Methadone: history, pharmacology, neurobiology, and use

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Opiates have provided relief from psychic and physical pain for millennia, but their abuse and control has created an international scourge of addiction, misery, crime, and disease. Furthermore, because opiates are frequently administered intravenously, abusers may suffer from and transmit infections, including HIV, hepatitis B, and hepatitis C. Methadone maintenance remains the most successful pharmacologic treatment available for addiction, and its development has revolutionized the conceptualization of addictive disease. This article provides a review of the history of methadone treatment, the pharmacology of methadone, and the neurobiology of its therapeutic use. We will discuss current clinical practice, factors that limit methadone's use, and potential future developments.

1. Important early precedents to methadone maintenance treatment

By the close of the 19th century, opium derivatives were widely available for the treatment of insomnia, pain, and diarrhea, principally as laudanum, and later as morphine. During the American Civil War, large numbers of soldiers were administered morphine for their painful injuries or diarrhea, and many became addicted, acquiring what became known as the "Army disease." Military personnel from the Spanish-American War and World War I replenished the membership of this group when they came home suffering from injuries (Musto, 1997). Another substantial group of opiate-addicted people were white, middle-class women who, around the turn of the century, liberally used over-the-counter tonics for various physical and psychological ills—including menstrual pain and depression (Courtwright, 1982). With both of these groups of users, the usual medical response of physicians was to quietly maintain addicted patients on morphine. Two other groups that had problems with addiction included patients with chronic medical disorders and criminals. This last group was represented to the public as "dope fiends." By 1920 this demonization of drug users became generalized to most opiate addicts (Davenport-Hines, 2002).

The practice of chronic opioid treatment or "maintenance" in the United States became more complicated with the passing of the Harrison Act in 1914 (reviewed in Waldorfet al., 1974). The interpretation of this act, with the support of the American Medical Association, led to the prohibition of the dispensing of "narcotics" for the sole purpose of managing people who were addicted. Wary of the potential for social unrest that might follow the termination of such treatment for thousands of addicted people, as well as by humanitarian concern for their well-being, morphine clinics were set up by both federal and city officials to help treat addicted patients (Musto, 1997; Waldorf et al., 1974). Clinic sites included New York City, Los Angeles, New Haven (Connecticut), Jacksonville (Florida), and Shreveport (Louisiana). Most of these morphine clinics managed to curtail illicit drug use, although patient's lives still revolved around their need for multiple daily self-administered doses. The New York City clinic attempted to detoxify and rehabilitate patients; this program was considered a failure (Musto, 1997). By 1920 the last of these clinics was closed by the Narcotics Bureau (Waldorf et al., 1974). However, these facilities created a precedent for the methadone maintenance programs that would later be developed by the research efforts of a team from The Rockefeller University (Musto, 1997), programs still using an opiate agonist but one with pharmacokinetics and pharmacodynamics very different from those of either heroin or morphine.

After the closure of the morphine clinics, many opiate-addicted people were incarcerated (Musto, 1997). As a result, the federal government set up a prison-hospital-farm complex in Lexington, Kentucky, in 1935. This was later followed by the creation of a similar institution in Fort Worth, Texas, in 1938. These complexes admitted both prisoners and voluntary patients, with the goals of treating addicted persons, as well as searching for cures for narcotic addiction and developing nonaddictive pain medication. Under the leadership of Dr. Clifton K. Himmelsbach, a great deal was learned about the effects of various opiates and the symptoms that followed their use and cessation. The goal of finding a "cure" or an effective long-term treatment remained elusive. In several prospective studies, it was shown that 70% to 90% of the patients who left the hospital relapsed within 2 years of their discharge (see Joseph et al., 2000). However, briefly during the 1950s, methadone was studied for detoxification, and Dr. Marie Nyswander (later instrumental in pharmacotherapeutic treatment of heroin addiction) learned of this research during her period of study there.

2. The return to maintenance: history, discovery, and development

In the late 1950s and early 1960s, a heroin epidemic swept through New York City with a marked increase in heroin-related deaths. Many groups called for the reestablishment of clinics that could distribute narcotics, including the American Medical Association (1956), the Joint Committee of the American Bar Association and the American Medical Association (1958), the New York Academy of Medicine (in 1955 and 1963), the Medical Society of the City of New York (1962), and President Kennedy's Advisory Commission (1963) (Joseph et al., 2000). Lewis Thomas, M.D., then head of the New York City Health Research Council (HRC), asked Vincent ; Dole, M.D., of The Rockefeller University to chair the Narcotic Committee of the Council, whose mission was to investigate the problem and consider possible medical interventions (Joseph et al., 2000).

Dr. Dole, already a respected physician scientist in the fields of obesity, hypertension, and lipid metabolism research, accepted the leadership of the committee of the HRC and in 1963 decided to change the focus of his laboratory to the pursuit of a pharmacotherapy for heroin addiction. He assembled a research team to join his laboratory. His first choice, based on his reading of her book *The Drug Addict as a Patient*, (Nyswander, 1958) was Dr.Nyswander, a psychiatrist and psychoanalyst who had long been engaged in the treatment of addiction. Her efforts had included setting up street-front clinics in Harlem for the treatment of addiction and spending a year working in the federal prison hospital at Lexington, Kentucky. Dr.Nyswander had a deep empathy for, and strong ability to make therapeutic connections with, addicted patients. She knew, however, that neither her efforts in the Harlem clinics nor the efforts of the federal prison hospitals had been able to make lasting changes in many addicted persons (Kreek and Reisinger, 1997). Dr. Dole also wished to recruit a young physician to do research in this area and turned to the New York Hospital, Cornell Medical Center, located near The Rockefeller University. Mary Jeanne Kreek, M.D., a resident in medicine, was selected. Dr. Kreek had been a Westinghouse Science Prize finalist, had worked at the National Institutes of Health, and, while a medical student at Columbia University College of Physicians and Surgeons, had treated heroin addicts during a rotation at the Bellevue Hospital detoxification service. Her contributions included knowledge of clinical research design and a thirst for understanding the biology of human diseases. With the permission of the University's president, Dr. Detlev Bronk, and the head of The Rockefeller University Hospital, Dr. Maclyn McCarty (codiscoverer of the role of DNA in 1944), this team brought heroin addicts to the unlocked inpatient unit of The Rockefeller University Hospital with the hope that they could develop an effective opioid maintenance treatment.

3. The functional state of the typical heroin user

Short-acting opiates, such as heroin, rapidly occupy μ-opioid receptors (see below). By changing the route of administration of the salt from intranasal ("snorting") to subcutaneous ("skin popping") or intravenous ("shooting," "mainlining"), users can hasten absorption and receptor binding. The more rapidly the drug is able to effect cellular processes after binding, the greater the intensity of the subjective experience, or euphoric "rush," which is followed by a period of peaceful somnolence, known as "nodding out." Heroin has a short duration of action, after which withdrawal commences (see Figure 1 and Table).

Subjectively, withdrawal is a state of anxious misery, pain, and an intense "hunger" for heroin. There is also a physiologic withdrawal syndrome characterized by autonomic activation, increased bowel motility, rhinorrhea, and pupillary dilation. Over time, with the development of tolerance and physical dependence, frequency and amount of heroin used increases. This is, in part, due to the reinforcing effects of the drug and, in part, as an effort to avoid withdrawal (negative reinforcement). Tolerance starts with the first dose and long before physical dependence is established. Once tolerance has occurred, escalating doses of drug are required to achieve positive effects, while the withdrawal symptoms worsen. The addict no longer attains a "high" without extraordinary and potentially lethal doses of heroin and spends much of the time trying to obtain enough drug to ward off withdrawal and feel "straight."

3.1. The Rockefeller University trials

Initial studies conducted over the first few weeks of 1964 by Dole et al. (1966) utilized morphine to verify the earlier observations and predictions about the lack of effectiveness for the treatment of opiate addiction. In fact, this trial was halted as patients alternated between periods of intoxication or withdrawal several times each day. Patients ruminated constantly about their dosing schedules and required continuing dose escalation because of the rapid development of tolerance.

Then, in early 1964, The Rockefeller University team chose to study methadone. Methadone, an orally effective synthetic opioid, was synthesized in the 1930s in Germany by I.G. Farben Industrie Hoechst-Am-Main, with the intent to develop an analgesic for wounded soldiers while allied forces controlled opium exports from the East; the drug was undergoing laboratory-based preclinical study. Soon after World War II, the U.S. military commission had identified this compound as being of possible therapeutic value and had officially brought it to the United States for study in the treatment of pain (at Lexington). Lilly took over manufacture of this generic product under the trade name Dolophine®. By the mid-1960s, long-term heroin-addicted volunteer research subjects reported that they had used "dollies" on the street to assist them in their withdrawal. On the basis of these reports, Dr. Nyswander's experience at Lexington and Dr. Kreek's observations at Bellevue, The Rockefeller University team selected this drug for study Kreek, 2000; Kreek and Reisinger, 1997).

Methadone, in contrast to heroin, has a slow onset of action, so it does not cause a reinforcing "rush." It is long-acting so that it may be administered once a day and provide a steady-state plasma concentration. Tolerance is negligible, so therapeutic doses can remain constant indefinitely. See Table 1 and Figure 1.

Because the research subjects were long-term heroin addicts (mean time of addiction was 14 years), methadone was started at 20 to 30 mg orally and titrated upwards in weekly increments of 10 to 20 mg, first to alleviate all signs and symptoms of opiate withdrawal and then purposefully to achieve maintenance doses between 80 and 120 mg in an attempt to achieve a high level of opiate tolerance and thus cross-tolerance. At that time, there were no techniques to determine pharmacokinetics, but clinical observation suggested that methadone had a long half-life, and so after several weeks of study the decision was made to combine the divided doses into a single oral daily dose. When the doses of methadone were thus slowly raised to 80 mg and above per day, physicians saw an unexpected transformation in patients (Hentoff, 1968). Dole (1988) wrote, "The fluctuation in clinical state became less and then disappeared . . . the patients seemed normal. Most remarkably, their interests shifted from the usual obsessive preoccupation with timing and dose to more ordinary topics."

3.2. Narcotic blockade

Ideally, a maintenance medication would not only reduce drug hunger (craving) and withdrawal, but also block the reinforcing intoxicating effects of short-acting opiates, that is, provide narcotic blockade. To test this, Dole, Nyswander and Kreek conducted two sets of double blinded studies in 1964 (Dole et al., 1966). The patients receiving methadone were intravenously administered heroin, morphine, Dilaudid ®, methadone, or saline in a double-blinded, randomly ordered Latin-square design. At doses between 80 mg and 120 mg, significant blockade was provided against opiate effects through the phenomenon of narcotic cross-tolerance. The patients did not feel any opiate-like effects, including euphoria, even when administered heroin in doses equivalent to those used on the street. Patients no longer wanted to buy opiates as they could not get "high."

3.3. The metabolic theory of addiction

Perhaps because of their varied backgrounds and experiences, the Rockefeller team was able to consider opiate addiction in a way that differed markedly from the prevailing view. At the time, the psychoanalytic conceptualization of heroin use was that it was an attempt to achieve oral gratification or to mask psychosis, a perspective that was about to change to the theory that it was an attempt to soothe psychic damage wrought by trauma (Yalisove, 1992). The behavioral psychologists, in turn, were beginning to understand the role of conditioning in addiction, but no therapies had yet been developed from these observations. The general public mostly saw heroin addiction as antisocial behavior, as a manifestation of a shoddy moral character, or as reflection of a "weak" personality.

Dole, Nyswander, and Kreek took the perspective that long-term addicts continued to use heroin and repeatedly relapsed to heroin use after detoxification, drug-free treatment, or imprisonment in an attempt to correct a fundamental metabolic imbalance. Whether the imbalance was caused by the drugs themselves, by the person's genetic endowment, by traumatic developmental and environmental experiences, or some combination of these factors was unknown. Their vision became known as the *metabolic theory.* This theory was reminiscent of the "immunochemical theory of opiate addiction" that was championed by some at the beginning of the 20th century (Musto, 1997). According to the older theory, the use of opiates created "antitoxins" within the individual. If that person stopped using opiates, the antitoxins would induce withdrawal. Thus the recommendation was to maintain the person on an adequate dose of morphine to keep these immunologic activities at bay. Dole, Nyswander, and Kreek shared with their predecessors of 50 years before the goal of establishing "physiologic balance," while maintaining that addiction was a disease.

4. Benefits of maintenance

In 1974, a report on the first 17,500 patients in treatment (1964–1973) was issued (Gearing, 1974, in Joseph et al., 2000). Those that remained in treatment experienced a 35% improvement in productive behavior (employment, education, homemaker status) over their status at entry. Although all patients had criminal records on treatment entry, arrests dropped from 201 arrests per 100 person years to 1.2 arrests per 100 person years. The death rates for those in methadone programs was only slighter higher than normal, whereas the rate for the group that left treatment was more than three times normal. In this study, only 25% of patients had alcoholism or any other drug abuse, and it was this subgroup that accounted for most of the discharges and poor outcomes.

The only controlled prospective trial of methadone maintenance was conducted in Sweden (Gunne and Grönbladh, 1981) and showed that 76% of the patients enrolled in methadone maintenance programs became employed and drug-free, whereas 6% of the control group members were rehabilitated. Further studies by this group (Grönbladh et al., 1990) revealed that mortality of street heroin addicts was 63 times expected, compared with 8 times expected in patients enrolled in methadone maintenance treatment. A further review by Ball and Ross (1991, in Joseph et al., 2000) confirmed the dramatic positive response to methadone maintenance treatment. Within 6 months, 77% of patients stopped intravenous heroin use, and there was a 79% reduction in all types of crime. Improvements accrued with length of treatment: after 4.5 years, almost all illicit drug use ceased.

An economic analysis and careful review of methadone treatment (McLellan et al., 2000; Barnett and Hiu, 2000) suggest that it is more cost-effective than a wide range of therapies for other chronic diseases in respect to both personal and public health. There are also considerable gains made by those in the community that do not inject drugs, for example, the reduced rate of HIV transmission (see below). Nevertheless, few medical insurance plans provide coverage for methadone treatment, and governments fail to invest adequate resources.

5. Infectious diseases: HIV and the hepatitis viruses

Patients abusing illicit drugs engage in behaviors with high risk for transmitting infectious diseases through unsafe sexual practices, sharing of inadequately cleaned drug administration paraphernalia, and inadequate health care. Methadone treatment has reduced HIV transmission in the opiate-dependent population. HIV infection in parenteral drug abusers was first identified by studying (1983–1984) anonymized sera of opiate-addicted and neurobiological research subjects banked from 1969 (Des Jarlais et al., 1984; Novick et al., 1986a, 1986b). Whereas 50% of the untreated intravenous drug abusing (IVDA) population tested HIV-positive, only 9% of those who were already enrolled and had remained in methadone maintenance programs from before the start of the epidemic (identified in this study to have arrived in New York City in 1978) had seroconverted by 1983.

A later prospective study of seronegative heroin addicts showed that over 18 months, the seroconversion rate of those in methadone maintenance was 3.5%, compared with 22% of their carefully matched peers out of treatment (Metzger et al., 1993). Once stable on methadone, patients not using other illicit drugs and who are not HIV-positive show improvements in numbers of natural killer (NK) cells, CD4 and CD8 cells, and NK cell activity (Novick et al., 1989).

Addicts may carry multiple hepatitis viruses (A, B, C, and D). Hepatitis B is a major infection among opiate-addicted populations Kreek et al., l972; Stimmel et al., 1975). Before 1985, over 80% of all IVDAs entering any treatment had one or more markers for HBV, although since 1985, with AIDS risk-reduction education, this number has fallen to below 50% in the USA and less than 30% in New York City. The hepatitis viruses are highly contagious and inoculation with an infected needle, filters, syringes, and other paraphernalia results in a very high likelihood of transmission. HBV, like HIV, is spread by sexual intercourse. With stable methadone maintenance, anti-HBV surface antibodies often appear, which stop progression. In other cases, only nonprotective core antibodies can appear with or without evidence of HBV DNA. When AIDS suppresses immune function, HBV may be reactivated. It is essential to vaccinate HBV marker-negative patients, as well as all health care staff, on entry to treatment with HBV vaccine. Borg et al. (1995) found that methadone-maintained patients respond normally to HBV vaccination with excellent adherence to the three-dose regimen and adequate immune response.

Hepatitis C virus (HCV), formally known as *non-A, non-B,* was not thought to be a pathogen until the mid-1980s. Studies have shown that by the seventies, many IVDAs were infected and that 80% to 90% of former IVDAs are now infected. The HCV is more contagious than HBV, but is rarely spread by sexual intercourse. HCV causes chronic hepatitis in 80% of all infected patients, cirrhosis in 20% over 20 years, and cancer in a portion of these (Novick et al., 1994; Piccolo et al., 2002). Treatment with ribavirin and pegylated interferon A can be implemented in methadone-maintained patients effectively despite their older age, more severe liver disease, and psychiatric comorbidity (Sylvestre, 2002). HDV no longer poses a significant threat, at least in the United States, because the percentage of heroin addicts with active replicating HBV is very low, and this is essential for the entry of HDV into cells (Kreek et al., 1990).

6. Pharmacology: pharmacokinetics

Methadone (4,4-diphenyl-6-dimethylamino-3-heptanone) is a synthetic full agonist at the m-opioid receptor. It has an asymmetric carbon atom, and the racemic mixture is generally used in maintenance therapy. In early studies, it was shown that substitution of the d(S)-enantiomer for the racemic mix resulted in withdrawal, and more recently it has been confirmed that the l(R)-enantiomer binds to the μ-receptor with ten times greater affinity than does the d(S)-enantiomer (reviewed in Borg and Kreek, 1998). It has recently been learned that both enantiomers are weak competitive antagonists at NMDA glutamate receptors, although this is more easily discerned with the inactive enantiomer (Gorman et al., 1997).

The distinct pharmacokinetic profile of methadone is crucial for its use as a maintenance medication (see Table 1). The racemic mixture has a half-life of approximately 24 hours, with the active l(R)-enantiomer possessing a half-life of 36 hours (Kreek et al., 1982; Nakamura et al., 1982). Taken too frequently, or by opioid-naïve patients, methadone will accumulate and cause sedation or respiratory depression, but once-a-day dosing will generally achieve relatively stable blood levels (Inturissi and Verebley, 1972; Kreek, 1973). Methadone has high oral bioavailability, avoiding the need for injection, and reaches peak blood concentration between 2 and 4 hours after ingestion (reviewed in Borg and Kreek, 1998). It is relatively lipid-soluble. Less than 3% enters the CSF. In vivo studies in knockout mice suggest that P-

glycoprotein may play an important role in transporting methadone across the blood-brain barrier, with a concomitant change in analgesic effects (Thompson et al., 2000). In theory, altered function of this protein, whether by genetic variation or by drug substrate interaction, could affect brain methadone levels.

Methadone binds directly to proteins, especially abundant on cell membranes in the liver, and to plasma proteins, chiefly albumin, globulins, and α_1-acid glycoprotein. Steady state is not attained until methadone is fully distributed and bound in tissues, and so blood levels continue to rise slowly for 4 to 6 weeks. Although patients sometimes complain about drug formulation changes (tablets versus liquid; differing flavors), there are no correlated changes in pharmacokinetics or dynamics (Eap et al., 2002).

7. Metabolism

Methadone is N-demethylated to inactive metabolites by liver and intestinal cytochrome P450-related enzymes, primarily CYP3A4, with some contribution from CYP2D6 (Iribarne et al., 1996). Other cytochromes, including CYP1A2, CYP2C9, and CYP2C19, have been implicated on the basis of observed interactions. Extensive uptake and storage by the liver occurs, but not extensive "first pass" metabolism and elimination. Mild or moderate liver failure is inconsequential for methadone dosing. In extremely severe liver disease, some adjustment may be needed, although loss of storage tissue may be more significant than disturbed metabolism so that dose increases (not decreases) are occasionally necessary (Novick et al., 1985). Excretion is via both urine and bile, so that the dose does not need be altered in renal failure (Kreek et al., 1980). Whereas extremes of urinary pH can affect elimination, this has little clinical relevance.

Inducers of CYP3A4 accelerate metabolism, so that withdrawal may be seen. Following observations of narcotic withdrawal in previously well-maintained methadone patients receiving rifampin for treatment of tuberculosis, Kreek et al. (1976) showed that the area under the plasma concentration curve (AUC) of methadone was significantly reduced with concomitant rifampin administration and with the onset of signs and symptoms of opiate withdrawal. The urinary excretion of a major methadone metabolite was also increased. Methadone dose needs to be increased, or its administration divided into twice-daily dosing. Alternative anti-tuberculosis drugs may be used in place of rifampin.

Similar pharmacokinetic studies revealed that phenytoin, commonly used for the treatment of epilepsy, decreased methadone concentrations by a mean of 2.4-fold. Significant opiate withdrawal symptoms appeared on initiation of phenytoin treatment (Tong et al., 1981). Carbamazepine also induces CYP 3A4 and so may decrease the half-life or plasma levels of methadone. Based on clinical observation and naturalistic study, barbiturates have also been reported to enhance methadone metabolism (Liu and Wang, 1984). Again, methadone dose may be increased or divided, or alternative drugs may be used. For example, valproic acid has not been shown to enhance methadone metabolism (Saxon et al., 1989).

Kreek et al. (198l) also showed that although alcohol, taken in high concentrations, may induce methadone metabolism once cleared from the body, social drinking does not affect methadone metabolism (Cushman et al., 1978).

Drugs used for the treatment of HIV may also be inducers of the cytochrome pathways. Case reports suggest that nucleoside reverse transcriptase inhibitors do not significantly induce or inhibit the CYP system. Nonnucleoside reverse transcriptase inhibitors, notably nevirapine and efavirenz, may precipitate methadone withdrawal through CYP3A4 induction with marked decreases in methadone concentrations (Heelon and Meade, 1999; Marzolini et al., 2000; Clarke et al., 2001, Bart et al., 2001), as can ritonavir, a protease inhibitor (Beauverie et al., 1998). Methadone slows the metabolism of AZT in some patients (Selwyn et al., 1989).

Inhibitors of CYP3A4 may raise methadone levels. Fluconazole increases AUC by 35% (Cobb et al., 1998), and ketoconazole and erythromycin probably interact in a similar fashion, given their actions at CYP3A4. Diazepam, a commonly prescribed benzodiazepine, does not alter the pharmacokinetics of methadone (Preston et al., 1986).

Case reports have suggested that interactions at CYP1A2 may contribute to significant increases in methadone AUC observed with fluvoxamine (DeMaria and Serota, 1999) and with ciprofloxacin (Herrlin et al., 2000). Nicotine induces CYP1A2 but does not seem to result in clinically significant changes. Interactions at CYP2D6 by drugs such as fluoxetine, paroxetine, and sertraline might be expected, but they have not been documented and do not cause clinical problems. Clinically, drug-drug interactions with methadone require a combination of factors, such as poor metabolism or multiple coadministered drugs inhibiting different metabolic sites (e.g., fluoxetine, ciprofloxacin, nicotine, and methadone in the patient described by Herrlin et al.).

As for most medications, there is individual variability in methadone plasma levels for a given dose Kreek et al., 1976; Eap et al., 2002). Phenotypic variation in CYP3A4 activity, CYP2D6, and α_1-acid glycoprotein subtype can be considerable, and this might influence disposition and metabolism. However, there is sufficient buffering by protein binding to limit variability in plasma levels.

A change in the volume of distribution may alter plasma methadone levels (Pond et al., 1985). Pregnancy increases the volume of distribution. Additional metabolism probably occurs in the placenta and fetus, and metabolism is further enhanced by high levels of progestins. Therefore, methadone dose must be increased over the course of the pregnancy and can be reduced to prepregnancy doses immediately after birth. End-stage liver disease or certain neoplasia may cause a rise in acute phase proteins such as a_1-acid glycoprotein or lower total protein so that dose increases may be needed.

Unbeknownst to patients, "natural" or "alternative" medications may also interfere with metabolism, although rigorous studies have not been performed. Unpublished reports of interactions include decreased methadone levels with St. John's Wort and increased levels with cat's claw, echinacea, goldenseal, chamomile and grapefruit juice. Treating physicians need to keep abreast of known interactions, but given the complexities, they must treat the patient's symptoms and function rather than any hypothesized effects.

Additional individual variability in response may, in theory, be attributed to genetic differences in receptor dynamics, but to date no such alterations have been found in humans.

8. Contemporary dosing practices

Based on the early studies of The Rockefeller University team (Dole et al., 1966), doses of 80 to 120 mg were recommended for maintenance. Today's opiate abusing population has changed. Average heroin purity has increased from about 3% to 30% up to 70% to 80%, especially in the northeastern United States, and prices have dropped. There are now increased numbers of addicts of a younger age who require higher doses of methadone to provide narcotic blockade (Bach and Lantos, 1999). Donny et al. (2002) have confirmed that higher doses of methadone (100 to 150 mg) may be needed to provide blockade against heroin administration. Strain et al. (1999) showed that in a research population, those patients treated with 80 to 100 mg of methadone had significantly lower numbers of opiate-positive urines than those treated with only 40 to 50 mg. Treatment retention, a major factor in successful treatment, doubles as the dose increases above 60 mg and doubles again for those receiving doses above 80 mg (Caplehorn and Bell, 1991).

To date, no controlled trials of medical safety, effectiveness, or treatment outcome have been performed using doses over 120 mg/d. Most studies exclude patients with serious psychiatric comorbidity or those on multiple and interacting medications. Patients may require higher doses of methadone for many reasons. In addition, such dose increases may reduce illicit drug use of benzodiazepines, alcohol, and stimulants (Borg et al., 1999). Clinics should accommodate patients with higher dose requirements, titrating to treatment response and side effect tolerability. However, doses exceeding 150 mg/d are only rarely needed and, according to federal guidelines (SAMHSA), must be justified on an individual case basis and only after permission has been granted to exceed this dose.

First doses should be between 20 and 40 mg, depending on tolerance, and a further 20-mg dose may be given on the first day after 4 to 6 hours if there is no intoxication and if withdrawal is present. Doses may be increased by 10 mg each day, again if no intoxication is present, up to 60 mg the first week. Thereafter, doses may be increased as much as 10% to 20% a week, being careful not to exceed the level of tolerance attained and holding at a dose of 80 to 120 mg/d for 4 weeks or more to attain a steady state in plasma levels.

It can take 6 months for most patients to become stabilized and for heroin use to be significantly reduced Kreek, 2000. In an ideal situation, there is an ongoing dialogue between the patient and the clinician as to what is the best dose (D'Aunno and Vaughn, 1992), with increases for ongoing use, craving, or withdrawal. Once at a stable dose, personalities appear to change, as antisocial behavior, aggression, and mood abnormalities associated with withdrawal and drug-seeking attenuate. Therapy may now assist patients to make the necessary psychological and social changes to improve their lives and to minimize their risk for relapse in the future.

9. Therapeutic dose monitoring

Blood levels should be obtained when patients complain of early morning abstinence or afternoon somnolence, when dose requirements exceed those customary, when a drug known to interact with methadone is to be prescribed, or when a patient becomes pregnant. A trough steady state level of 200 ng/ml is usually achieved with 80 mg/d, although this has not been systematically validated. The ratio of peak to trough gives some indication of rate of metabolism. A doubling is typical, whereas a ratio >3.5 indicates rapid metabolism. The active (l)R enantiomer is not selectively measured by the analytical technologies currently used in most studies. Given the multitude of pharmacodynamic and pharmacokinetic factors altering methadone's effects in an individual, the clinician must treat the patient rather than the dosage.

10. Side effects and toxicity

Side effects that may persist during chronic treatment with steady doses of methadone include sweating, constipation, and weight gain Kreek, 1973; Kreek, 1978). Increased perspiration, which is not sufficient to impair thermoregulation or performance in hot conditions, persists in more than 50% of patients. Pharmacologic options may be considered in extraordinary circumstances. Constipation occurs in all cases, especially during induction, but persists in less than 20% after 3 years. Bulk and softening laxatives should be used, but severe or persistent symptoms can be treated with low doses of oral naloxone or methylnaltrexone (not commercially available) (Kreek et al., 1983; Culpepper-Morgan et al., 1992; Stephenson, 2002). Decreased libido and menstrual abnormalities are common during cycles of heroin use, secondary to disruption of the pulsatile secretion of luteinizing hormone (LH). Methadone maintenance allows normalization of LH levels. Female patients should be advised that they will regain their normal chance of becoming pregnant as secondary amenorrhea disappears and normal menstrual cycles with ovulation recommences within 1 year. Methadone stimulates prolactin secretion, and during initiation of treatment levels, are greater than normal. Although attenuation occurs over time, daily peaks of administered methadone still stimulate acute rises of prolactin, but these remain within normal limits. Galactorrhea has been reported only rarely as a side effect during early treatment.

Because of its long half-life, methadone is more likely to be found on autopsy and named as a potential cause of death than other opiates; however, it is often an incidental postmortem finding unrelated to cause of death (Karch and Stephens, 2000). Careful review of all lethal drug intoxications in Switzerland over a 4-year period (Perret et al., 2000) suggests that methadone overdoses among patients in methadone maintenance clinics is rare and occurs mainly when physicians either ascend doses too rapidly during early treatment or allow take-home doses for patients who are new to treatment and subject to misuse of other illicit drugs including sedatives. Although this kind of study has not been undertaken in the United States, the pattern is nonetheless likely to be similar. In fact, introduction of methadone maintenance may reduce the risk for death, especially in conjunction with harm reduction interventions. In the U.S., accidental overdose in children has been reported but has been markedly reduced by the use of child-resistant containers for take-home doses. People not in maintenance clinics may self-medicate with methadone that has been illegally diverted from patients. These people may overdose by taking doses that are too high for their level of tolerance or by using methadone in conjunction with other drugs in their blood that increase lethality (e.g., sedatives).

A third problem may be arising in the United States and other countries. Physicians are becoming increasingly aware of methadone's usefulness as a medication for pain. They fail, however, to recognize that it is a very powerful opiate with a slow onset, and the result is that the dose provided is too strong for nontolerant or weakly tolerant patients.

Overdose may be managed with opiate antagonists. Naloxone, with a half-life of 20 to 30 minutes, must be administered repeatedly or as an infusion for 28 to 40 hours or until the patient has 2 hours of sustained alertness. Nalmefene, with a half-life of 6 to 8 hours, may be preferred and should be given in repeated doses or as an infusion for as long as necessary. In the case of a buprenorphine overdose, however, naloxone does not seem to be able reverse the effects Kreek, 1996.

Methadone maintenance does not appear to be detrimental to cognitive functioning. Early studies of attention (Appel and Gordon, 1976), of driving performance, and of IQ scores measured on entry to treatment and 10 years after (Gordon and Lipset, cited in Lowinson et al., 1998) strongly support this. A recent publication (Mintzer and Stitzer, 2002) reports reductions in psychomotor speed and decision making, as well as response inhibition in a cohort of unstable methadone-maintained patients continuing to use heroin (50%) and cocaine (40%). Patients in methadone maintenance clinics may have suffered more drug overdoses, head injuries, and alcohol abuse than normal populations (Darke et al., 2000). To date, studies that have attributed cognitive dysfunction to methadone have been confounded by patients with polysubstance abuse, comorbid medical and psychiatric disorders, or doses that are not stable.

10.1. LAAM and the potential for cardiovascular toxicity

Orlaam® (levacetylmethadol), a long-acting derivative of methadone, can be useful for patients suffering early morning abstinence or requesting dosing every 2 or 3 days without taking methadone doses home for self-administration. Recently, the European Medicines Evaluations Agency recommended suspension of the marketing authorization of Orlaam following identification of 10 incidents of serious cardiac arrhythmias, including torsade de pointes (EMEA, 2000). The American Methadone Treatment Association has not recommended interference at this time. A recent retrospective chart review (Krantz et al., 2002) identified 17 patients who developed torsade de pointes while taking methadone. The authors suggest that high-dose methadone may be associated with serious arrhythmias, especially in conjunction with other drugs that may prolong the QTc interval or interfere with CYP 3A4 activity, and cite in vitro evidence suggesting that methadone affects cardiac conduction (e.g., Katchman et al., 2002). However, the cohort was a mixture of patients with cancer, preexisting cardiac disease, hypokalemia, use of tricyclic antidepressants, and abuse of alcohol and cocaine. In addition, there are no other case reports of such problems, even from clinics that occasionally use high doses of methadone (more than 120 mg/d). For example, neither a systematic 10-year follow-up of patients maintained on up to 120 mg/d (Novick et al., 1993) nor almost 40 years of clinical practice (Joseph et al., 2000) have indicated any increased cardiac risk. Cardiac status need not receive special attention in patients inducted into maintenance treatment, and physicians should not be deterred from adequate dosing. To be prudent, an ECG may be considered in patients on very high doses of methadone or those with other risk factors for cardiac arrhythmias (e.g., family or personal history or use or abuse of proarrhythmiagenic drugs, including cocaine).

11. Pregnancy

Methadone can be used safely in pregnancy; this offers an opportunity to engage the woman in treatment at a time at which she may be motivated to change her life (Finnegan and Kendall, 1997; Pond et al., 1985). Mothers who continue to use heroin have greater infant mortality and morbidity and worse prenatal care, and abrupt withdrawal from opiates (including methadone) can precipitate preterm labor. In pregnancy, for reasons discussed previously, methadone doses may need to be increased and divided doses may be given twice a day. Opiate withdrawal in the neonate may or may not occur; if so, it manifests in the first 72 hours as distress, rooting, and rarely, myoclonic jerks. Neonate withdrawal is treated simply with an opium tincture (paragoric), along with dim lights, quiet, and swaddling.

Methadone is not teratogenic, and numerous studies have failed to show any increased risk for abnormalities in children exposed to methadone in utero if they received prenatal care. Breast milk contains less than 2.1% of the active enantiomer (Pond et al., 1985; Begg et al., 2001), and assuming no other contraindication, breast-feeding should be encouraged.

12. Length of treatment

Although maintaining patients on methadone for life is unfortunately restrictive because of current regulations, outcome after dose reduction and elimination is poor. Studies (summarized in Magura and Rosenblum, 2001) have found that even when patients are deemed ready for dose elimination, only 20% to 30% are abstinent from illicit drugs after 3 years. Most relapse in the first few months. Anglin et al. (1989) reported the effects on patients when their methadone maintenance program was closed: 52% transferred to private methadone and other programs, 59% used heroin over the 2 year follow up, and substantially greater criminal activity and incarceration occurred in those that did not transfer to another treatment facility. Zanis and Woody (1998) reported that after 1 year, 8% of discharged patients died, compared with 1% of nondischarged patients. Positive predictors of abstinence after discharge include being recommended by a counselor, remaining in treatment at least 6 months but preferably more than 3 years, having no urine samples positive for illicit drugs for 6 months, being stably employed or otherwise financially stable, and having no physical or mental health problems. It is essential that those discharged from clinics to jails be offered opportunities to receive methadone treatment while incarcerated. It is also important to offer readmission to patients who relapse after dose elimination. Cycles of relapse and readmission must be anticipated given the nature of the illness and the relative brevity of treatment. Long-term treatment should be considered for most patients.

Opiate addicts have deranged hormonal axes detectable months after discontinuing heroin (Kreek, 1973), indicating long-standing neuroendocrine disturbances that correlate with behavioral and mood changes. People experience protracted withdrawal on stopping opiates that can persist for months or years, with malaise, depression, anxiety, insomnia, or pain accompanied by drug craving. The decision to taper methadone may be based on social pressure, adverse side effects, a desire to be free of regulatory restrictions, a desire to get high again, or a desire to be free of all drugs. These reasons should be explored, distortions corrected, and risk assessment and adequate monitoring provided.

Once the decision is made, patients should be tapered slowly. Initial dose reduction may be 10 mg per month until a dose of 30 to 40 mg is reached; this dose reduction continues thereafter to 2 to 5 mg per month, according to withdrawal and mood changes, and must be accompanied by increased psychosocial support. Some clinics, mindful of individual suggestibility, use a single-blind tapering method, keeping the patient in treatment for some time after the tapering is completed. Patients on higher methadone doses do not have more difficult tapers. Indeed, more patients successfully complete dose taper and elimination when treated adequately with a higher dose (Strain et al., 1999).

13. Challenges to effective treatment

Although there are almost one million long-term opiate addicts in the USA, only 12% are enrolled in methadone maintenance treatment (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998). In addition, despite the wealth of data indicating that doses above 80 mg bring markedly improved outcomes, doses remain woefully inadequate. D'Aunno and Pollack (2002) report that in 2000, 35.5% of patients still received doses below 60 mg/d (down from 79.5% in 1988) and only 32.4% received doses greater than 80 mg/d. The reasons for this include (1) philosophical or "belief system" objections to the treatment of addictive diseases through the use of even a targeted medication; (2) social, societal, and familial opposition to methadone treatment; (3) the influence of polysubstance abuse; and (4) the restrictive nature of the clinics and the methadone regulations.

Philosophical objections are often rooted in a misunderstanding of methadone. The metabolic theory of addiction (and the idea that methadone rebalances a deranged physiology) has not been widely accepted by either the drug-treatment field or the general public. The therapeutic community movement, 12-Step Fellowship groups (e.g., Alcoholics Anonymous and Alanon), and much of mainstream "drug-free" treatment have traditionally opposed the use of methadone, despite its demonstrated utility as an agent for controlling opiate dependence and the failure of other treatments to achieve treatment success rates that were vaguely comparable. (Ironically, Dr. Dole was on the advisory board of Alcoholics Anonymous when its cofounder Bill W. asked him to develop a "version" of methadone for alcoholics.)

These groups' objections that methadone maintenance substitutes "one drug [addiction] for another," is a distortion that reveals a lack of understanding of methadone's pharmacology. The result is that methadone patients are frequently discriminated against and are often treated poorly even by those in the substance-abuse treatment field. An important distinction exists between the capacity for a drug to induce dependence and its likeliness to cause addictive behavior. *Dependence* refers to the capacity for withdrawal to develop if the drug is withheld or opposed by an antagonist. *Addiction*, on the other hand, can be defined as "a behavioral pattern characterized as loss of control over drug use, compulsive drug use, and continued use of a drug despite harm" (Liaison Committee on Pain and Addiction, 2001). Patients do not use methadone in this latter way; its phamacokinetics limits the "hit" or "high" achievable. Substantial evidence suggests that opiate dependence precedes legitimate and most illicit methadone use, which treats the deleterious effects of that condition.

Social, societal, and familial opposition to methadone commonly takes two forms. In the first, family and friends put pressure on patients to end their use of methadone. As a result, patients may prematurely discontinue their methadone treatment before they have developed a life structure and network to support and facilitate long-term abstinence. Another form of opposition is the refusal to allow methadone clinics to be built or introduced in a neighborhood or, in some cases, in an entire state. In addition, the major media outlets and mass communication networks portray methadone maintenance and methadone patients in a derogatory way. The result is that the opiate-dependent population is greatly underserved by the existing methadone treatment system.

As note above, providers continue to give patients inadequate doses. D'Aunno and Pollack (2002) have found that low doses are more likely to be administered in clinics in which clinical supervisors believe in an abstinence model of treatment. Other providers believe methadone should be a short-term intervention and that low doses will result in less severe withdrawal symptoms than high doses. Each of these points is contested by research cited above. Federal and state regulations have improved this situation over the last few years. D'Aunno and Pollack (2002) also note that clinics treating more African-American patients prescribe lower doses; they speculate that reasons for this include lower funding and less well-trained staff.

A fourth factor is that of polysubstance abuse. In the early days of methadone treatment, polysubstance was a common factor in the background of patients; however, their pattern of use had evolved to the point at which heroin was the sole drug of choice for roughly 80% of the patients (Joseph et al., 2000); the remaining 20% typically presented with alcohol dependence. Consequently, for a large proportion of patients, the elimination of heroin terminated their drug use. Over the past three decades, substance use patterns have changed dramatically, and now patients frequently present with comorbid abuse of or dependence on alcohol, cocaine, and benzodiazepines. Methadone, while effective as a treatment for heroin dependence, has little or no direct effect on the use of these other substances, although participation in a therapeutic treatment clinic can reduce all drug use over time (D'Aunno and Pollack, 2002; Borg et al., 1999). Given the overwhelming caseloads that are typical of many methadone clinics, it is difficult for staff members to address these problems effectively. This also has an impact on the societal perception of methadone clinics. Successful methadone patients tend to blend into mainstream society; those with multiple addictions who are not prospering are then seen inaccurately as a reflection of methadone treatment as a whole.

The final problem facing methadone treatment is the nature of the clinics and the regulations that govern them. Far too frequently, a methadone clinic is a depressing, oppressive, and regimented facility. The frequent economic dependency and poly-drug abuse that is seen in methadone-maintained patients is mistakenly ascribed to the treatment rather than to factors present on entry into treatment; this has lead to further restrictions in funding and provision of care. Restrictive rules governing the distribution and dispensing of methadone lends a criminal rather than clinical tone. The need to make daily pick-ups during limited clinic hours can make it difficult for people to attend work or school regularly. Morale suffers among low-paid counselors with enormous and complex caseloads, so that even the most valiant may flounder or fail to meet therapeutic goals. Such clinics are not attractive, and many opiate-dependent individuals choose to stay away, remaining at risk for the deleterious effects of addiction and its accompanying lifestyle. As noted above, studies have repeatedly shown that the longer the duration of treatment (be it methadone-based or medication-free), the greater the chance for abstinence and overall life improvement. Given the high rate of relapse to opiates, many advocates believe that methadone should be viewed as the "insulin" of substance abuse treatment: a medication that should be taken long-term to stabilize a physiologic imbalance. Clearly, an aversive treatment environment does not serve this goal well.

14. Mechanisms of action and receptor level changes

For a full discussion of this important yet complex level of function, please see (Kreek2002).

15. Neuroendocrine system changes

From an evolutionary perspective, an organism's survival requires a response to stress that is appropriate to the challenge: deficient or excessive response is costly. Exogenous opiates such as heroin suppress the stress response when it is needed. The opioid peptides are essential components of the stress system. The anterior pituitary gland releases proopiomelanocortin (POMC) in response to the hypothalamic release of corticotrophin-releasing factor. POMC is processed into multiple fragments, including adrenocorticotrophic hormone (ACTH), which stimulates the adrenal glands to release cortisol, providing negative feedback to the hypothalamus and anterior pituitary while mediating immune and hormonal components of the response to stress and pain. Another peptide fragment of POMC is b-endorphin, the longest (31 amino acids) and most robust of the endogenous opioids. When addicts administer multiple daily doses of exogenous, short-acting opiates (e.g., heroin), they suppress their HPA axis, have lowered plasma ACTH and cortisol, and experience a flattened circadian rhythm (Kreek, 1973). In withdrawal the HPA axis is activated, and these signs and symptoms of opiate withdrawal precede the autonomic changes (Culpepper-Morgan and Kreek, 1997). When cortisol production is blocked by metyrapone, preventing normal negative feedback to the HPA, alternative regulatory systems, principally tonic inhibition by the opioid system, are revealed. Active heroin addicts have a blunted response to metyrapone (Kreek, 1973). Of potentially great importance, drug-free former heroin addicts have a hyperresponsive HPA, suggesting a relative opioid deficiency (Kreek et al. 1984). Most importantly, patients maintained on stable daily dose of the long-acting opioid methadone have an HPA normally responsive to metyrapone challenge (Kreek, 1973; Schluger et al., 2001). It may be that this enables patients to respond to stress more appropriately and without relapse to opiate abuse. Once on a stable dose of methadone, patients cease being preoccupied by drugs. In animals, triggers for relapse include, in descending order of efficacy, priming doses of drugs, stressors, or cues associated with prior drug use (Stewart, 2000). Similarly, in studies of cocaine-dependent humans, careful and personalized stress arousal paradigms increase craving and plasma cortisol (reviewed Sinha, 2001), although parallel studies have not yet been performed in opiate-dependent addicts. Other hormonal systems are also affected. Short-acting, m-opioid agonists with their pulsatile effects inhibit the pulsatile release of luteinizing hormone, with a resulting fall in testosterone in males and secondary amenorrhea in females. Through direct inhibition of the tuberoinfundibular dopamine system (where m- and k-receptors are present directly on the dopaminergic cell bodies), prolactin release from the anterior pituitary gland is increased, contributing to decreased libido. Methadone maintenance treatment normalizes these hormonal axes (Kreek, 1973). Circadian rhythm, ACTH and cortisol release, gonadal hormone secretion, and natural killer function are restored. Prolactin release continues to be stimulated at peak methadone levels, indicating ongoing dopamine inhibition. PET studies demonstrate that 19% to 32% of m-opioid receptors are occupied in stabilized methadone maintenance patients on moderate to high doses (see Kling et al., 2000). This leaves a large functional m-opioid receptor reserve that might allow the opioid system to continue to play its role in endocrine and immune function, with daily methadone administration still permitting a diurnal surge in cortisol. The atypical responsivity to stressors, such as that modeled by metyrapone, may be central to the acquisition of, maintenance of, and relapse to drug addiction. Such vulnerability may derive from environmental or developmental trauma, through inherited traits, or simply through exposure to sufficient drug, all with the outcome of an increased likelihood of developing an addiction. This hypothesis provides important opportunities for drug development (Kreek et al., 2002) and understanding of the biology of addiction. Different drugs of abuse may affect the HPA in varying ways. For example, cocaine and alcohol may activate the HPA Axis (Schulger et al., 2001; O'Malley et al., 2002). It is possible that some alcoholic patients may be seeking HPA activation to compensate for basal hypo-responsivity or because they find the activation itself reinforcing (O'Malley et al., 2002).

16. Methadone and the immune system

Immune dysfunction has been noted in addicted populations since the 1950s. The immune, opioid, and neuroendocrine systems are closely interrelated (see Jessop, 2002). There are few in vivo studies of immune function in opiate-addicted populations. Novick et al. (1989) compared the immune function of methadone-maintained patients and active parenteral abusers and showed "normalized" NK cell activity and lymphocyte function.In vivo studies of intravenous drug abusers have shown impaired immune function (Nair et al., 1986). Clinical studies, discussed above, report a lowered rate of HIV seroconversion in patients enrolled in methadone programs, normal response to HBV vaccination, and treatment for HCV. On a community level, the treatment of addicts reduces the risk for transmission of HIV.

Although there are numerous in vitro and animal studies of opiate exposure, the results remain inconsistent.

17. New directions in treatment

Certain patients are appropriate for office-based methadone maintenance and receive their methadone once a month. Such medical methadone maintenance is increasingly available (Novick and Joseph, 1991; Novick et al., 1994; Novick et al., 1988). To be eligible, patients must be abstinent from all illicit drugs for several years, be working, and be sufficiently stable to tolerate a lack of clinic structure. Methadone can be dispensed each month, either from the practitioner's office or by a selected and approved pharmacy (Raisch et al., 2001; King et al., 2002). Patients are then able to participate in normal occupational and social activities unencumbered by frequent visits to a clinic.

In addition to a growing pharmacologic flexibility, a rise in creative psychosocial interventions has occurred. Cognitive-behavioral treatments, incorporating the relapse prevention model of Marlatt and Gordon (1985), help patients understand the role of cues and triggers in the elicitation of craving while also facilitating the development of coping strategies for addressing the issues that arise in high-risk situations. These approaches have proven to be useful in a number of studies (Lovejoy et al., 1995; Rawson et al., 2002).

Motivational interviewing (Miller et al., 1995) is a therapeutic intervention that addresses the ambivalence that many substance-dependent patients feel about discontinuing substance use. This intervention has the potential to be useful not only with patients who are considering leaving methadone treatment prematurely but also with patients who are continuing to use opiates or other substances while they are in methadone treatment.

Contingency management, or the linkage of positive reinforcements to the exhibition of desired behavior, is rising in prominence in the treatment field. This approach has been used to reduce the use of opiates, cocaine, and other drugs of abuse in methadone-based and drug-free settings (Petry, 2000; Silverman et al., 1996; Stitzer et al., 1993). The patient is tested for substances—preferably using a method that provides immediate results. If they are drug-free, patients immediately receive a reinforcement, which has included take-home bottles of methadone, changes in methadone dose, clinic privileges, money, vouchers for desired goods, contracted interpersonal reinforcements, and opportunities to draw prizes from a cabinet (Petry, 2000). Essential to the model is that the reinforcement be *contingent* on the presentation of the drug-free urine; that is, the patient must receive the reinforcement immediately. This approach, in both methadone-based and drug-free clinics has led to successful reductions in opiate, cocaine, alcohol, marijuana, nicotine, and benzodiazepine use (Petry, 2000).

Another significant intervention that needs further development is the introduction of methadone maintenance treatment into therapeutic communities. Although a handful of innovative programs utilize both modalities (e.g., Su Casa in New York City), most do not, reflecting an ideological split between those who view addiction as metabolic dysfunction and those who consider it a character disorder. De Leon et al. (1995) were able to create a day program (Passages) for methadone patients, using therapeutic community practices. When members who remained in the Passages program for 6 months or more were compared with methadone patients in standard treatment, the therapeutic community members showed greater reductions in their cocaine, heroin, and IV drug use, as well as lower levels of criminal involvement and psychological distress (De Leon et al., 1995). Many countries already have a network of therapeutic communities in existence. With the worldwide rise in heroin use being matched by an increased interest in opiate agonist pharmacotherapy, the integration of methadone into these already existing institutions could provide some opportunities for increased therapeutic effectiveness.

Much work is needed to understand how methadone stabilizes opiate addicts, as well as to optimize treatment. Although optimal dose is well established, many patients leave treatment prematurely or continue to abuse other drugs, and it may be that more rapid induction or enhancement of treatment with group or individual treatment may help some patients more than others. Because retention is the strongest predictor of abstinence, Goldstein et al. (2002) have developed an aggressive outreach program to re-engage treatment drop-outs.

18. Summary

Patients with addiction continue to face stigma and inadequate care. Despite abundant evidence of the efficacy of methadone maintenance, its provision remains too scarce, its doses too low, and its treatment times too short. Attitudes about addiction remain rooted in moral constructs that have more to do with cultural beliefs than with receptor theory, and compassion for patients with addiction seems to come more slowly than scientific publications. The history and biology of methadone provides an opportunity to see a true paradigm shift in action: the application of scientific principles has brought personality change, redemption. and existential renewal to thousands of patients and the scientists and health care professionals fortunate enough to accompany them.

19. See also

Opioid receptors, multiple
Opioid detoxification
Heroin (diacetylmorphine)
Addiction
Addiction, anatomy of

20. References

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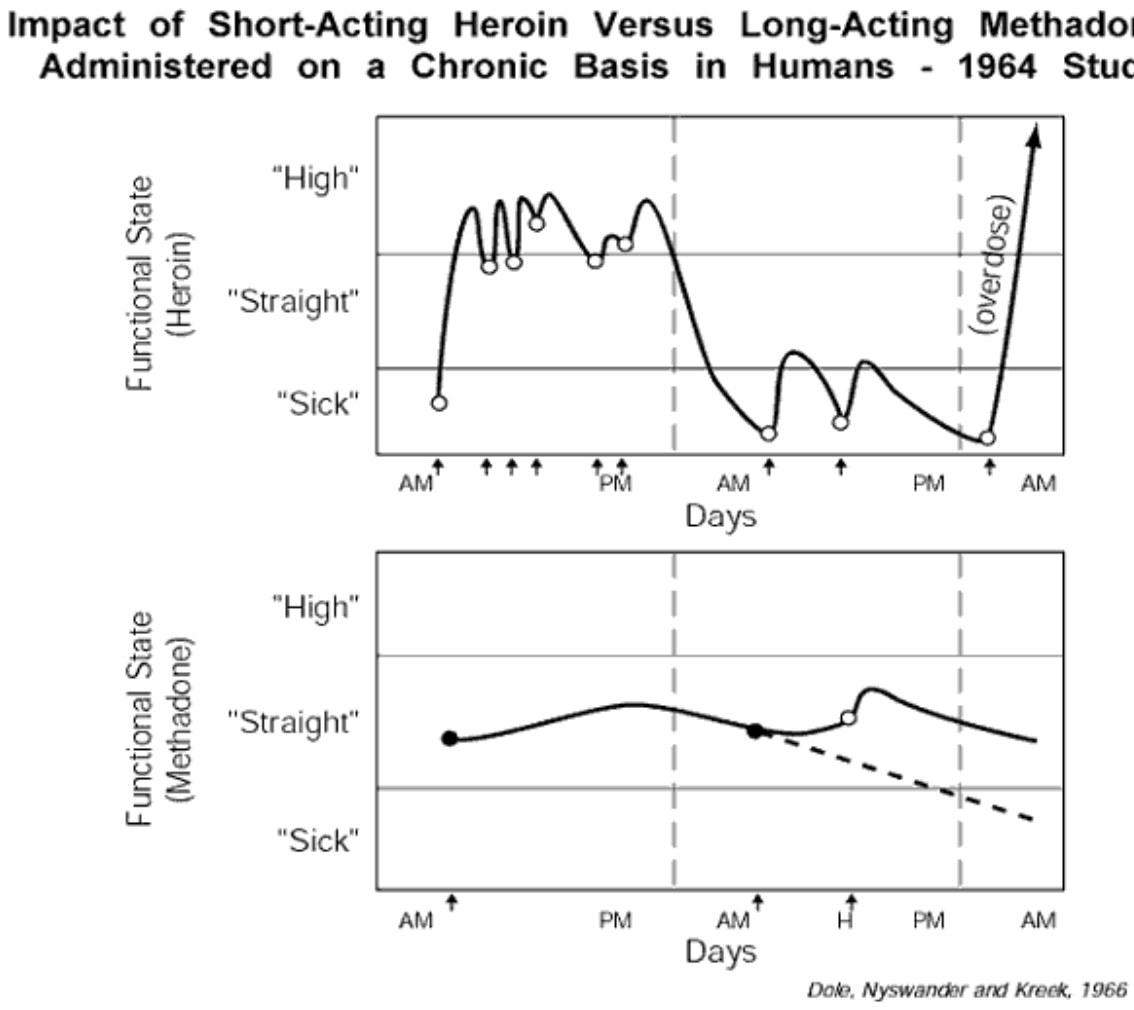

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Figure 1. Impact of short-acting heroin versus long-acting methadone administered on a chronic basis in humans (From Dole VP, Nyswander ME, Kreek MJ, 1966: Narcotic blockade. *Arch Intern Med* 118:304-309).

Table 1: Heroin versus Methadone*

	Heroin	Methadone
Route of administration	Intravenous	Oral
Onset of action	Immediate	30 minutes
Duration of action	3–6 hours**	24–36 hours
Euphoria	1–2 hours	None (at appropriate dose)
Withdrawal symptoms	After 3–4 hours	After 24 hours

*Effects of high dosages of drug or therapeutic agent in tolerant individuals

** Includes action of major metabolite, morphine

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