadone level within the therapeutic range for the full 24 hours and a higher divided dose will be needed for optimal results. However, these cases are unusual. Usually patients after stabilization for some months on a 60 to 80 mg/d dose can be lowered to the 40 to 60 mg/d range without difficulty. Some can be maintained successfully with even lower doses but, except the rare cases in which full tolerance to the narcotic effects of methadone may not be developed, there is no compelling reason for prescribing doses that are only marginally adequate. As with antibiotics, the prudent policy is give enough medication to ensure success.

This perhaps is too casual an answer to the question of optimal dosage. If the instruments and funding required for repeated measurement of methadone blood levels were generally available (which they are not) it would be apparent that any rigid set of dosing guidelines would be misleading. The levels vary substantially from patient to patient receiving the same daily doses (Kreek, 1973; Holmstead, Anggard & Gunne, 1978). Analytic data, if available, would permit a fine-tuned adjustment of doses to optimal amounts for individual patients. Fortunately, this laboratory support is not needed. An experienced clinician can judge the adequacy of the dose from the effects. Symptoms of abstinence can be distinguished from anxiety, and narcosis from neurasthenia, by carefully listening to the symptoms, considering their timing in relation to the daily dose of methadone, noting the patient's response to a change in dose, and evaluating his or her emotional stability. The patient's clinical state is correlated reliably with the blood level and the degree of tolerance.

Some maintenance programs, committed philosophically to low-dose regimens, expose their patients to a significant degree of abstinence each day, as the blood level falls into the low range (Dole & Nyswander, 1983). Other programs, seeing the medication as psychological rather than pharmacological treatment, give methadone as a reward for good behavior and withhold it for drug abuse and other infractions of rules. The results are generally poor, as might be expected from the fact that limiting or withholding medication that reduces drug hunger increases the need for illicit narcotics.

Alternative Theory

The hypothesis suggested herein- that narcotic-seeking behavior is a symptom of deranged receptor function- is most directly challenged by treatment of addicts with an antagonist such as naltrexone to block all narcotic actions. Use of antagonists stems from traditional views of addiction as a pleasure-seeking escape from reality employed by persons of weak will who are living in a stressful environment. Add to this the postulated influence of conditioned reflexes that generate an irresistible craving for narcotic when the addict is in the company of other drug users, and one has a theory of addiction (Wilker, 1958). The escapist-conditioning explanation is so plausible that it has influenced medical thinking and public health policy for three decades. Although this conception has never led to a treatment with consistent success, the failure has been excused by the practical difficulty of removing stress and bad companions from the environment of an addict and by the inability of counselors to eliminate character defects.

According to the conditioning theory, antagonist treatment, which blocks the narcotic effects of heroin and related drugs, should insulate the addict from temptation, especially after he has found them to be unrewarding. With no reinforcement, the interest in the narcotic should subside and the patient should become responsive to counseling. Again, there is an explanation for the repeated failures of antagonist treatment to stop heroin use during the past ten years: addicts can easily quit treatment and return to the illicit drug. Current research in some laboratories, aimed at development of implantable preparations of antagonist, is intended to close this loophole.

From the perspective of the receptor derangement theory, this approach is pharmacologically wrong. Antagonist drugs block the action of natural ligands as well as that of illicit narcotics. If the basic problem leading to relapse is a failure of the modulating system to return to normal function after withdrawal of narcotic, than antagonist treatment adds to the problem. The issue, therefore, is clearly drawn. If long-lasting, implantable preparations of narcotic antagonists prove to be as successful as methadone maintenance treatment in rehabilitation of addicts, this certainly would be a useful result. Further research is needed to determine whether the result was in fact due to deconditioning or to a positive interaction with endogenous opioid processes. On the other hand, if the treatment with implanted antagonist fails, then proponents of the conditioning theory should reconsider their position. This important experiment, if conducted, should be well documented and independently evaluated.

The Future

Apart from theory, the most striking fact is the physiological normality of maintenance patients. Persons who have taken a constant daily dose over a period of months to years are indistinguishable from normal peers. Despite a daily dose that would induce a coma in a naive patient, the patients are normally alert and functional; they live active lives, hold responsible jobs, succeed in school, care for families, have normal sexual activity and normal children, and have no greater incidence of psychopathology or general medical problems than their drug-free peers. Surprisingly, considering the constant input of narcotic, they have a normal response to painful stimuli, including specifically the warning symptoms of surgical emergencies.

All this does not fit neatly into the pharmacology learned from experiments involving single injections of narcotic drugs. The molecular biology of adaptation to chronic narcotic input must be better defined before we can fully understand the pharmacology of maintenance. Somehow the receptors adapt to a steady level of occupancy. They react to a change in conditions, either in degree of receptor occupation by ligands or in the intensity of sensory stimuli, while being adapted to a constant high level of narcotic in tissue fluids.

Here, then, are basic questions to be answered by molecular biologists: How can this system function normally under such abnormal conditions? Why is stability of narcotic concentration more important than the absolute level? Are chronic adaptive changes completely reversible?

Needless to say, any attempt to relate behavioral disorders to molecular processes must start with an oversimplified model. Much more work is needed to take account of the diversity of narcotic receptors and endogenous ligands, the dynamics of receptor formation and internalization, the release of second messengers, and the interactions of modulating processes with other parts of the nervous system (Snyder, 1979; Ariena, 1984). Nevertheless, the broad outline of a metabolic theory of narcotic addiction is coming into view. Two general conclusions emerge from the experience to date: it is not necessary to await an ultimate reduction of addictive behavior to molecular terms before effective treatment can be provided. On the contrary, effective treatment, empirically found, can lead to a better understanding of molecular processes.

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Comparison Chart of Illicit Heroin Addiction and Stabilized Methadone Maintenance

Topic	Illicit Heroin Addiction	Stabilized Methadone Maintenance
Onset of action	Immediate	Thirty minutes
Duration of action	Four to 6 hours	Twenty-four to 36 hours or half life
Route of administration	Injection, snorting, smoking, several times a day	Orally administered once per day
Effective dose	Not applicable	For many patients 60 mg/day is lowest effective dose; doses between 80 and 120 mgs/day are most effective for preventing HIV transmission, retention in treatment, reducing the use of other drugs and increasing social productivity
Overall safety	Potentially lethal	Medically safe, no toxic effects found in patients maintained on methadone for up to 18 years
Overdose	Can die from overdose of narcotics; potentially lethal, even for tolerant individuals death can occur quite fast without proper medical treatment with narcan	A degree of protection from death by overdose is achieved when receiving 100 mg/day or more; methadone is potentially lethal for non tolerant individuals, death can occur but more slowly than heroin overdose however, overdose reaction can be reversed and person's life saved if narcotic antagonist such as narcan is prescribed for 24-36 hours
Narcotic effects of other opiates	Feels narcotic effects of opiates	At 80 mgs/day or more narcotic effects of opiates are blocked (if tried)
Withdrawal syndrome	Can be severe, but can be controlled with methadone	Less severe than heroin but more extended, can be controlled by slow reduction in methadone dose
Mood alteration	Constant swings	None, if patient is not emotionally disturbed or using other drugs
Euphoric effects	Approximately 2 hours duration after administration	None after administration
Tolerance level	Increasing dosage needed	Stable level at same dose

Narcotic craving	Recurring	Relieved and blocked
HIV transmission	Effective transmission	Transmission of HIV by injection reduced or eliminated for patients who remain in treatment
Immune and endocrine functioning in HIV- persons	Impaired	Normalizes during treatment
Immune system HIV+ persons	Rapid progression to AIDS	Preliminary studies indicate that progression to AIDS is slower
Hypothalamus Pituitary Adrenal Axis	Suppressed	Normalizes during treatment
Libido/Sexual functioning	Impaired	Normalizes during treatment
Female menses	Impaired	Normalizes during treatment
Pregnancy	Serious problems difficult to treat	Problems can be brought under control with medical, social and prenatal care
Fetal environment	Stressful for fetal development	Not stressful, helps create stable environment for normal development of the fetus
Emotional affect	Impaired	Normal, if patient is not emotionally disturbed or using other drugs
Pain and emotion	Blunted	Feels normal pain and experiences normal range of emotions if not using other drugs
Intellectual functioning	Impaired	Normal if person is not emotionally disturbed or using other drugs
Physical reaction time	Impaired	Normalizes during treatment
Personal relationships	Disrupted	Restored with counseling
Social functioning	Impaired	Normalizes with counseling
Vocational rehabilitation and education	High proportion of failure	High proportion of success in vocational rehabilitation, education and employability
Employment	Difficult if not impossible to hold a job	Can function in every level and type of profession e.g., bus driver, lawyer, doctor, teacher or pilot
Mental illness	Difficult to treat	Treatable if integrated resources exist, however many psychiatric services discriminate against methadone patients and will not accept them
Poly drug abuse	High level (alcohol, crack, cocaine, nicotine)	High level but potentially treatable
Criminal activity	Constant high level	Reduced level or eliminated
Effect on community	Destructive, high crime and death rates, transmission of disease	A good methadone program contributes to public safety, reduces crime, reduces mortality and improves quality of life for all
Criteria for addiction	Fits criteria for addiction as listed in the "Diagnostic and Statistical Manual of Mental Disorders"	Does not fit criteria for addiction, methadone maintenance is a thoroughly researched and effective medical treatment
Life-style	Heroin addiction is about acquired infection and death	Methadone maintenance treatment is about good health and life (Methadone chemotherapy normalizes a deranged physiology so patients can stabilize their lives.)

Defining An Addiction

The formal diagnosis of "psychoactive substance dependence" is now made if at least three of the following statements are true.

- The substance is taken in larger amounts or over a longer period than the person intended.
- There is a persistent desire or unsuccessful efforts to stop.
- The person spends a great deal of time trying to get the substance (e.g., robberies to raise the money), taking it or recovering from its effects.
- Using the substance disrupts important social obligations or work activities.
- The person continues to use the substance despite knowing that it is causing problems (e.g., drinking even though it makes an ulcer worse).
- There is a marked tolerance: the person needs increased amounts of the substance to become intoxicated or has a marked reduction of the desired effect if using the same amount.
- There are withdrawal symptoms.
- The substance is taken to avoid the withdrawal symptoms.

Source: Diagnostic and Statistical Manual of Mental Disorders III, 1980.

II.
Methadone Maintenance Treatment

Methadone Maintenance Treatment and Clinical Issues
by
Herman Joseph

The History of Methadone Maintenance

Methadone maintenance treatment has been thoroughly researched and carefully evaluated for almost three decades. It has received more scientific scrutiny and evaluation than any other medical treatment or human service program (Ball & Ross, 1991; Brecher, 1972; Des Jarlais, Joseph, Dole & Schmeidler, 1983; Dole & Joseph, 1978; Dole & Nyswander, 1976; Dole & Nyswander, 1965; Dole, Nyswander & Warner, 1968; FDA, 1989; Gearing, 1970; Gearing & Schweitzer, 1974; GAO, 1990; Gordon, 1970; Hartel, Selwyn, Schoenbaum et al, 1988; Joseph & Dole, 1970; McLellan, Arndt, Metzger, Woody & O'Brien, 1993; Newman & Cates, 1977; Parrino, 1992; Simpson, 1981; Stimmel, Goldberg, Cohen & Rotkopfe, 1978). Most evaluations have shown that, when correctly implemented, the treatment is capable of producing remarkable improvements in patients who were previously dysfunctional heroin addicts. Methadone maintenance patients throughout the world have been restored to productive lives, relations with families and children have been reestablished, many have furthered their educations, obtained employment and improved their physical and mental health. Nevertheless, contrary to scientific evidence, methadone maintenance treatment remains a controversial issue among substance abuse treatment providers, public officials and policy makers, the public at large and the medical profession itself.

Methadone was synthesized in Germany during World War II as a substitute for morphine when supplies of opium from Turkey were cut off by the United States and their allies. The drug was brought to this country after the war and studied in 1946 at the United States Public Health Hospital in Lexington, Kentucky. It was found to be similar in its effects to morphine but possibly longer acting. Clinical research showed that the drug could be used effectively in the treatment of the opiate abstinence syndrome by substituting it for morphine and slowly tapering down the dose over a period of about one week to ten days (Brecher, 1972). Until the development of methadone as a maintenance medication in 1964, the primary use of methadone in the treatment of addiction was to withdraw addicts from heroin, a procedure that differs from maintenance and exploits only a few of the potentially useful properties of the

medication.

By the late 1960s in New York City, heroin related mortality was the leading cause of death for young adults between the ages of 15 and 35 (Joseph & Dole, 1970). Serum hepatitis cases related to injection of narcotics with contaminated needles were increasing. A record number of addicts were being arrested for drug-related crimes, including possession, sales, robbery and burglary, and overcrowded jail facilities with no medical care to ease withdrawal were creating havoc (Brecher, 1972; Inciardi, 1988; Joseph, 1992; Joseph & Dole, 1970). By 1968, the Manhattan County Jail for Men (known as the Tombs) was racked by riots because of the severe overcrowding and lack of medical care for arrested addicts. With the medical and legal professions calling for a reevaluation of American narcotic policies in respect to treating addicts, the climate was more favorable to challenge the Bureau of Narcotics' anti-maintenance position.

In 1962, Dr. Vincent P. Dole, a specialist in metabolism at the Rockefeller University was appointed to look into the situation by Dr. Lewis Thomas, chair of the Narcotics Committee of the Health Research Council of New York City. After studying the scientific, public health and social ramifications of the addiction problem in the city, Dr. Dole received a grant from the Health Research Council to establish a research unit at the Rockefeller University to investigate the feasibility of opiate maintenance.

In preparing for his research he read the book, The Drug Addict As A Patient by Dr. Marie E. Nyswander (1956), a psychiatrist who had extensive experience treating addicts. She had served as a physician at the U.S. Public Health Service Hospital in Lexington, Kentucky, treated addicts in private psychiatric practice, established a store front for treating addicts in East Harlem and was the psychiatrist for the Musicians Clinic, a program which treated addicted musicians (Hentoff, 1969). Dr. Nyswander believed addicts could be treated within the medical profession rather than through incarceration in the criminal justice system. However, she believed that many would have to be maintained on narcotics in order to function, since the majority relapsed despite many hospitalizations, withdrawal and therapy (Brecher, 1972; Courtwright, Joseph & Des Jarlais, 1989). Dr. Nyswander joined Dr. Dole's research staff in 1964. At the same time, a young clinical investigator, Dr. Mary Jeanne Kreek, completing her training in internal medicine and neuroendocrinology at the New York Hospital-Cornell Medical Center, was also recruited to join the research team.

Maintenance with low doses of morphine was administered to the first two patients who had used narcotics for at least eight years and had extensive criminal histories related to their addictions (Brecher, 1972; Dole & Nyswander, 1967). Both had previously attempted therapy and had withdrawn from heroin several times, only to relapse. Since morphine has a half life of four to six hours, the patients required injections at least four times per day. As tolerance developed to the morphine, they required increasing amounts administered at more frequent intervals to remain comfortable. And they remained preoccupied with drugs, apathetic and sedated from the narcotizing effects of the morphine.

The researchers knew that morphine's effects are similar to heroin. It was not a good choice as a maintenance drug. While criminal behavior might be reduced because the drug would be obtained legally, the patient would remain dysfunctional. Impairment would result from morphine's narcotizing qualities and the short half life of the drug requiring several injections per day. With the development of tolerance increasing amounts would be needed to remain comfortable over a short period of time. Similar results were obtained for other short-acting narcotics such as hydromorphone, codeine, oxycodone and meriperidine (Dole, 1988; Dole, 1980; Dole, Nyswander & Kreek, 1966). A distinct disadvantage of most of the short-acting narcotics was that to be maximally effective they had to be injected.

With the failure of short-acting narcotics to properly maintain patients, the research revolved around the choice of a possible maintenance medication that was orally administered and long acting. Methadone appeared to have these qualities and was selected based on the observations of addicts being withdrawn from heroin and research into its use as an analgesic in the experimental treatment of pain (Dole, 1988; Joseph & Dole, 1970; Kreek, 1973). In 1964, the technology was not yet available to measure the blood levels of heroin, morphine and methadone. The results concerning the outcome of methadone as a maintenance medication depended on the observations and insights of the researchers.

The Eight Important Findings That Distinguish Methadone as a Preferred Maintenance Drug

Once methadone was established as a proper maintenance medication at doses of 80 to 120 mg/day, eight important findings were noted. These findings would constitute the basis of a maintenance program capable of permitting otherwise intractable addicts to function normally within society (Dole, 1988; Dole, 1980; Dole & Nyswander, 1965; Dole, Nyswander & Kreek, 1966; Gordon, 1970; Joseph & Dole, 1970; Kreek, 1978; Kreek, 1973; Newman & Cates, 1977).

1. The narcotic craving described by addicts as a major factor in relapse and the continued illegal use of heroin was relieved. This is perhaps the most important property of methadone, thus allowing addicts to live a stable life.

2. Tolerance to the narcotic effects of all opiate class drugs is blocked. At doses beginning at 80 mgs/day tolerance is held at a high enough level to block the euphoric and tranquilizing effects of all opiate class drugs. Should the patient administer any opiate, including methadone, either orally, through injection or by smoking the effect will be blocked. Also, beginning at 80- mg/day the patient is protected from overdose and respiratory depression if large amounts of narcotics should be administered. This protection is strengthened at higher doses of 100 mg/day or more.

3. Stabilized patients do not experience any euphoric, tranquilizing or analgesic effects. Their affect is clear and enables them to socialize and work normally without the incapacitating properties of short-acting narcotics such as morphine or heroin.

4. There is no change in tolerance levels. Therefore, the same dose of methadone can be prescribed to a patient for an indefinite period of time (e.g. 20 years). This effect contrasts with other opiates such as morphine and heroin whose dose must be increased.

5. Methadone can be taken orally by patients once per day. This eliminates the use of needles for injection and immediately reduces the risk of HIV infection and other serious conditions caused by using unsterile needles.

6. Studies undertaken over the past two decades, primarily by Dr. Mary Jeanne Kreek of The Rockefeller University, and corroborated by other scientists throughout the world have established the long-term medical safety of methadone maintenance treatment (Kreek, 1992; Kreek, 1987; Kreek, 1986; Kreek, 1978; Kreek, 1973; Kreek et al, 1972; Novick, Richman, Friedman et al, 1993). There are no toxic effects, somatic damage or functional deficits associated with or attributable to methadone for patients who are stabilized at appropriate doses including those receiving over 100 mgs/day, who are not heavily abusing other drugs (e.g., alcohol and cocaine), and who have remained in continuous treatment for up to 18 years. There are minimal nontoxic side effects, such as constipation, that can be treated; excessive sweating that in most cases subsides over time; and decreased libido and, in some males, delayed orgasm that normalizes within the first few months of treatment or with dose adjustment (Kreek, 1978; Kreek, 1973). Methadone is safe for persons who have been properly stabilized, since methadone can be lethal for nontolerant persons who will require emergency treatment with narcan for about 24 to 36 hours if they should accidently ingest a dose prescribed for a tolerant patient.

7. Motor coordination, reaction time and intelligence tests to determine if patients can function normally have been administered to patients maintained on high doses of methadone (over 80 mg/day). No significant differences have been found between maintained patients and the non-maintained controls. On some tests the patients even exceeded the performance of the controls. Patients' intelligence scores also improve over time. The conclusion was that patients are able to function within normal parameters when prescribed the high doses of methadone necessary for maintenance (Gordon, 1970).

8. It should be understood that tolerance to the analgesic effects of methadone are quickly achieved and methadone patients can be treated for severe acute and chronic pain by administration of morphine, as would any other patient (Dole, Nyswander & Kreek, 1966). Morphine, or any other short-acting narcotic, can be given at regular or more frequent time intervals and at higher levels in accordance with the patient's tolerance. Mixed agonist/antagonist drugs such as Talwin, Nubain and Stadol should never be administered to a methadone patient. Methadone will block the euphoric and tranquilizing effects of short-acting narcotics however, the analgesic or pain killing properties of short-acting narcotics will be able to penetrate the blockade phenomenon and the patient will receive the necessary pain relief (Payte, Khuri, Joseph & Woods, 1994).

In conclusion, methadone when prescribed as a maintenance medication functions as a normalizer for a deranged physiology and not as a mood altering narcotic substitute (Dole, Nyswander & Kreek, 1966; Joseph & Dole, 1970). Also, methadone maintenance is a corrective but not a curative regimen.

Admissions Protocols

Initially the criteria for admission to methadone conformed to the needs of a strict research protocol (Brecher, 1972; Gearing & Schweitzer, 1974; Joseph & Dole, 1970). Only addicts between the ages of 21 and 40 were admitted. The upper age limit was based on the theory that addicts begin to mature out of addiction over the age of 40. The applicants had to be addicted to heroin for at least four years and have relapsed after previous attempts at withdrawal from heroin and treatment. Addicts who were polysubstance users, including alcoholics and those afflicted with major psychiatric and medical problems such as tuberculosis, were not considered eligible. Initially women of child bearing age and pregnant addicts were not permitted because the effects of methadone on the reproductive system and developing fetus were not known and the researchers were investigating a new medical procedure (Joseph & Dole, 1970). As methadone treatment proved to be successful and medically safe, the admission criteria were gradually modified.

Today, the regulations of the Food and Drug Administration (FDA) allow heroin addicts to be admitted with a one year addiction history including current use (FDA, 1993). The lower age

limit has been reduced to 16, however applicants between the ages of 16 and 18 must have two prior episodes of either withdrawal from heroin or drug free treatment and parental consent or be declared emancipated before being admitted. The upper age limit has been eliminated since it is now known that while a group of addicts do mature out the majority do not. It has subsequently been learned that untreated addicts have high death rates at young ages, may be incarcerated or become seriously alcoholic (Dole & Joseph, 1978; Joseph & Appel, 1985). Women of child bearing age and pregnant women are now accepted and, with special medical justification, a pregnant woman can be admitted with an addiction history of slightly less than one year. Applicants with major medical conditions and polysubstance abuse problems including alcoholism are now eligible for treatment (FDA, 1993).

Methadone Maintenance Expands:
The Gearing Study and Subsequent Evaluations

In 1965, under the guidance of Dr. Ray Trussell, the New York City Commissioner of Hospitals, the initial research project was expanded and transferred to the Manhattan General Hospital in New York City where a heroin withdrawal program had previously been established. An impartial unit to evaluate the expansion and progress of methadone treatment was created at the Columbia University School of Public Health and Administrative Medicine with Dr. Frances Rowe Gearing as the chief of evaluation. The unit's work was reviewed by an independent committee composed of physicians and scientists with Dr. Henry Brill as its chairman. The committee made recommendations for further evaluation, research and expansion of the program (Joseph & Appel, 1992; Joseph & Dole, 1970). Thus, methadone maintenance received rigorous scrutiny and evaluations with follow-up studies that continue to this day.

No matter what country, ethnicity, sex, education or economic background of the patients, studies evaluating methadone have been consistent. The following summarizes the findings from major studies conducted over the past approximate three decades.

1. When placed on an adequate dose of methadone (e.g., 80 to 120 mgs/day), heroin use by patients is significantly reduced within the first two months of treatment and eventually either eliminated or significantly curtailed with time in treatment (Ball & Ross, 1991; Cooper, 1992; Dole & Nyswander, 1965; Dole, Nyswander & Kreek, 1966; GAO, 1990; Schuster, 1989).

2. Crime related to drug use is reduced significantly within the first year of treatment and the reductions continue with time in treatment. These trends persist irrespective of cities, culture or era. A study of 1,870 methadone patients admitted to treatment in New York City in the 1960s showed that arrest rates decreased 95 percent when compared to arrest rates three years prior to entering and three years after entering treatment (120 vs 5.5 arrests per 100 man years) (Gearing, 1970; Gearing & Schweitzer, 1974). The city of Hong Kong introduced methadone treatment for its addicts in 1976 and subsequently there was an 85 percent reduction in the number of heroin addicts admitted to prisons in the city from 1976 to 1980 (Newman & Cates, 1977). In 1985, a study of methadone programs in Baltimore, Philadelphia and New York City found a 79 percent decrease in the number crimes committed by patients during their first six months of treatment as compared to their last episode of addiction (Ball & Ross, 1991). Criminal behavior declined the longer patients were in treatment.

3. Productive behavior as measured by employment, school attendance or homemaker status increases with time in treatment. When the program was first implemented in 1964, the patients were able to obtain jobs in manufacturing, trades and construction. Within the first year of treatment, about 60 percent were socially productive (Dole & Joseph, 1978). These trends continued into the 1970s. However, with the change in the employment market from manufacturing to service jobs, the lower levels of education among new admissions, the periodic economic downturns, increased homelessness, cocaine/crack use and HIV infection among the patients, productivity and employment levels for patients declined from a high of about 60 percent in the late 1970s to about 28 percent in 1994 (Gearing & Schweitzer, 1994; Joseph, 1992; Kreek, 1992; Randall, 1994).

4. Poly drug abuse and alcoholism affect a significant minority of the patients. Generally speaking, those patients that are dually addicted when entering methadone treatment continue poly drug abuse and alcoholism, unless they are treated for these conditions. Prior to the AIDS epidemic, the physical effects of alcoholism were the major causes of death for patients in treatment and the second major cause of death after heroin overdose in the posttreatment period (Joseph & Appel, 1985). However, with the high prevalence of HIV infection among methadone patients in treatment HIV infection has become the major cause of death (Joseph & Springer, 1990)

5. Studies by Ball and Ross (1991) and McClellan and colleagues (1993) demonstrate the need for psychosocial services in methadone programs to ensure their maximum potential in helping patients. In the 1980s and currently in the 1990s, new admissions present serious social, psychological and medical problems to clinics. Among the problems are homelessness, cocaine/crack addiction, alcoholism, HIV infection, drug resistant TB, mental illness, chronic unemployment, poor education and a host of social problems (Joseph, 1992; Joseph & Appel, 1992).

6. In an important study, McLellan and colleagues (1993) have shown that while methadone alone is effective for some patients, the addition of services results in better treatment outcomes for a greater number of patients. All patients in the study were maintained at 60 mgs/day or more of methadone and dose was increased as needed if use of opiates

persisted. Patients were assigned to one of three service components: (1) Minimal care included an adequate dose of methadone but no other services. (2) Standard care included an adequate dose of methadone plus counselling. (3) Enhanced services included an adequate dose of methadone plus counseling, on-site medical/psychiatric/employment services and family therapy.

The study found that patients involved in enhanced program services showed significant improvements in social adjustment and employment status, with significant decreases in alcohol and cocaine use and illegal activity. McLellan also reported that when dysfunctional patients receiving minimal care were given standard care, the improvements in reduction of illicit opiate and cocaine use were significant and occurred rapidly within a period of four weeks. Patients receiving enhanced care in the McLellan study made significantly greater improvements than those receiving standard or minimal care.

7. A study of socially productive methadone patients (employed, in school or homemakers) by Joseph and Des Jarlais (1980) shows that patients are able to hold positions across the spectrum of the job market. To qualify for an interview in this study, patients had to be in treatment for at least four years, not involved with illicit drugs or criminality for at least three years, and be employed outside the field of drug treatment, drug-related research or drug-related social services. Furthermore, they had to have addiction histories of four or more years.

   It was found that among the 47 who met these criteria and volunteered for taped interviews at three programs the daily methadone doses ranged from 5 to 100 mg/day with patients at the low dose level withdrawing from the program. About 54 percent of the patients interviewed were receiving between 60 and 100 mg/day. There were no particular relationships between dosage and salary levels. The patients were primarily employed in jobs and professions in private industry. Some examples of jobs at different dose levels included an attorney who was withdrawing (5 mgs/day), an architect (30 mgs/day), a rock musician (30 mgs/day), two truck drivers (40 and 100 mgs/day), an auto mechanic (40 mgs/day), a window cleaner on skyscrapers (60 mgs/day), a producer of documentary films (70 mgs/day), two housewives (20 mgs/day and 90 mgs/day), a computer technology worker (90 mgs/day), a chef in a gourmet restaurant (100 mgs/day) and a road construction laborer (100 mgs/day).

   At the time of the interviews 72 percent of the patients had one continuous episode of treatment, 21 percent were in their second episode of treatment and 6 percent in their third episode of treatment. Patients with two or more episodes of treatment relapsed to use of heroin during their posttreatment periods in spite of their good adjustments, including gainful employment, and had to re enter treatment.

   All of the patients were acutely aware of the stigmatization of being maintained on methadone. For over half of this group, no one at work knew about their addiction history or enrollment in methadone treatment. In cases where somebody did know, it was usually an immediate supervisor, personnel administrator or a trusted colleague. This pattern of concealment was carried over into their family and social lives. Old friends who were aware of the patient's prior addiction history may or may not have known about their current treatment. Patients, however, rarely told new friends about their prior addiction or methadone treatment. The patients also concealed their enrollment in methadone treatment from members of their own immediate families. Parents, siblings and children may not have been told about methadone and were under the impression that the patients were cured and had "kicked their habits." The exceptions were spouses who were aware of the patients' histories and enrollment in treatment.

   Only 13 percent socialized with other methadone patients. The great majority socialized with family and "straight people. Since the patients did not use other drugs and took their methadone as directed, concealment of their methadone status was made easier by the absence of narcotic effects, the ability to work and interact socially without impairment.

The work of Drs. Dole and Nyswander has had a great impact on the treatment of heroin addicts in the United States today. First, they brought the treatment and care of addicts into the medical profession, albeit a controlled isolated and highly regulated clinical system. Nevertheless, this was an incredible accomplishment in itself, considering the lack of understanding of opiate addiction as a metabolic condition at that time and the 50 year history of treating heroin addiction as a criminal justice problem. However, it must be emphasized that methadone maintenance did not expand because society wanted to provide treatment for heroin addicts. To the contrary, the main concern was reducing the number of crimes committed by addicts. That included the curtailment of the spread of addiction-related infections, such as HIV and hepatitis.

Their second accomplishment was the launching of the first and most effective harm reduction program. Harm reduction takes a public health approach toward the problem of drug use with pragmatic strategies to reduce the harm that drugs do to the individual and society. The emphasis on drug enforcement and punishment as the primary strategies to control drug use is replaced with education, prevention and treatment. Today the methadone maintenance program has been expanded and is the major public health program for the treatment of heroin addition in the United States. From 1964 through 1994 there have been over approximately 2,000,000 patient-years on methadone maintenance treatment in the United States. Presently, there are about 115,000 persons known to be enrolled in approximately 850 methadone maintenance treatment programs in 40 states. Also, methadone maintenance programs are expanding throughout the world to prevent the transmission of HIV.

A Review of Methadone Treatment:

Outcome and Follow-up Studies

The major findings of follow-up studies of discharged methadone patients in the United States and Europe have found that a large majority are unable to maintain abstinence and eventually relapse to daily heroin use. Despite the fact that many of these studies were conducted prior to the homelessness, AIDS and crack/cocaine epidemics, they are remarkably consistent across ethnic, racial and cultural differences. These studies are important since they show that the majority of discharged patients were unable to make sustained good post-treatment adjustments in a less threatening era. The studies include those by Ball and Ross, 1991; Cushman, 1980; Des Jarlais, Joseph, Dole and Schmeidler, 1983; Dole and Joseph, 1978; Dole and Nyswander, 1976; Gearing & Schweitzer, 1974; Gunne, Gronbladh and Ohlund, 1993; Joseph and Dole, 1970; Simpson, 1981; Stimmel, Goldberg and Cohen et al, 1978.

The overwhelming evidence is that the majority of patients who leave methadone maintenance, irrespective of their type of discharge (favorable vs. unfavorable) and their individual prospects for successful abstinence, eventually relapse to daily use of narcotics. Today, persons who are HIV- and leave methadone treatment are at high risk of contracting HIV after leaving treatment because of the high rate of relapse to drug use.

1. Death rates for patients who leave treatment are more than twice the rate of patients who remain in treatment. Excessive posttreatment deaths are usually associated with factors involving the injection of heroin (e.g., overdose and transmission of infectious diseases) and violence. Death rates are excessive irrespective of the type of discharge, but former patients with favorable terminations have lower death rates than those discharged for other reasons. Within the past six years AIDS has become the major cause of death in many methadone programs. In some areas it is estimated that about 50 percent of new admissions to methadone maintenance treatment are infected with HIV.

2. In most studies about 80 percent of the former patients relapse to use of heroin and/or other narcotics within approximately two years after leaving treatment. Excessive, life threatening use of alcohol and other drugs (e.g., cocaine) effects a substantial number of former patients who may not relapse to heroin. In one study, only eight percent of the former patients were abstinent from daily use of narcotics, non-opiate drugs and life threatening alcoholism after one episode of methadone treatment.

3. Gender, ethnicity and level of education did not predict posttreatment daily narcotic use. While these factors may influence decisions to enter treatment, they appear to have little or no influence in preventing relapse to daily heroin use after leaving treatment.

4. Years of heroin use, time in treatment, abuse of drugs while in treatment, employment status and type of discharge were the factors that contributed most to predicting posttreatment heroin use. Patients who were able to remain abstinent after leaving usually used heroin for shorter periods prior to entering treatment than those who relapsed. They also remained in treatment longer, did not abuse other drugs, were fully employed and received a favorable termination from treatment.

5. Although social rehabilitation is important for a positive posttreatment adjustment, the duration of a heroin addiction may also be a crucial factor for patients to remain abstinent after terminating treatment. Patients in good standing with longer histories of heroin addiction have higher probabilities for relapse than patients in good standing with shorter periods of addiction. Also, longer durations of methadone treatment contribute to posttreatment abstention, implying that pharmacological and biological factors may also influence post treatment outcomes. These include the type of narcotic (heroin-short acting vs. methadone-long acting), the route of administration (oral vs. injection), and the circumstances under which a narcotic is administered. Even under the most optimistic conditions, patients in good standing still have a high probability of posttreatment relapse. Therefore, there should be no moral judgement on the part of treatment staff, family, friends or employers if patients in good standing relapse after leaving treatment. Patients who relapse after leaving treatment should be allowed to reenter the program without feeling guilty or a failure.

6. In the Des Jarlais, Joseph, Dole and Schmeidler (1983) study, using the various factors to predict post treatment abstention, it was found that about 70 percent of those who met optimal conditions for discharge, relapsed to daily use of heroin in comparison to the 90 percent who relapsed when conditions were less than optimal.

These studies emphasize the importance of retaining patients in methadone treatment. Even patients whose individual prospects for successful abstinence are optimal are likely to eventually relapse to daily use of heroin. Factors that contribute somewhat to successful outcomes after discharge from treatment are favorable discharge, stable life style and a shorter period of illicit heroin use. Programs which encourage patients to withdraw from methadone are not setting policies based on scientific evidence, nor are they serving their community.

Patients who do decide to withdraw from methadone and leave treatment should be given the facts regarding their prospects for abstinence and encouraged to return to treatment should they relapse to heroin use. Patients who do return to treatment because they have relapsed should never be made to feel guilty and every effort should be made to help them understand that this is the nature of their disease and that their decision to return to treatment was positive.

Achieving An Effective/Adequate Methadone Dose

Numerous studies have indicated that the most effective range for methadone maintenance is between 80 to 120 mg/day at the beginning of treatment (Ball & Ross, 1991; Ball, Lange, Myers & Friedman, 1988; Cooper, 1992; Dole, Nyswander & Kreek, 1966; GAO, 1990; Hartel, Selwyn, Schoenbaum et al, 1988; Kreek, 1992; Kreek, 1986; Payte & Khuri, 1992; Schuster, 1989). Methadone dose should be determined, like the prescribing of any other medication, through consultation between physician and patient. During the later stages of treatment the dosage may be either lowered or raised depending on the requirements of the patient.

The original research upon which methadone maintenance is predicated was based upon a dose range of about 80 mg to 120 mgs/day (Dole, Nyswander & Kreek, 1966). For a dose of methadone to be effective three types of phenomena must be met:

1. Relief of drug craving that begins at about 60 mgs per day for most patients (Dole, Nyswander & Kreek, 1966; Kreek, 1988; Kreek, 1986).

2. A high enough tolerance level must be reached to block the narcotic effects of all opiate drugs, including methadone itself if it should be administered. This blockade effect begins at about 70 to 80 mgs/day and the effect is strengthened at the higher doses (100 to 120 mgs/day) (Dole, Nyswander & Kreek, 1966; Kreek, 1988; Kreek, 1986).

3. The patient must be able to function normally without the impairing effects of narcotics namely, euphoria, tranquilization and analgesia. The patient must be able to maintain physical coordination and dexterity (Dole, Nyswander & Kreek, 1966; Kreek, 1988; Kreek, 1986).

At high doses (e.g. 100 mg/day), patients have a degree of protection from heroin overdose. At this level they are less likely to succumb to respiratory depression if they should administer illicit narcotics to challenge the blockade (Dole, Nyswander & Kreek, 1966). This is especially important at the beginning of treatment, when patients may experiment with heroin to test the effectiveness of the medication (Hartel, Selwyn, Schoenbaum et al, 1988). For the patient entering treatment methadone dose is the most critical element to ensure the patient's later adjustment.

The Importance of Achieving An Effective Methadone Dose

All clinical surveys implemented in the United States and world wide validate the importance of prescribing an adequate and effective dose (80 to 120 mg/day) of methadone (Ball, Lange, Myers & Friedman, 1988; Ball & Ross, 1991; Blix & Grondbladh, 1988; Caplehorn & Bell, 1991; Cooper, 1992; D'Aunno & Vaughn, 1992; Dole & Joseph, 1978; GAO, 1990; Kreek, 1992; Payte & Khuri, 1992; Schuster, 1989). The following studies confirm the clinical findings of the original study by Drs. Dole, Nyswander and Kreek (1966) and reported in the article "Narcotic Blockade."

1. In a review of the literature, Hargreaves (1983) indicated that patients appear to do better on the higher doses within the range of 50 to 100 mg/day. This is especially true at the beginning of treatment when patients need full pharmacological support. The review recommended that NIDA encourage state agencies to allow local programs to prescribe methadone up to a dose level of at least 100 mg/day.

2. Watters and Price (1985) reviewed 44 methadone maintenance programs and determined that dose was the single most important factor related to retention in treatment. The higher the dose, the longer patients remained in treatment.

3. Hartel and colleagues (1988) undertook what is probably the largest and most sensitively designed study at Montefiore Hospital in the Bronx. Hartel, an epidemiologist, examined the records of approximately 2,400 methadone patients over a 15-year period. She identified a trend line that started at about 70 mgs/day and began to achieve real clinical significance at 80 mgs/day. With the higher doses, from 80 to about 100 mg/day, patients had better retention in treatment, less HIV infection and less polysubstance use, including cocaine and crack.

4. A comprehensive study by Ball and Ross (1991) of six programs located in Baltimore, New York City and Philadelphia demonstrated that patients reduced their use of IV heroin by 71 percent compared with their pre-admission drug use. The study followed the IV heroin use of 407 patients over a period of one month and found that the higher the methadone dose, the less the frequency of heroin use. About 27.9 percent of the 204 patients receiving 45 mg/day or less used heroin, compared to only 5.4 percent of the 203 patients maintained on doses greater than 45 mg/day. And, for those patients maintained on doses of 75 mg/day or greater, no evidence of heroin use was found.

5. In Australia, Caplehorn and Bell (1991) showed that retention in treatment increased by a factor of about two across each of three stratified levels of dose: <60 mg/day, 60-79 mg/day, and 80+ mg/day. Patients stabilized at a blockade level of 80+ mg/day or greater have longer periods of treatment than patients maintained on lower doses. Variables usually associated with good treatment outcomes, such as employment, educational level and degree of criminality, appeared to have less of an impact on retention than the patient's dose of methadone.

6. In a nationwide study of 172 randomly selected methadone maintenance treatment programs, 72 percent responded representing approximately 20 percent of the programs in operation. D'Aunno and Vaughn (1992) found that about half of the programs encouraged patients to withdraw from methadone within six months after admission to treatment. Sixty-eight percent of the programs set an upper limit for methadone doses at 50 mg/day.

   In addiction to the above findings, D'Aunno and Vaughn (1992) determined that patients maintained on the higher doses remained in treatment longer. Positive treatment outcomes were more likely in programs with flexible take-home privileges and in programs that included patients in decisions related to dosage. They recommended monitoring and, in certain cases, changing the treatment practices of programs prescribing inadequate doses with minimal patient participation in decision making. Programs treating high percentages of African-American patients, younger populations and the unemployed appeared to have set lower dose limits for patients and on the average administered lower doses of methadone. Many of these programs may have encouraged patients to withdraw from methadone and leave treatment prematurely, and had less patient participation in decision making.

7. The United States General Accounting Office (GAO) reviewed 24 methadone programs in eight states and concluded that "60 milligrams of methadone is the lowest effective dose to stop heroin use and low dose maintenance (20 to 40 mg) is inappropriate" (GAO, 1990). The GAO report indicated that in an effective program no more than 20 percent of the patients should have positive urine screenings for heroin at any given time.

8. Results of a recent reader survey undertaken by the Addiction Treatment Forum (1993) reported a mean dose of 56.58 mg/day and a median dose of 60 mg/day for the 203 programs that responded. While this dose is above the average dose reported by D'Annuno and Vaughn (45 mg/day), about 50 percent of the patients included in this survey are below the optimum dose range of 80 to 100 mg/day as recommended by NIDA (Schuster, 1989), the GAO (1990) and the studies reviewed in this article.

Pharmacology of Methadone

After oral ingestion, methadone goes directly to the intestinal tract and about 98 percent of the drug is absorbed and bound mostly in the liver and the remainder is stored in nonspecific tissues throughout the body (Borg, Ho & Kreek, 1992; Dole, 1988; Kreek, 1988; Kreek, 1986). This bound methadone acts as a reservoir and is gradually released back into the blood stream. With an adequate daily dose, the blood level of methadone is steadily maintained and continuously buffered by the reserve in the tissues and liver over a 24- to 36-hour period.

The daily dose of methadone must be adequate and concentrated in the blood between 150 to 600 ng/ml, (1) which is equivalent in the average patient to about 80 to 100 mg/day. A smooth flat curve of circulating methadone is achieved with a peak level occurring between two and six hours after ingestion. Since the patient is tolerant to the narcotic effects of methadone, the peak level of concentration does not produce narcosis. The concentration of methadone in the blood is therefore stabilized by its reversible binding to nonspecific tissues and the liver (Dole, 1988; Kreek, 1988; Kreek, 1986). Most importantly, with an adequate, steady and stable concentration of methadone circulating in the blood, the m receptor sites within the brain and central nervous system are continuously occupied by methadone (Dole, 1988).

Because of differences in metabolism and body weight, methadone dose must be determined individually to maintain appropriate methadone blood levels throughout the 24-hour period. If a patient metabolizes methadone at a fast rate, the dose should be increased until a steady state is achieved. A few patients may need 100 to 120 mg/day or greater. On the other side of the spectrum, those patients with slow metabolic rates may be able to adjust on doses lower than 60 mg/day. Patients who do not receive an adequate dose of methadone will experience drug hunger and symptoms of the abstinence syndrome within a 24-hour period (Kreek, 1988; Kreek, 1986).

Determining Dosage Through Blood Levels

Physicians in Europe and the United States have been determining methadone dose by measuring plasma levels (Blix, 1990; Lorimer, Schmid, Grunberger, Jagsch, Linzmayer & Presslich, 1991; Tennant, 1987). Methadone plasma levels were measured at the peak hours after dosing, two, four and 24 hours, and by then raising the methadone dose until a stable plasma level is achieved throughout the 24-hour period. Methadone plasma levels should never be used to set an upper dosing limit and it is important that dose be determined individually through consultation with the patient who should feel comfortable and be able to function. The refinement of this technology in methadone treatment is important so that dose levels be given a

scientific basis.

At present, 150 ng/ml is generally accepted as the lowest plasma level of methadone that will maintain the 24-hour steady-state effect (Borg, Ho & Kreek, 1992). The optimum dose is the level at which there is adequate methadone to provide constant availability to the opiate receptors. The optimum 24-hour mean plasma level may be more in the 400 ng/ml range. Loimer and colleagues (1991) suggest that "methadone plasma concentrations of 400 ng/ml are necessary to suppress any further opiate action and to provide stabilized maintenance. Therefore, to achieve relief of narcotic hunger and to ensure a narcotic blockade, a range of 80 to 120 mgs/day would, at least at the beginning of treatment, be reasonable for patients entering treatment.

Problems in Achieving a Stable Methadone Dose

On average a dose range of 80 to 120 mgs/day will relieve narcotic hunger and ensure a high enough level of tolerance for narcotic blockade. However, there is a small group of patients, perhaps 5 percent, who are fast metabolizers (Tennant, 1987). These patients may need doses in excess of 120 mgs/day to achieve a steady plasma level of methadone for 24-hours. Any drug that stimulates the liver's microsomal enzyme-oxidizing system may accelerate the metabolism of methadone and produce withdrawal symptoms (Kreek, 1987). Again, the proper procedure is to increase the dose to over 100 mg/day to treat patients receiving medications that stimulate the liver's microsomal enzyme-oxidizing system. Another strategy is to increase the dosage and administer the medication in split doses, half in the morning and half in the evening. Medication known to produce these effects are rifampin for drug-restraint TB and dilantin and carbamazepine for patients with epileptic seizures (Kreek, Garfield, Gutjahr et al, 1976). Excessive use of barbiturates, other sedative hypnotic drugs and alcohol may also produce withdrawal symptoms (Tong, Pond, Kreek et al, 1981). A recent investigation on the effects of cocaine/crack on the endogenous opioid receptor-ligand system has reported that crack/cocaine increases the number of opiate receptors in the brain (Unterwald, Horne-King & Kreek, 1992). While the impact of this effect on methadone dose has not been studied, taken with other evidence that the majority of cocaine/crack using methadone patients request dose increases, it is likely that the use of cocaine/crack can disrupt the ratio of methadone binding to receptors. The increase in the number of opiate receptors may necessitate an increase in methadone in order to maintain an adequate dose.

The dose of methadone, as in any other medication, is critical to achieving a therapeutic effect. The most effective method to determine the proper and adequate dose is through measurement of methadone blood levels, which should be between 150 to 600 ng/ml and is equivalent in the average patient to about 80 to 100 mgs/day. Patients not receiving an adequate dose do not obtain the benefits of the medication, including the blocking of drug craving and hunger, the blocking of any euphoric effects should heroin be tried, and a degree of protection from respiratory depression and opioid overdose should illicit heroin be attempted. For the opiate-dependent person methadone when prescribed adequately acts as a stabilizer of a dysfunctional physiology by maintaining adequate opiate receptor occupation over a 24- to 36-hour period.

Methadone Dose and Policy

Many states, regions and/or programs limit methadone dose by not prescribing any dose above 50 mg/day despite the evidence to the contrary that doses below 50 mg/day are not effective for most patients (Cooper, 1992; D'Annuno & Vaughn, 1992; GAO, 1990). Medical decisions about dose should be based on sound scientific knowledge and clinical evaluation, rather than on public biases or politics (Ball & Ross, 1991). It cannot be over emphasized that using methadone as a tool to control social behavior is destructive to patients self-esteem and their therapeutic relationship to the program (Dole, 1988), and that decisions regarding methadone dosage not based on sound medical principles in fact, prevent the effective treatment of narcotic addiction (Cooper, 1992; Schuster, 1989). Kreek (1988 & 1986; Borg, Ho & Kreek, 1992) states that whatever method is used to determine methadone dosage, either through blood levels or observation of the patient, "methadone dosage should never be used for social rewards or punishment" as dependence has been medically induced.

Since dose is clinically determined, patients take home medication should not be linked to the amount of methadone prescribed, i.e. patients on lower doses allowed take home medication while those on higher doses receive no take home privilege at all. This encourages patients to prematurely lower their methadone dose resulting in the possible return to drug use and risk of HIV infection. In addition, methadone should never be used as a behavioral tool to manipulate the patient to comply with program policy (Brecher, 1972). Methadone medication should not be withheld or delayed, except for medical reasons. Program policies that encourage manipulation of patient behavior and control in order to comply are destructive to the patients trust in the program. Knowledge of dose should never be withheld. Methadone patients have the right to know their dose as do other medical patients (D'Annuno & Vaughn, 1992). The harm of withholding the amount of methadone prescribed is damaging to patients' feelings of self-worth, trust in the program, their subsequent adjustment and retention in treatment (D'Annuno & Vaughn, 1992).

The Medical Safety of Methadone

The steady state of blood plasma levels produced by an adequate daily dose of methadone normalizes the deranged physiological functioning of the endocrine and immune systems induced

by heroin addiction (Dole, 1988). The following studies validate the medical safety of long term methadone treatment.

Studies of socially rehabilitated methadone patients in continuous treatment for over ten years, active heroin addicts and non-drug using healthy controls have shown that natural killer cell activity of the immune system was impaired for the heroin-addicted population. However, killer cell activity of the immune system was normal for the methadone patients and non-drug using healthy controls (Novick, Ochshorn, Ghali et al, 1989). All subjects and controls in this study were HIV negative therefore drug injection during heroin addiction can impair immune functioning independent of HIV infection.

Female menses which may have been interrupted while using heroin are restored to normal for the majority of opiate dependent women maintained on methadone (Kreek, 1992; Kreek, 1986). Therefore, women maintained on methadone are able to experience normal pregnancies. Human sexuality and fertility are seriously impaired while persons are dependent on heroin. Libido and fertility can be restored within a normal range of functioning for both male and female patients who are maintained on adequate doses of methadone. However, those who abuse alcohol, cocaine or other drugs may experience reductions in libido and disruptions in the reproductive system (Kreek, 1992). Women of child bearing age should be advised of this upon entering treatment.

Major medical problems effecting methadone patients are usually related to unhealthy life styles and unsterile injecting practices of the previous heroin addiction. Common medical problems include HIV infection, AIDS and drug-resistant TB; chronic liver disease resulting from either chronic alcoholism with cirrhosis or hepatitis usually contracted through use of contaminated needles to inject heroin and/or cocaine; and chronic illnesses presented at the time of admission to the program (Kreek, 1992; Kreek, 1986; Novick, Joseph, Croxson et al, 1990; Novick, Khan & Kreek, 1986). Upon entering methadone maintenance treatment these conditions can either be managed or treated, thus improving the patient's health (Kreek, 1992; Novick, Richman, Friedman et al, 1993).

A recent study of 110 methadone patients in treatment for 11 to 18 years showed that for most patients long term methadone treatment has facilitated social rehabilitation (e.g., employment, family stability, cessation of criminal activity, reduction or elimination of heroin addiction and polydrug use) and resulted in an overall improvement of their health (Novick, Richman, Friedman et al, 1993). Medical problems in this advancing age group of methadone patients are similar to those medical problems found in the general middle-aged and older populations (e.g., cardiac problems, cancer, etc.). Heroin addiction has either been completely eliminated or greatly curtailed with a reduced incidence of diseases related to the use of contaminated needles; reduction in the incidence of sexually transmitted diseases; improved endocrine and immune functioning; and less frequent abuse of cocaine and alcohol, although these drugs continue to pose significant problems for some patients.

Methadone Treatment and AIDS

HIV entered the heroin injecting population in New York City in the late 1970s. In the 1980s examination of stored blood collected in the 1970s from addicts and three deceased infants revealed the presence of HIV (Des Jarlais, Friedman, Novick et al, 1989; Novick, Khan & Kreek, 1986). Retrospective estimates indicate that by 1980, prior to the discovery of the HIV virus, about 35 percent of the heroin injectors in New York City were already infected. In the mid 1980s, prevalence of HIV infection among intravenous drug users increased to about 55 percent, and by 1990 the prevalence had leveled off to about 50 percent (Des Jarlais, Friedman, Novick et al, 1989; Marmor, Des Jarlais & Cohen, 1987).

Injecting and non injecting drug users, their sexual partners and their offspring are at high risk for contracting HIV. The prevalence of HIV infection among patients entering methadone maintenance treatment in New York City varies from about 21 percent to about 60 percent depending on the program and its geographic location (Joseph & Springer, 1990).

When properly administered, methadone maintenance treatment can be a highly effective intervention to reduce transmission of HIV among injecting heroin addicts and provide medical services and referrals. Evidence collected in Europe and the United States validates the findings of laboratory and clinical studies about the effectiveness of adequate methadone treatment in preventing transmission of HIV and in the treatment of infected individuals. Several independent studies have shown that successful methadone maintenance treatment reduces risk behavior to contract and transmit HIV.

1. Abdul-Quader and coworkers (1990) have reported that the frequency of injection was significantly reduced with time in methadone maintenance treatment. Studies from Uppsala, Sweden and the South Bronx in New York City showed that patients who entered methadone maintenance treatment before 1983 and continued in treatment had significantly lower rates of AIDS and HIV infection than patients who entered after 1983 (Blix & Grondbladh 1988; Hartel et al, 1988).

2. A study of 58 socially rehabilitated long-term methadone maintenance patients (employed, not using drugs and socially stable) show that all were seronegative for antibody to HIV,

however 91 percent had one or more markers for hepatitis B infection (Novick, Joseph, Croxson et al, 1990). These patients were enrolled in methadone maintenance treatment for approximately 16.9 years and were maintained on a median dose of 60 mg/day (range 5 to 100 mg/day). Prior to entering methadone maintenance treatment, individual patients had injected heroin for an average of 10.3 years and engaged in high-risk behaviors for contracting HIV (e.g., sharing needles, shooting drugs in shooting galleries, having sexual contacts with other substance abusers without protection).

3. The potential for normalization of endocrine and immune functioning is especially crucial when treating HIV positive methadone patients. The evidence of immune restoration from HIV negative methadone patients hints that there may be a partial restoration of immune functioning for HIV positive methadone patients (Kreek, 1993). While this is not proven, there are many other advantages for HIV positive heroin users to be placed and maintained on methadone.

4. Weber and coworkers (1990) conducted a three-year prospective study in Switzerland that followed a group of HIV-infected methadone maintenance patients and a contrast group of HIV-infected heroin users who did not enter methadone maintenance treatment. The results showed that a significantly lower proportion of methadone maintenance patients progressed to AIDS as compared with the untreated heroin users (24 percent versus 41 percent) within the period of the study.

Methadone programs are placed in a unique position to monitor HIV and other infectious diseases and provide clinical prevention and intervention. For example, AZT can be administered as well as medications for drug-resistant TB. Most importantly, clinics can offer AIDS prevention, counseling and referrals for services that exist in the community. Special methadone clinics and programs can be developed that serve patients infected with HIV (e.g., St. Claire's MMTP, Beth Israel AIDS program on 125th Street).

Methadone Treatment and Pregnancy

The information presented here is collected from the Treatment Improvement Protocol (TIP) on Pregnancy and Substance Abusing Women (Kandall, 1993) sponsored by the Center for Substance Abuse Treatment chaired by Janet Mitchell, M.D., M.P.H. of the Harlem Hospital Medical Center in New York City.

It is important for the health of the fetus that pregnant heroin users be placed in treatment during the first trimester of pregnancy (Kaltenbach & Finnegan, 1992). Since heroin is a short-acting drug with a half-life of four to six hours, the pregnant heroin addict will be subjected to periodic daily episodes of withdrawal resulting in fetal stress and risking intrauterine death. Methadone prescribed in adequate doses provides a relatively non-stressful environment in which the fetus can develop throughout pregnancy because of its long-acting duration (Kandall, 1993).

Entrance into methadone maintenance treatment during the first trimester of pregnancy is also associated with higher infant birth weights (Kaltenbach & Finnegan, 1992). There is evidence that methadone maintenance treatment, combined with prenatal services, promotes fetal growth, while continued use of heroin during pregnancy may result in infant morbidity (Kandall, 1993). The pregnant methadone-maintained patient may experience withdrawal symptoms and need an increase in the daily dose of the medication because of changes in metabolism and blood plasma levels of methadone, especially in the third trimester (Kaltenbach & Finnegan, 1992; Kandall, 1993).

Methadone maintenance with psychosocial counseling and prenatal care is recommended as the treatment of choice for opioid dependent pregnant women. The safety to the fetus of slow withdrawal from opiates has not been documented. Medical withdrawal of opioid dependent women (including methadone maintained women) is not recommended during pregnancy because of increased risk to the fetus of intrauterine death even under the most optimal circumstances such as close medical monitoring. Also, there are no research data that suggest withdrawal in one trimester is worse than in others, although some physicians have serious concerns of withdrawing a pregnant woman prior to 14 weeks and after 32 weeks of the pregnancy (Kandall, 1993).

Current research shows that doses below 60 mgs/day are "not effective and hence not appropriate" and "low dose policies for pregnant patients are often associated with increased drug use as well as reduced program retention." Methadone dose should be "individually determined by absence of subjective and objective abstinence symptoms and the reduction of drug hunger" (Kandall, 1993).

Most importantly, methadone dose may have to be increased or split (half in the morning and evening) to produce a beneficial effect during the later stages of pregnancy since greater plasma volume and renal blood flow during pregnancy can contribute to a reduced plasma blood level of methadone. Therefore, the pregnant woman's initial maintenance dose may be inadequate to prevent narcotic craving, and suppress symptoms of the abstinence syndrome resulting in the subsequent return to heroin use and relapse (Finnegan, 1993; Kaltenbach & Finnegan, 1992; Kandall, 1993). Pregnant methadone maintained patients should be counseled about the effects of pregnancy on their maintenance dose and the possibility of their needing a dose increase during pregnancy. It is most important that pregnant patients understand that the fetus will also feel it if they experience symptoms of the abstinence syndrome, so they will not resist a

necessary increase in their dose. In addition to this pregnant patients should also be advised of the safety of methadone to the fetus and assured that dose has no relationship to the newborn being born drug dependent. The comfort of the mother and the fetus should be of paramount concern and understood by the mother.

Guidelines for Methadone Maintenance and Pregnancy

Methadone maintenance is strongly encouraged for all pregnant opioid-dependent women (Kandall, 1993). It provides the following advantages:

- Reduces illegal opioid and needle use as well as use of other drugs
- Helps to remove the opioid-dependent woman from the drug-seeking environment and eliminates the necessary illegal behavior
- Prevents fluctuations of the maternal drug level that may occur throughout the day
- Improves maternal nutrition and increases the weight of the newborn
- Improves the woman's ability to participate in prenatal care and other rehabilitation efforts
- Enhances the woman's ability to prepare for the birth of the infant and begin homemaking
- Reduces obstetrical complications

Breast feeding of neonates is recommended if the pregnant woman maintained on methadone is HIV negative. Although minute traces of methadone have been found in mother's milk, they are of such low density as to be pharmacologically inert and do not cause physical dependency for the neonate. However, if the mother is HIV positive, breast feeding is not recommended since the HIV will be transmitted to the baby (Finnegan, 1993; Kaltenbach & Finnegan, 1992; Kandall, 1993).

Talwin, Nubain, Stadol and other agonist/antagonists should not be prescribed during pregnancy because of the dramatic withdrawal this class of drugs can precipitate thereby endangering the fetus. Narcan or any narcotic antagonist should never be given to pregnant substance-using women except as a last resort to reverse severe narcotic overdose. Administration of a narcotic antagonist, such as naltrexone to a pregnant opiate dependent woman could result in spontaneous abortion, premature labor and/or stillbirth. The long term effects and safety of clonidine in pregnancy are not known at the present time. Therefore, the drug should not be prescribed to pregnant opiate dependent women for withdrawal (Kandall, 1993).

Neonatal Withdrawal

Paregoric and phenobarbital are recommended for neonatal withdrawal symptoms (Kandall, 1993). However, some physicians may prefer paregoric for treatment of neonatal opiate withdrawal symptoms (Neuspiel, 1993). Kaltenbach and Finnegan (1992) report that neonatal abstinence symptoms are not related to the mother's methadone dose. Finnegan (1993) indicates that treatment of the opiate withdrawal symptoms in neonates is an easily treatable condition when prescribing paregoric. If the mother is a polysubstance user, however, both paregoric and/or phenobarbital may be necessary to withdraw the neonate (Kandall, 1993). The proper drugs to use in withdrawing a neonate are dependent on the drugs used by the mother.

Conclusion

Methadone maintenance treatment, developed by Drs. Vincent Dole and Marie Nyswander in the 1960s at The Rockefeller University has been thoroughly researched and evaluated during the past thirty years. Several variables distinguish methadone as a preferable maintenance medication including, the lack of mood altering effects, the blocking of drug craving or hunger, the blocking of the effects of heroin, protection from overdose, no change in tolerance level, oral administration with a half life of 24 to 36 hours, and medically safe (nontoxic with minimal side effects). A small number of methadone patients are aberrant metabolizers and some medications may speed liver metabolism. These patients may need doses in excess of 120 mg/day.

For the long term heroin addict methadone maintenance treatment is truly a life saving medication. Thousands of once formerly considered intractable heroin addicts have been restored to productive lives. Methadone maintenance stabilizes a physiology deranged by illicit heroin use and normalizes endocrine and immune functioning and is the best prevention of HIV

infection. Heroin addiction to be sure is a complex problem involving sociological and psychological factors, however because of the recent discoveries of the endogenous opioid receptor-ligand system the importance of biology can not be ignored. Methadone, therefore, acts as a normalizer for a deranged physiology in maintenance treatment and not a mood altering narcotic. Methadone maintenance is replacement therapy for the neurological deficits caused by heroin addiction. As such it is therapeutic, but not a curative. Communities should welcome methadone programs because they reduce addict-related crime and reduce morbidity and mortality related to the transmission of infection. The quality of life in a community is improved for all residents by the presence of a well administered methadone maintenance program.

Notes

(1) The abbreviation for nanogram is ng. Return

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III.

Special Topics for Methadone Treatment

The Methadone Maintained Patient and the Treatment of Pain*

by
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Opiate addiction and the most effective treatment for it, methadone maintenance, are not well understood within the medical profession. The reasons for this are complex and can be traced back to the Harrison Narcotic Act of 1914. Physicians were the first group to be persecuted by this legislation which did not consider opiate dependence a legitimate medical condition and forbade the prescribing of opiates solely for the purpose of maintaining dependence. At the time the majority of opiate-dependent persons were middle class women (housewives) and physicians or other medical professionals who had access to drugs. Nevertheless, many physicians attempted to pursue a humane course of medical treatment by continuing to prescribe their "necessary" narcotics. Authorities were determined to make an example of these mostly family doctors, so many physicians were arrested, imprisoned and lost their medical licenses and practices. It must be emphasized that these were not unscrupulous physicians, rather many were concerned about the patients they had treated for years.

Over the years, the medical profession's early experience with the Harrison Narcotic Act has evolved into the dictum "stay away from addicts" they are nothing but trouble and addiction is not a doctor's domain. By the 1930s, this attitude became prevalent in medical schools with physicians receiving little or no training in addiction, which remains to this day. The lack of training on addiction, drug dependence and prescribing medication for pain has resulted in much confusion among clinicians (Portenoy & Payne, 1992). Added to this confusion is the strict regulating of narcotic drugs whose main impact has been to cause the under prescribing of narcotic drugs for the relief of pain. Physicians have become concerned about addiction when prescribing for pain relief. Yet the fact is that when morphine is taken to relieve pain it rarely causes addiction. However, there is evidence that the medical profession is changing. Addiction treatment has recently become a subspecialty within the American Medical Association.

The unwarranted fear of addicts and the fear of prescribing opioid analgesics has been given a name, addictophobia. The education of physicians in the pharmacology of opioids and their ability to relieve pain, along with training in the basics of addiction, will help eliminate these attitudes. However, belief that addiction is a behavioral problem will no doubt persist until the biological causes are discovered and understood.

Clarifying Terminology

Tolerance is a pharmacologic property of all opioid drugs and is characterized by the need for increasing doses in order to maintain the original effects (Jaffe, 1985). Tolerance to the reinforcing effects of opioids, and the need to increase the dose in order to maintain the initial effects, is considered an important aspect of addiction. The belief that tolerance will develop to the analgesic effects of opiates in the opiate-naive patient and thus interfere with analgesic efficacy continues despite evidence to the contrary (World Health Organization, 1969). Studies have demonstrated that tolerance to the analgesic effects of opiates occurs only in patients with chronic and worsening pain (Foley, 1985; Twycross, 1983). Patients treated for prolonged periods with opiate drugs for nonmalignant pain fail to demonstrate the need for escalating doses in order to achieve pain relief (Portenoy & Foley, 1986; Portenoy, 1989).

Physical dependence is also a pharmacologic property and is defined solely by the abstinence syndrome or what is more commonly known as withdrawal (Jaffe, 1985). Much of the misunderstanding about physical dependence and addiction occurs because these terms are often erroneously used for one another. Physical dependence is a pharmacological property of all opioid drugs, as is tolerance while addiction is identified based on psychological or behavioral manifestations of the underlying disease.

Narcotic addiction as we know it, is characterized by drug craving, compulsive use, deviant behaviors and most commonly relapse after withdrawal from the drug. It is interesting to note that methadone has a significantly lower potential for abuse than heroin, morphine, etc., based on its slow onset of action with a relative lack of reinforcing effects. The term drug abuse is used to define any compulsive drug-taking behavior that is not within accepted societal or cultural mores. However, experts in the field are beginning to use this term less because of the moral implications, and prefer to use the term "drug use" in its place. It must be stressed that the behavior associated with compulsive drug taking is quite different from the behavior of a patient with a history of illicit drug use who requests medication to relieve pain.

It must be emphasized that it is unjustified for physicians to be reluctant to prescribe a sufficient dose of medication in order to relieve pain. Since medically caused addiction to opiates rarely occurs, their application to relieve pain should be pursued aggressively and early in order to promote health and healing. Furthermore, it is illogical for physicians to under prescribe opiate analgesics for patients suffering with the pain of terminal cancer or any other fatal condition for fear of addicting them. For these patients the focus should be on relieving the pain of the disease and dying and thus allowing them to live out their final days with their family and in comfort.

The Opiate-Dependent Person and Pain

Methadone patients who are hospitalized with acute or chronic pain conditions are at high risk for receiving inadequate medication for relief of pain. There are several major reasons for this. First, many health professionals incorrectly believe that methadone patients will obtain pain relief from the methadone. Secondly, attitudes of the medical staff about illicit drug use may overwhelm the need to provide adequate pain relief and complaints from the patient are perceived as manipulations to receive opioids for other than pain relief. Another potential factor for under treatment is the failure of the medical staff to recognize the potential for tolerance in methadone-maintained patients. The result is that a large majority of methadone patients who have needed medication for pain relief did not receive an adequate dosage, or even any at all. As former drug users methadone patients often perceive the medical profession as unsympathetic and prejudiced based on earlier experiences. The rehabilitated methadone patient very often continues to be excluded by those responsible to provide comfort and relief. Whatever factors may contribute to the under treatment of methadone patients the end result is the undermining of the therapeutic alliance.

Some clinicians incorrectly assume that the methadone-maintained patient has no need for pain relief. Patients maintained on methadone have developed a tolerance or resistance to the narcotic, analgesic (pain killing) and tranquilizing properties of methadone. Consequently, they feel pain to the same degree as persons who are not maintained on methadone and need adequate doses of morphine or other narcotics to relieve acute and chronic episodes of pain.

These authors know of no studies that have evaluated the effects of tolerance and its potential in reducing the efficacy of analgesics (Portenoy & Payne, 1992). Several studies have found that the usual regimen used to provide pain relief for the non opiate tolerant patient can also be used to treat those maintained on methadone (Kantor, Cantor & Tom, 1980; Rubenstein, Spior, & Wolff, 1976). However, these studies did not assess directly the relief of pain, or evaluate the role of tolerance in achieving analgesia (Sawe, Hansen, Ginman et al, 1980). Since these factors were not considered these authors encourage clinicians to evaluate dosage in consultation with the patient in order to ascertain that adequate analgesia has been achieved for proper healing and health of the patient.

Some methadone patients who have been hospitalized for surgery have reported that their methadone doses were lowered in the hospital and as a result they experienced withdrawal symptoms while hospitalized (National Alliance of Methadone Advocates, Inc., 1994). Other reports have been received that some patients were even told to detoxify from methadone prior to surgery since it is incorrectly believed that methadone may interfere with analgesia or their health condition (Payte, 1994). In summary it must be emphasized that the opiate-dependent patient must be treated with the same dignity and respect as any other patient. When treated humanely and with compassion the opiate-dependent patient is no more difficult to treat than non dependent patients, although they may be a little more distinctive than the ordinary patient.

Methadone patients or opiate dependent individuals should never be given mixed opiate agonist/antagonist drugs as this will precipitate the abstinence syndrome and can cause serious problems. Commonly used drugs in this class include Talwin, Nubain and Stadol.

The methadone-maintained patient is easily treated for chronic pain. Physicians need not be concerned with those methadone patients maintained on a blockade dose of 80 mg/day or greater to feel any euphoric effects from short-acting narcotics (Dole, Nyswander & Kreek, 1966). The methadone will block it. Even lower doses of methadone will produce a partial blockade

effect. It must be emphasized that in order to produce adequate analgesia in methadone patients short acting narcotics may have to be prescribed in higher doses and greater frequency than that needed for the opiate naive patient. Since, methadone patients at a blockade dose are protected from respiratory depression so the concern of the physician should be to achieve satisfactory analgesia.

Usually a sensitivity to narcotics can be determined through an interview with the patient and in these cases the initial dose of pain medication can be given in small increments while observing the patient until analgesia is achieved. Treating the methadone patient for pain on a blockade dose is easier than the patient whose dose only provides a partial blockade. Inadequate pain relief may result in the former illicit drug user to seek additional drugs for the relief of pain, thus placing them at a great risk of relapse. Illicit heroin and cocaine are readily available in urban and rural locales and therefore easy to obtain for hospitalized patients in pain.

Fears of Patients with a History of Illicit Drug Use

Many former illicit drug users may be fearful of losing control and thus refuse any analgesia. First and foremost their request for no pain medication should be respected. However, in some patients eventually pain may overcome this fear and a request for pain medication may be made. Before this point is reached the clinician should discuss and make clear all the issues with the patient. Methadone patients receiving a blockade dose should be assured that their daily dose of methadone will block any euphoric effects of the drug and that analgesics will only produce relief of pain. Methadone patients on lower doses can similarly be advised of a partial blockade and that in all probability they will feel very little euphoria, if any at all from pain medication. Furthermore it should always be emphasized that analgesia for acute pain will probably only be necessary for a short time and that relief of pain is essential for a quick and healthy recovery. Some methadone patients may fear that their maintenance dose will have to be increased. Again these patients should be reassured that this problem has been studied and that an increase in their maintenance dose will not be necessary (Kantor, Cantor & Tom, 1980). Ultimately, the final decision should always rest with the patient, and the attending physician should make sure that these requests are respected.

Protocols for Pain Relief

There are several regimens that can be used with the methadone-maintained patient. None of these protocols have been demonstrated to be superior to the others, and physicians should rely on their own experience and observation, as well as listening to the patient. A common protocol and probably the easiest, is to continue the base line maintenance dose of methadone and supplement it with intermittent increments of a shorter-acting narcotic. Opiate-dependent individuals will metabolize narcotic analgesics faster and can rapidly develop tolerance to the analgesic effects of a short-acting narcotic and will probably require an increased dose and a more frequent dosing schedule (Kreek, 1983). The best advise to follow is that of the late Dr. Marie Nyswander who taught physicians to "listen to the patient."

Other regimens are somewhat problematic, but may be useful for some instances. One strategy is to increase dose of the long-acting narcotic, namely methadone, until the desired pain relief is achieved. In order to produce a sustained analgesia with methadone for a non opioid dependent patient, at least three doses per day are required. There is no advantage in using methadone for analgesia since the analgesic duration only lasts about four to six hours (Sawe, Hansen, Ginman et al, 1981). Methadone-maintained patients will quickly develop tolerance to the analgesic effects of methadone making this method only useful for short periods, if at all (Selwyn, 1992).

A final method is to completely abandon the long-acting narcotic methadone and institute a regimen to completely meet the needs of the patient's pain relief. Again another problem arises since short-acting opioids will probably be metabolized quicker in patients with a history of opioid drug use. They will rapidly metabolize short-acting opioids and develop tolerance to the analgesic properties faster thus making it difficult to achieve a maintenance dosage without development of some symptoms of the abstinence syndrome (Kreek, 1983).

Should these later two protocols be utilized and a problem occurs, such as the patient experiencing the beginning symptoms of the abstinence syndrome or analgesia is not achieved, the patient may perceive that they are being used to experiment on. No matter how erroneous this belief may be this attitude will undermine the ability to have a good therapeutic relationship with the patient. Persons with a history of drug use, as mentioned previously, have often had very bad experiences with the medical profession making them suspicious towards any clinician. Overcoming these attitudes is the art of medicine and they can be if the patient is treated with honesty, sincerity and dignity. Should it be necessary to choose any regimen that will either increase or decrease the maintenance dose of methadone it should be done in consultation with the physician treating the patient for their drug dependence.

Intramuscular Administration of Methadone

For some conditions, especially abdominal surgery the methadone-maintained patient may need their medication administered via intra muscular (IM) injection. There is the illogical belief

by physicians that methadone administered this way is stronger while in fact, "30 mg is 30 mg." Many hospitalized methadone patients requiring IM administration have reported that their daily dose was cut in half. This places these methadone patients at a distinct disadvantage. Methadone-maintained patients not receiving a blockade dose and especially those receiving 40 mg/day or less will begin to experience symptoms of the abstinence syndrome and will probably experience immediate discomfort within the 24-hour period. If these patients also require pain medication they will be experiencing pain and withdrawal symptoms simultaneously. Methadone patients on a blockade dose of 80 mg/day or greater will probably not experience any initial discomfort when their usual methadone dose is cut in half because it is administered IM, at least for awhile. As their methadone blood levels slowly drop these patients, formerly receiving a blockade dose of methadone (80 mg/day or more), are no longer protected against respiratory depression and, more importantly, the lower methadone dose of 40 mg/day may only partially block any euphoric effects of an opioid administered for relief of pain.

Perhaps the most cautious strategy when administering methadone IM is to administer half in the morning and half in the evening. Perhaps this is where the confusion began regarding the halving of the dose. A few methadone patients who are not taking a blockade dose above 80 mg/day and who are sensitive to methadone may experience an initial sedation when their medication is administered IM. It must be emphasized that every effort should be made to maintain a methadone patient on their usual maintenance dose which was prescribed by a physician experienced in addiction treatment. The methadone patient will be reassured if his maintenance dose is maintained promoting a therapeutic relationship and a healthy outcome. Many physicians are concerned about the unusually high doses required for methadone maintenance: doses that would normally cause respiratory depression and possibly even death in the non opiate tolerant patient. However, it cannot be over emphasized that doses over 80 mg/day are necessary for methadone to be effective and adequate in blocking drug craving and hunger. Once drug craving is controlled with an effective dose the methadone patient can live a relatively normal and stable life.

AIDS and Pain Management

The care of patients who have a history of illicit drug use and are infected with HIV are of critical relevance when considering pain management. The complexity of the issues in treating these patients requires that the first step in their management should be a comprehensive assessment. First and foremost, all attempts should be made to obtain proper treatment for the illicit drug use. Clinicians not knowledgeable in addiction treatment should seek professional expertise when treating patients who are drug users. This will avoid acting-out behavior. Every effort should be made to assure these patients that an adequate maintenance dose of methadone will be given to them while they are hospitalized. Pain management for these patients may be difficult and require a greater frequency of monitoring. The use of a written contract which is kept in the medical record and defines the regimen and explicitly states the responsibilities of both the patient and the physician may be helpful in treating these patients.

Included in the contract should be the responsibilities of the patient after they are discharged from the hospital. The contract should have the methods used to renew prescriptions and the response to lost or stolen medication. One way to handle the problem of lost or stolen medication is to advise the patient in the contract that should this occur it will have to be reported to the police. The police report will have to be presented and placed in the patient's record before any replacement medication can be prescribed. Furthermore, it should be emphasized to the patient that medication will be replaced "only" once and therefore should only be used if the medication is truly lost or stolen. For patients who are not hospitalized or do not have a place to secure pain medication more creative protocols may have to be used. Certainly, one method is to only prescribe pain medication one day at a time. Such an arrangement could be made with a local pharmacy.

Summary

The methadone-maintained patient experiences normal pain and therefore needs adequate analgesic medication to relieve pain. At a blockade dose of 80 mg/day the methadone-maintained patient is protected from respiratory depression and will not experience drug craving or hunger or any euphoric effects of any short-acting opiates prescribed for relief of pain. Clinicians should not feel apprehensive about the large doses prescribed to methadone patients to treat drug dependence. Methadone will not interfere with the prescribing of opiates for analgesia. Detoxifying from methadone or any opiate is not recommended and can temporarily effect the health of the maintained individual. Perhaps the easiest protocol for pain management of the methadone patient is to prescribe adequate short-acting opiates while maintaining the maintenance dose of methadone. If it is necessary to change the maintenance dose of methadone it should be done in consultation with the patient and the clinician who is treating the patient for their drug dependence. If reasonable conditions of pain management are followed the methadone patient should be no different than any other patient treated for acute or chronic pain.

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The Functional Potential of the Methadone Maintained Person

by
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In 1967 the initial investigation of the function potential of methadone maintained patients was begun. At the 4th National Methadone Conference Gordon, Warner and Henderson (1972) reported on their extensive study evaluating the "psychomotor and intellectual performance of ex-heroin addicts," who were the first to be maintained on methadone as part of their treatment for opiate addiction. The conclusions derived from those early studies showed that, receiving methadone as part of the treatment for heroin addiction did not have any adverse affects on either cognitive functioning or perceptual motor learning and performance. A later report (Gordon, 1973) summarized field and laboratory studies of the performance of ex-addicts maintained on methadone, from 1964 to 1972. This paper reviews both the earlier work as well as research by other investigators.

This review is divided into two major sections, Laboratory Studies and Field Studies. The laboratory studies included perceptual-motor, reaction-time and sustained attention tasks, as well as tests of cognitive and intellectual functioning. Field studies were primarily concerned with driving experiences of methadone patients as well as general assessments of job performance, compared with relevant control subjects. There were also one or two studies that assessed patient behavior on-the-job.

Laboratory Studies

Prior to the studies to be reported on, only Isbell and colleagues (1948) had evaluated the effects of chronic administration of methadone in humans, which was conducted with institutionalized addicts to determine the addiction liability of methadone.

Intellectual Functioning

The Isbell study had indicated that methadone might have a detrimental effect on intelligence, therefore, one of the concerns of the early studies by Gordon et al (1972) was to examine intellectual functioning after patients were stabilized on maintenance doses of methadone. The results for 155 patients, whose initial maintenance dose ranged from 70-100 mg/day of methadone taken orally, did not show any departure from expected distributions of IQ scores found in the general population. An absence of cases in the lowest IQ categories was also noted.

Subsequently, Gordon and Lipset (1976) followed up on 30 of the 155 patients who had originally been tested for intellectual functioning, approximately 112 months later. When tested initially, these patients, had been maintained on an average of 79 mg of methadone, and on follow-up, the average daily dose was 69 mg. The tests used were alternate forms of the Wechsler Adult Intelligence Scale (WAIS). Twenty-five patients showed gains in IQ, one stayed the same, and four showed modest declines. Intellectual functioning in the follow-up, as in the original testing, was normal.

Later studies of cognitive functioning have arrived at similar conclusions. A study by Pugliese (1974) found no difference between age and education matched methadone patients and controls, when they were tested with the Wonderlic, a form of intelligence test. This study was concerned with the employability of methadone patients. A study by Lombardo (1974) also found that when educational level was taken into account methadone patients maintained on 50 or 80 mg per day showed IQs in the normal range.

A study concerned with memory processes by Grevert and colleagues (1977) found that methadone treatment had no effect on memory, in a study that compared memory performance prior to and after three months of treatment.

Laboratory Studies of Performance

Reaction-time Studies

Studies of reaction-time measure decision time as well as motor response times, which are sensitive to drug effects. The first study by this writer (1970), compared 18 male and 9 female methadone patients stabilized on average daily doses of 100 mg, with matched drug-free recently detoxified heroin addicts, and college students. The task consisted of one simple and two more complex reaction-time (RT) tasks. Methadone patients, both male and female, were either equal to or superior to control subjects on two of the tasks, and on the most complex choice RT task.

Later, Gordon and Appel (1972) studied the RTs of methadone patients when they were 24 hours abstinent from their daily dose and compared their performance when they were one-hour post daily methadone dose. Again, overall results for male and female patients indicated no methadone effect, and RTs were either equal to or superior to relevant control subjects. One interesting finding in the latter study indicated that working patient's RTs were more rapid than those of nonworking patients.

Three additional studies (Chesher, 1985; Kelley, Welch & McKnelley, 1978; Rothenberg et. al., 1977) have appeared which reported on reaction-times of methadone patients in laboratory type tests of attention. Some evidence was found that indicated patients may respond more rapidly than controls.

Sustained Attention

Appel (1982) studied the performance of methadone patients on a continuous performance task, where responses were made to an unusual signal after subjects were required to ignore varying strings of regular signals. Different rates of signal presentation were used. Methadone patients did not differ from drug-free ex-addicts or opiate naive subjects. There were differences in response latencies among patients - working methadone patients performed better at the high signal rates, and had longer latencies and poorer accuracy at the low rates. Nonworking patients made more false positive errors at the high signal rate than the other groups.

Appel and Gordon (1976) used the digit symbol sub-test of the Wechsler Adult Intelligence Scale (WAIS) to study patients' abilities to follow a code in substituting digits for two-dimensional pictorial symbols in a paper and pencil speed test. Working patients did not differ from controls, but nonworking patients experienced poorer performance. No evidence was found that patients who spent the longest times in treatment (8 years) were any poorer than patients who had only been in treatment for 11 months.

Rothenberg et al (1977) has found that methadone patients had faster response times than controls, and that there was no difference in maintenance of attention between patients and other groups of subjects.

Perceptual-motor Skill

Isbell et al (1948) had indicated that methadone might slow some aspects of perceptual motor functioning. In early studies (Gordon, Warner & Henderson, 1972), perceptual-motor performance was measured by means of the rotary pursuit test (a task used to measure learning and performance in an eye-hand coordination task), over the period of a year or so. Patients exhibited normal functioning.

Moskowitz and Sharma (1979) reporting on skills performance of patients maintained on methadone for at least six months, concluded that patients failed to show impairment on the most obviously relevant skills performance tasks. These studies represent the most comprehensive evaluation of the performance of methadone patients found so far. A series of eight experiments on various sub-skills related to driving behavior were conducted. They included performance in a driving simulator in which patients and control subjects were subjected to a variety of experiences which required close attention and accurate responses. Tests were conducted just before and two hours after the daily methadone doses of both 60 mg and 80 mg of methadone. While two of the sub-tests gave evidence of a methadone effect, patients compensated by more rapid response times. Methadone is also mentioned in another report (Stapleton, Guthrie & Linnoila, 1986) as having an effect on eye movements, but an assessment of the consequences is lacking. Moscowitz and Sharma (1979) felt that the more rapid reaction-times shown by methadone patients, more than compensated for any potential oculomotor slowing. A final study undertaken by Kelley, Welch and McKnelley (1978) of various functional parameters, also failed to find any important evidence of negative impact on overall functional status.

An interesting study by Ho and Dole (1979) indicates that methadone-maintained persons do not differ from drug-free ex-heroin addicts in their perception of somatic pain, a finding of some significance in terms of functional status.

The general conclusion of available laboratory studies of methadone patients is that there does not appear to be any socially relevant barrier to their ability to perform a variety of tasks such as those found in industrial settings or in driving motor vehicles.

Field Studies

Field studies reviewed here have relevance to the question of functional capacity of persons maintained on methadone as part of their treatment for heroin addiction. A recent evaluation study of methadone treatment by Ball and Ross (1991), has found a general relationship between maintenance dose and cessation of heroin use. It appears that the critical dosage level is 71 mg of methadone per day. Those patients maintained on doses lower than 70 mg of methadone, are much more likely to use heroin. The finding implies that daily levels below 70 mg result in incomplete tolerance. This would lead to the suggestion that future studies of functional potential, take into account the methadone dose level needed to maintain tolerance.

The studies reported on below fall into two categories; studies of employability of methadone patients and reports of their performance as motor vehicle operators.

Employability

Two studies relate to employability (Double & Koenigsberg, 1977; Yankowitz & Randell, 1977). Both studies indicated that ex-heroin addicts maintained on methadone function quite well as skilled laborers and office workers. This

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matches the conclusions arrived at in an earlier study (Gordon & Lipset, 1976).

Driving Behavior

Driving motor vehicles is an area of considerable public concern, given the widespread misuse of alcohol and other drugs. An earlier review (Gordon, 1976) found that there was little cause for concern about narcotic use generally and specifically for methadone use, when it is used as a maintenance drug. Since the earlier review there are a number of additional reports that have appeared (Babst, Newman, Gordon & Warner, 1973; Blomberg & Preusser, 1974; Maddux, Williams & Ziegler, 1977; Moskowitz & Sharma, 1979; Stapleton, Guthrie & Linnoila, 1986). In these studies, methadone maintained individuals did not differ from age-matched non-drug users or abstinent ex-heroin addicts. The studies reported on both traffic violations and accidents, and report confirmation of interview data collected from patients, by means of the patients' actual motor vehicle driving records obtained from official sources. A recent review by Chesher (1985) finds that based on studies of skills related to driving, or based on epidemiological findings, narcotics, including methadone, generally do not appear to be a source of concern in road crashes.

Conclusion

The general conclusion of this reviewer is that there is considerable confidence in the fact that maintenance on methadone at appropriate dosage levels, as part of treatment for heroin addiction, has little if any affect on ability to function in any capacity for which the person is qualified.

The foregoing conclusion should not seem so surprising in view of the fact that even heroin addicts (Caplowitz, 1985) while using heroin, as well as those maintained on morphine as part of their treatment for heroin addiction (Waldorf, Orlick & Reinarman, 1974), were able to be gainfully employed and successful in a wide variety of positions.

Recently it was reported that large doses of opiates are being chronically administered to individuals suffering from otherwise intractable pain (New York Times, 1993). The use of opiates, in the manner reported, for pain management, not only relieves suffering, but enables affected individuals to function normally. The main disability they suffer is stigma for their presumed "addict" status.

The lesson the we learn from this, is that addictive behavior, is a construct that is biological in origin and modulated by social and behavioral factors. Narcotics per se can cause physical dependence, tolerance, and craving. However, the social context of a person's narcotic use and way of life determines the nature of addictive behavior. In conclusion, methadone patients who are either building or rebuilding their lives or who are functioning normally within the community are not "addicts" but medical patients being treated for a chronic condition.

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Selective Attention in Opiate Dependent Individuals:
A Pilot Study Investigating the Effects of Endorphin Levels on Attention
by
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Introduction

Theorists such as Dole and Nyswander (1976), Goldstein (1972) and others have considered the possibility that there are physiological differences between opiate dependent and non-opiate dependent individuals. This study seeks to explore this possibility. Opiate dependent individuals may have a deficiency of endogenous opioids which they attempt to supplement by the use of opiates (Goldstein, 1976). The present research investigates the effect on attention that occurs by varying systemic levels of endorphins, the internal, or endogenous opioids.

In 1973 three laboratories found evidence of opioid receptors in vertebrate animals, with the highest concentration in the brain (Pert & Snyder, 1973; Simon, Hiller & Edelman, 1973; Terenius, 1973). Investigations followed that led to the discovery of naturally occurring, or endogenous, opioids, called endorphins that bind to these receptor sites (Goldstein, 1976; Hughes, Smith, Kosterlitz, Fothergill, Morgan & Morris, 1975; Terenius, 1975). Goldstein (1976) suggested that opioid receptors were related to emotional responses to pain.

A rich concentration of opioid receptor sites is located in the Locus Coeruleus (LC), an area of the brain that mediates attention (Kuhar, Pert & Snyder, 1973). Investigators found that applying morphine, or producing chemical lesions to the sites in the LC, interfered with the ability of the neurons to fire (Aghajanian, 1978; Pepper & Henderson, 1980; Arnsten, Segal, Loughlin & Roberts, 1981). Other investigators determined that the LC neurons responded selectively to complex, arousing stimuli (13). These studies indicate that the endorphin system plays a broader role than that of relaying information about pain and anxiety. It also plays a role in the processing of attentional information through the LC.

Implication that the endorphin system affects attentional mechanisms leads to questions regarding the effects on processing of simple and complex stimuli. Easterbrook (1959) has theorized that attention to a limited range of cues is preferable for certain tasks. Studies by Kahneman (1973) suggest that performance of a simple task requires limiting attention to a narrow range of cues, and conversely, the ability to attend to a wider range of cues facilitates performance on a complex task.

Naloxone and naltrexone are opiate antagonists; they block the ability of opiates to bind to the receptor sites, and inhibit the effects of opiates. The work of Arnsten (1981) and Arnsten et al (Arnsten, Segal, Loughlin & Roberts, 1981; Arnsten & Segal, 1979) suggests that naltrexone may operate to narrow the range of cues to which individuals attend. This may be desirable for performance on simple tasks, but inhibit performance on complex tasks. Gritz et al (1976) reported that naltrexone facilitated performance of opiate users on a simple task of selective attention. Appel and Gordon (1976) used a task of selective attention, the Digit Span sub-test of the Wechsler Adult Intelligence Score (WAIS), to compare subjects in methadone

maintenance treatment with opiate-naive controls, and found no significant difference.

The above theories, discoveries and studies suggest that different levels of endogenous opioids should have an effect on the performance of simple and complex tasks of selective attention. Simply put, individuals with different levels of opioids in their system will respond differently to attentional cues. Opiate dependent individuals may have a deficiency of endogenous opioids (Goldstein, 1976). Treatment modalities for these individuals provide environments that affect systemic endorphins by controlling the use of exogenous opioids. Methadone maintenance treatment provides supplemental opiates, drug free residential treatment prohibits the ingestion of opiates, and treatment with naltrexone blocks the effect of both endogenous and exogenous opiates.

The present study investigates a model that states that: 1) the ability to respond to attentional cues is affected by endorphin levels, 2) this can be observed behaviorally when endorphin levels are manipulated, and 3) the nature of treatment for opiate dependency manipulates these levels.

The hypotheses are based on the theory that performance on tasks of selective attention is dependent on the systemic levels of endogenous opioids. If this is true, 1) methadone-maintained individuals and opiate-naive controls should respond similarly on simple and complex tasks of selective attention, because, though there may be a deficiency of endogenous opioids in this treatment population, methadone supplements this deficiency; 2) abstinent opiate-dependent individuals, who are not provided with opioid supplements should achieve lower scores on both simple and complex tasks of selective attention than scores achieved by both methadone treated individuals and by opiate-naive controls; and 3) if naltrexone does indeed help narrowly focus attention, individuals in naltrexone treatment should receive higher scores on simple tasks of selective attention than those of individuals in any of the other groups. However, because both endogenous and exogenous opioids are blocked, their scores on complex tasks should be lower than those of all other subjects. There should also be a greater difference in scores on both tasks within this group than those found in all the other groups.

The Study

Three groups consisted of subjects who were in treatment for opiate dependence. Group I consisted of 12 subjects in methadone maintenance treatment, Group II was made up of 12 subjects in treatment at a drug-free residential facility, and the eight subjects in Group III were in naltrexone treatment. Group IV was a control group made up of 12 opiate-naive subjects. All subjects were male and ranging in age from 21 to 44. All subjects were tested for near vision with the Nearpoint Rotochart. They were also tested with the Digit Symbol sub-test of the WAIS for the ability to distinguish and identify the numbers and symbols necessary for completing the various tasks, and to replicate the attentional task used by Appel and Gordon (1976).

Two forms of a paper and pencil Symbol Identification Test were developed by the investigator and evaluated for this research. They were used to evaluate performance on simple and complex tasks of selective attention. Both forms of the tests were administered in counterbalanced order.

Results

The first set of hypotheses contended that there would be no significant differences in scores on both the simple and complex tasks between the methadone maintained subjects and the opiate-naive controls was supported by the data. These results are consistent with research suggesting that opioids are involved in mediating attention, and suggests the need for opiate-dependent individuals to receive supplementation.

The second set of hypothesis claimed that abstinent opiate users would have lower scores on simple and complex tasks of selective attention than methadone-maintained subjects and opiate-naive controls. Although the difference between the scores of the groups were not statistically significant, the results of all the comparisons were in the predicted direction.

The third set of hypotheses is based on the contention that naltrexone narrows the range of cues to which individuals attend by blocking the effects of endogenous opioids. Predictions are that individuals receiving treatment with naltrexone would have higher scores on simple tasks of selective attention than all other groups and lower scores on complex tasks than all other groups. It was also predicted that naltrexone treated subjects would show the greatest differences between scores of simple attentional tasks and scores on complex tasks. As before, all the results were in the predicted direction, but did not reach significance.

Summary

That there were no significant differences between groups overall served to confirm some hypotheses, specifically those that predicted similarities in function between methadone and control groups. But these results, at first glance, may be seen as weak in general, since differences that were found between the groups were not statistically significant.

On the other hand, it would be impossible to dismiss the hypotheses since the results were all in the predicted direction. A closer look at the differences between scores on the simple and complex tasks for all groups reveals consistently predicted trends. The absence of statistical significance may be due to an inadequate sample size. Increasing the number of subjects in each group may yield more significant results by differentiating discrete differences in attention between the groups.

The differences in attentional functioning sought in the present study may be more effectively measured with a combination of behavioral and physiological measures, specifically, highly demanding vigilance tasks combined with physiological measures of evoked potential at the brainstem and cortical levels.

The consistent trends revealed in this study not only prevent dismissal of the hypotheses and the theories that gave rise to them, but are actually indications that this is a fertile area for research. There are benefits in pursuing this investigation, not only for opiate dependent individuals, but also for individuals diagnosed with attentional deficits. Understanding the role of the endorphin, or endogenous opioid system in selective attention is an important step in helping to uncover the causes of some types of attentional deficits and in furthering the understanding of opiate dependency.

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