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NIH Consensus Development Conferences are convened to evaluate available scientific information and resolve safety and efficacy issues related to a biomedical technology. The resultant NIH Consensus Statements are intended to advance understanding of the technology or issue in question and to be useful to health professionals and the public.

NIH Consensus Statements are prepared by nonadvocate, non-Federal panels of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session, (2) questions and statements from conference attendees during open discussion periods that are part of the public session, and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the consensus panel and is not a policy statement of the NIH or the Federal Government.

Reference Information

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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.
Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this consensus statement were identified as having no financial or scientific conflict of interest, and all signed conflict of interest forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH consensus panels are selected specifically because they are not professionally identified with advocacy positions with respect to the conference topic or with research that could be used to answer any of the conference questions.
Abstract

Objective

The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Effective Medical Treatment of Opiate Addiction. The statement provides state-of-the-art information regarding effective treatments for opiate addiction and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. Upon completion of this educational activity, the reader should possess a clear working clinical knowledge of the state of the art regarding this topic. The target audience of physicians for this statement includes, but is not limited to, psychiatrists, family practitioners, psychologists, and behavioral medicine specialists.

Participants

A non-Federal, nonadvocate, 12-member panel representing the fields of psychology, psychiatry, behavioral medicine, family medicine, drug abuse, epidemiology, and the public. In addition, 25 experts from these same fields presented data to the panel and a conference audience of 600.

Evidence

The literature was searched through Medline and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.
**Conclusions**

Opiate dependence is a brain-related medical disorder that can be effectively treated with significant benefits for the patient and society, and society must make a commitment to offer effective treatment for opiate dependence to all who need it. All opiate-dependent persons under legal supervision should have access to methadone maintenance therapy, and the U.S. Office of National Drug Control Policy and the U.S. Department of Justice should take the necessary steps to implement this recommendation. There is a need for improved training for physicians and other health care professionals and in medical schools in the diagnosis and treatment of opiate dependence. The unnecessary regulations of methadone maintenance therapy and other long-acting opiate agonist treatment programs should be reduced, and coverage for these programs should be a required benefit in public and private insurance programs.

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**Consensus Process**

The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel’s final revisions.
Introduction

In the United States before 1914, it was relatively common for private physicians to treat opiate-dependent patients in their practices by prescribing narcotic medications. While the passage of the Harrison Act did not prohibit the prescribing of a narcotic by a physician to treat an addicted patient, this practice was viewed as problematic by Treasury officials charged with enforcing the law. Physicians who continued to prescribe were indicted and prosecuted. Because of withdrawal of treatment by physicians, various local governments and communities established formal morphine clinics for treating opiate addiction. These clinics were eventually closed when the AMA, in 1920, stated that there was unanimity that prescribing opiates to addicts for self-administration (ambulatory treatment) was not an acceptable medical practice. For the next 50 years, opiate addiction was basically managed in this country by the criminal justice system and the two Federal Public Health Hospitals in Lexington, Kentucky, and Fort Worth, Texas. The relapse rate for opiate use from this approach was close to 100 percent. During the 1960s, opiate use reached epidemic proportions in the United States, spawning significant increases in crime and in deaths from opiate overdose. The increasing number of younger people entering an addiction lifestyle indicated that a major societal problem was emerging. This stimulated a search for innovative and more effective methods for treating the growing number of individuals dependent upon opiates. This search resulted in the emergence of drug-free therapeutic communities and the use of the opiate agonist methadone to maintain those with opiate dependence. Furthermore, a multimodality treatment strategy was designed to meet the needs of the individual addict patient. These three approaches remain the main treatment strategies being used to treat opiate dependence in the United States today.

Opiate dependence has long been associated with increased criminal activity. For example, in 1993 more than one-quarter of the inmates in State and Federal prisons were incarcerated for
drug offenses (234,600), and prisoners serving drug sentences were the largest single group (60 percent) in Federal prisons.

In the past 10 years, there has been a dramatic increase in the prevalence of human immunodeficiency virus (HIV), hepatitis B and C viruses, and tuberculosis among intravenous opiate users. From 1991 to 1995, in major metropolitan areas, the annual number of opiate-related emergency room visits increased from 36,000 to 76,000, and the annual number of opiate-related deaths increased from 2,300 to 4,000. This associated morbidity and mortality further underscore the human, economic, and societal costs of opiate dependence.

During the last two decades, evidence has accumulated on the neurobiology of opiate dependence. Whatever conditions may lead to opiate exposure, opiate dependence is a brain-related disorder with the requisite characteristics of a medical illness. Thus, opiate dependence as a medical illness will have varying causative mechanisms. There is a need to identify discrete subgroups of opiate-dependent persons and the most relevant and effective treatments for each subgroup. The safety and efficacy of narcotic agonist (methadone) maintenance treatment has been unequivocally established. Although there are other medications (e.g., levo-alpha acetylmethadol [LAAM] and naltrexone, an opiate antagonist) that are safe and effective in the treatment of opiate addicts, the focus of this consensus development conference was primarily on methadone maintenance treatment (MMT). MMT is effective in reducing illicit opiate drug use, in reducing crime, in enhancing social productivity, and in reducing the spread of viral diseases such as AIDS and hepatitis.

Approximately 115,000 of the estimated 600,000 opiate-dependent persons in the United States are in MMT. Science has not yet overcome the stigma of addiction and the negative public perception about MMT. Some leaders in the Federal Government, public health officials, members of the medical community, and the public at large frequently conceive of opiate dependence as a self-inflicted disease of the will or as a moral flaw. They also regard MMT as an ineffective
narcotic substitution and believe that a drug-free state is the only valid treatment goal. Other obstacles to MMT include Federal and State government regulations that restrict the number of treatment providers and patient access. Some of these Federal and State regulations are driven by disproportionate concerns about methadone diversion, concern about premature (e.g., in 12-year-olds) initiation of maintenance treatment, and concern about provision of methadone without any other psychosocial services.

Although a drug-free state represents an optimal treatment goal, research has demonstrated that this goal cannot be achieved or sustained by the majority of opiate-dependent people. However, other laudable treatment goals, including decreased drug use, reduced criminal activity, and gainful employment can be achieved by most MMT patients.

To address the most important issues surrounding effective medical treatment of opiate dependence, the NIH organized this 2½-day conference to present data on opiate agonist treatment for opiate dependence. The conference brought together national and international experts in the fields of the basic and clinical medical sciences, epidemiology, natural history, and prevention and treatment of opiate dependence, and broad representation from the public.

After 1½ days of presentations and audience discussion, an independent, non-Federal consensus panel, chaired by Lewis L. Judd, M.D., Mary Gilman Marston Professor, Chair of the Department of Psychiatry, University of California, San Diego School of Medicine, weighed the scientific evidence and wrote a draft statement that was presented to the audience on the third day. The consensus statement addressed the following key questions:

- What is the scientific evidence to support a conceptualization of opiate addiction as a medical disorder, including natural history, genetics and risk factors, and pathophysiology, and how is diagnosis established?
● What are the consequences of untreated opiate addiction to individuals, families, and society?

● What is the efficacy of current treatment modalities in the management of opiate addiction, including detoxification alone, nonpharmacological/psychosocial treatment, treatment with opiate antagonists, and treatment with opiate agonists (short term and long term)? And, what is the scientific evidence for the most effective use of opiate agonists in the treatment of opiate addiction?

● What are the important barriers to effective use of opiate agonists in the treatment of opiate addiction in the United States, including perceptions and the adverse consequences of opiate agonist use and legal, regulatory, financial, and programmatic barriers?

● What are the future research areas and recommendations for improving opiate agonist treatment and improving access?
What Is the Scientific Evidence to Support a Conceptualization of Opiate Dependence as a Medical Disorder, Including Natural History, Genetics and Risk Factors, and Pathophysiology, and How Is Diagnosis Established?

The Natural History of Opiate Dependence

Individuals addicted to opiates often become dependent on these drugs by their early twenties and remain intermittently dependent for decades. Biological, psychological, sociological, and economic factors determine when an individual will start taking opiates. However, it is clear that when use begins, it often escalates to abuse (repeated use with adverse consequences) and then to dependence (opioid tolerance, withdrawal symptoms, compulsive drug-taking). Once dependence is established, there are usually repeated cycles of cessation and relapse extending over decades. This “addiction career” is often accompanied by periods of imprisonment.

Treatment can alter the natural history of opiate dependence, most commonly by prolonging periods of abstinence from illicit opiate abuse. Of the various treatments available, MMT, combined with attention to medical, psychiatric, and socioeconomic issues, as well as drug counseling, has the highest probability of being effective.

Addiction-related deaths, including accidental overdose, drug-related accidents, and many illnesses directly attributable to chronic drug dependence explain one-fourth to one-third of the mortality in an opiate-addicted population. As a population of opiate addicts ages, there is a decrease in the percentage who are still addicted.

There is clearly a natural history of opiate dependence, but causative factors are poorly understood. It is especially unclear for a given individual whether repeated use begins as a medical disorder (e.g., a genetic predisposition) or whether socioeconomic and psychological factors lead an individual to try, and
then later to compulsively use, opiates. However, there is no question that once the individual is dependent on opiates, such dependence constitutes a medical disorder.

**Molecular Neurobiology and Pathogenesis of Opiate Dependence: Genetic and Other Risk Factors for Opiate Dependence**

Twin, family, and adoption studies show that vulnerability to drug abuse may be a partially inherited condition with strong influences from environmental factors. Cross-fostering adoption studies have demonstrated that both inherited and environmental factors operate in the etiology of drug abuse. These cross-fostering adoption studies identified two distinct genetic pathways to drug abuse/dependence. The first is a direct effect of substance abuse in a biologic parent. The second pathway is an indirect effect from antisocial personality disorder in a biologic parent, leading to both antisocial personality disorder and drug abuse/dependence in the adoptee. Family studies report significantly increased relative risk for substance abuse (6.7-fold increased risk), alcoholism (3.5), antisocial personality (7.6), and unipolar depression (5.1) among the first-degree relatives of opiate-dependent patients compared with relatives of controls. The siblings of opiate-dependent patients have very high susceptibility to abuse and dependence after initial use of illicit opioids. Twin studies indicate substantial heritability for substance abuse and dependence, with half the risk attributable to additive genetic factors.

**Neurobiological Substrates of Opiate Dependence**

Dopaminergic pathways from the ventral tegmentum (VT) to the nucleus accumbens (NA) and medial frontal cortex (MFC) are activated during rewarding behaviors. Opiates exert their rewarding properties by binding to the “mu” opioid receptor (OPRM) at several distinct anatomical locations in the brain, including the VT, NA, MFC, and possibly the locus coeruleus (LC). Opiate agonist administration causes inhibition of the LC. Chronic administration of opioid agonists causes adaptation to the LC inhibition. Rapid discontinuation of opioid agonists (or administration of antagonists) results in excessive LC
neuronal excitation and the appearance of withdrawal symptoms. Abnormal LC excitation is thought to underlie many of the physical symptoms of withdrawal, and this hypothesis is consistent with the ability of clonidine, an alpha-2 noradrenergic agonist, to ameliorate opiate withdrawal.

Regional Cerebral Glucose Metabolism in Opiate Abusers

Two independent human studies (using positron emission tomography) suggest that opiates reduce cerebral glucose metabolism in a global manner, with no regions showing increased glucose utilization. A third study demonstrates decreased D2 receptor availability in opiate-dependent patients compared with controls. Opiate antagonist administration produced an intense withdrawal experience but did not change D2 receptor availability.

Diagnosis of Opioid Dependence

Opioid dependence (addiction) is defined as a cluster of cognitive, behavioral, and physiological symptoms in which the individual continues use of opiates despite significant opiate-induced problems. Opioid dependence is characterized by repeated self-administration that usually results in opioid tolerance, withdrawal symptoms, and compulsive drug-taking. Dependence may occur with or without the physiological symptoms of tolerance and withdrawal. Usually, there is a long history of opioid self-administration, typically via intravenous injection in the arms or legs, although recently the intranasal route or smoking also is used. Often there is a history of drug-related crimes, drug overdoses, and family, psychological, and employment problems. There may be a history of physical problems, including skin infections, hepatitis, HIV infection, or irritation of the nasal and pulmonary mucosa. Physical examination usually reveals puncture marks along veins in the arms and legs and “tracks” secondary to sclerosis of veins. If the patient has not taken opiates recently, he or she may also demonstrate symptoms of withdrawal, including anxiety, restlessness, runny nose, tearing, nausea, and vomiting. Tests for opioids in saliva and urine can help
support a diagnosis of dependence. However, by itself, neither a positive nor a negative test can rule dependence in or out. Further evidence for opioid dependence can be obtained by a naloxone (Narcan) challenge test to induce withdrawal symptoms.

Evidence That Opioid Dependence Is a Medical Disorder

For decades, opioid dependence was viewed as a problem of motivation, willpower, or strength of character. Through careful study of its natural history and through research at the genetic, molecular, neuronal, and epidemiological levels, it has been proven that opiate addiction is a medical disorder characterized by predictable signs and symptoms. Other arguments for classifying opioid dependence as a medical disorder include:

- Despite varying cultural, ethnic, and socioeconomic backgrounds, there is clear consistency in the medical history, signs, and symptoms exhibited by individuals who are opiate-dependent.

- There is a strong tendency to relapse after long periods of abstinence.

- The opioid-dependent person’s craving for opiates induces continual self-administration even when there is an expressed and demonstrated strong motivation and powerful social consequences to stop.

- Continuous exposure to opioids induces pathophysiologic changes in the brain.
What Are the Consequences of Untreated Opiate Dependence to Individuals, Families, and Society?

Of the estimated total opiate-dependent population of 600,000, only 115,000 are known to be in methadone maintenance treatment (MMT) programs. Research surveys indicate that the untreated population of opiate-addicted people is younger than those in treatment. They are typically in their late teens and early to middle twenties, during their formative, early occupational, and reproductive years. The financial costs of untreated opiate dependence to the individual, the family, and society are estimated to be approximately $20 billion per year. The costs in human suffering are incalculable.

What is currently known about the consequences of untreated opiate dependence to individuals, families, and society?

Mortality

Before the introduction of MMT, annual death rates reported in four American studies of opiate dependence varied from 13 per 1,000 to 44 per 1,000, with a median of 21 per 1,000. Although it cannot be causally attributed, it is interesting to note that after the introduction of MMT, the death rates of opiate-dependent persons in four American studies had a narrower range, from 11 per 1,000 to 15 per 1,000, and a median of 13 per 1,000. The most striking evidence of the positive impact of MMT on death rates is studies directly comparing these rates in opiate-dependent persons, on and off methadone. Every study showed that death rates were lower in opiate-dependent persons maintained on methadone compared with those who were not. The median death rate for opiate-dependent persons in MMT was 30 percent of the death rate of those not in treatment. A clear consequence of not treating opiate dependence, therefore, is a death rate that is more than three times greater than that experienced by those engaged in MMT.
Illicit Drug Use

Multiple studies conducted over several decades and in different countries demonstrate clearly that MMT results in a marked decrease in illicit opiate use. In addition, there is also a significant and consistent reduction in the use of other illicit drugs, including cocaine and marijuana, and in the abuse of alcohol, benzodiazepines, barbiturates, and amphetamines.

Criminal Activity

Opiate dependence in the United States is unequivocally associated with high rates of criminal behavior. More than 95 percent of opiate-dependent persons report committing crimes during an 11-year at-risk interval. These crimes range in severity from homicides to other crimes against people and property. Stealing in order to purchase drugs is the most common criminal offense. Over the past two decades, clear and convincing evidence has been collected from multiple studies showing that effective treatment of opiate dependence markedly reduces the rates of criminal activity. Therefore, it is clear that significant amounts of crime perpetrated by opiate-dependent persons are a direct consequence of untreated opiate dependence.

Health Care Costs

Although the general health status of people with opiate dependence is substantially worse than that of their contemporaries, they do not routinely use medical services. Typically, they seek medical care in hospital emergency rooms only after their medical conditions are seriously advanced. The consequences of untreated opiate dependence include a much higher incidence of bacterial infections, including endocarditis, thrombophlebitis, and skin and soft tissue infections; tuberculosis; hepatitis B and C; AIDS and sexually transmitted diseases; and alcohol abuse. Because those who are opiate-dependent present for medical care late in their diseases, medical care is generally more expensive. Health care costs related to opiate dependence have been estimated to be $1.2 billion per year.
**Joblessness**

Opiate dependence prevents many users from maintaining steady employment. Much of their time each day is spent in drug-seeking and drug-taking behavior. Therefore, many seek public assistance because they are unable to generate the income needed to support themselves and their families. Long-term outcome data show that opiate-dependent persons in MMT earn more than twice as much money annually as those not in treatment.

**Outcomes of Pregnancy**

A substantial number of pregnant women who are dependent on opiates also have HIV/AIDS. On the basis of preliminary data, women who receive MMT are more likely to be treated with zidovudine. It has been well established that administration of zidovudine to HIV-positive pregnant women reduces by two-thirds the rate of HIV transmission to their infants. Comprehensive MMT, along with sound prenatal care, has been shown to decrease obstetrical and fetal complications as well.
What Is the Efficacy of Current Treatment Modalities in the Management of Opiate Dependence, Including Detoxification Alone, Nonpharmacological/Psychosocial Treatment, Treatment With Opiate Antagonists, and Treatment With Opiate Agonists (Short Term and Long Term)? And, What Is the Scientific Evidence for the Most Effective Use of Opiate Agonists in the Treatment of Opiate Dependence?

The Pharmacology of Commonly Prescribed Opiate Agonists and Antagonists

The most frequently used agent in medically supervised opiate withdrawal and maintenance treatment is methadone. Methadone’s half-life is approximately 24 hours and leads to a long duration of action and once-a-day dosing. This feature, coupled with its slow onset of action, blunts its euphoric effect, making it unattractive as a principal drug of abuse. LAAM, a less commonly used opiate agonist, has a longer half-life and may prevent withdrawal symptoms for up to 96 hours. An emerging treatment option, buprenorphine, a partial opioid agonist, appears also to be effective for detoxification and maintenance.

Naltrexone is a non-addicting specific “mu” antagonist with a long half-life, permitting once-a-day administration. It effectively blocks the cognitive and behavioral effects of opioids, and its prescription does not require special registration. The opioid-dependent person considering treatment should be informed of the availability of naltrexone maintenance treatment. However, in actively using opiate addicts, it produces immediate withdrawal symptoms with potentially serious effects.
Medically Supervised Withdrawal

Methadone can also be used for detoxification. This can be accomplished over several weeks after a period of illicit opiate use or methadone maintenance. If methadone withdrawal is too rapid, abstinence symptoms are likely. They may lead the opiate-dependent person to illicit drug use and relapse into another cycle of abuse. Buprenorphine holds promise as an option for medically supervised withdrawal because its prolonged occupation of “mu” receptors attenuates withdrawal symptoms.

More rapid detoxification options include use of opiate antagonists alone; the alpha-2 agonist clonidine alone; or clonidine followed by naltrexone. Clonidine reduces many of the autonomic signs and symptoms of opioid withdrawal. These strategies may be used in both inpatient and outpatient settings and allow medically supervised withdrawal from opioids in as little as 3 days. Most patients successfully complete detoxification using these strategies, but information concerning relapse rates is not available.

The Role of Psychosocial Treatments

Nonpharmacologic supportive services are pivotal to successful MMT. The immediate introduction of these services as the opiate-dependent patient applies for MMT leads to significantly higher retention and more comprehensive and effective treatment. Comorbid psychiatric disorders require treatment. Other behavioral strategies have been successfully used in substance abuse treatment. Ongoing substance abuse counseling and other psychosocial therapies enhance program retention and positive outcome. Stable employment is an excellent predictor of clinical outcome. Therefore, vocational rehabilitation is a useful adjunct.

Efficacy of Opiate Agonists

It is now generally agreed that opiate dependence is a medical disorder and that pharmacologic agents are effective in its treatment. Evidence presented to the panel indicates
that availability of these agents is severely limited and that large numbers of patients with this disorder have no access to treatment.

The greatest experience with such agents has been with the opiate agonist methadone. Prolonged oral treatment with this medication diminishes and often eliminates opiate use, reduces transmission of many infections, including HIV and hepatitis B and C, and reduces criminal activity. Evidence is now accumulating suggesting that LAAM and buprenorphine are effective in such patients.

For more than 30 years, the daily oral administration of methadone has been used to treat tens of thousands of individuals dependent upon opiates in the United States and abroad. The effectiveness of MMT is dependent on many factors, including adequate dosage, duration plus continuity of treatment, and accompanying psychosocial services. A dose of 60 mg given once daily may achieve the desired treatment goal: abstinence from opiates. But higher doses are often required by many patients. Continuity of treatment is crucial—patients who are treated for fewer than 3 months generally show little or no improvement, and most, if not all, patients require continuous treatment over a period of years and perhaps for life. Therefore, the program has come to be termed methadone “maintenance” treatment (MMT). Patient attributes that have sometimes been linked to better outcomes include older age, later age of dependence onset, less abuse of other substances including cocaine and alcohol, and less criminal activity. Recently, it has been reported that high motivation for change has been associated with positive outcomes.

The effectiveness of MMT is often dependent on the involvement of a knowledgeable and empathetic staff and the availability of psychotherapy and other counseling services.

The latter are especially important since individuals with opiate dependence are often afflicted with comorbid mental and personality disorders.
Because methadone-treated patients generally are exposed to much less or no intravenous opiates, they are much less likely to transmit and contract HIV and hepatitis. This is especially important since recent data have shown that up to 75 percent of new instances of HIV infection are attributable to intravenous drug use. Since for many patients a major source of financing the opiate habit is criminal behavior, MMT generally leads to much less crime.

Although methadone is the primary opioid agonist used, other full and partial opioid agonists have been developed for treatment of opiate dependence. An analogue of methadone, levo-alpha acetylmethadol (LAAM), has a longer half-life than methadone and therefore can be administered less frequently. A single dose of LAAM can prevent withdrawal symptoms and drug craving for 2 to 4 days. Buprenorphine, a recently developed partial opiate agonist, has an advantage over methadone; its discontinuation leads to much less severe withdrawal symptoms. The use of these medications is at an early stage, and it may be some time before their usefulness has been adequately evaluated.
What Are the Important Barriers to Effective Use of Opiate Agonists in the Treatment of Opiate Addiction in the United States, Including Perceptions and the Adverse Consequences of Opiate Agonist Use and Legal, Regulatory, Financial, and Programmatic Barriers?

Misperceptions and Stigmas

Many of the barriers to effective use of MMT in the treatment of opiate dependence stem from misperceptions and stigmas attached to opiate dependence, the people who are addicted, those who treat them, and the settings in which services are provided. Opiate-dependent persons are often perceived not as individuals with a disease but as “other” or “different.” Factors such as racism play a large role here but so does the popular image of dependence itself. Many people believe that dependence is self-induced or a failure of willpower and that efforts to treat it will inevitably fail. Vigorous and effective leadership is needed to inform the public that dependence is a medical disorder that can be effectively treated with significant benefits for the patient and society.

Increasing Availability of Effective Services

Unfortunately, MMT programs are not readily available to all who could and wish to benefit from them. We as a society must make a commitment to offering effective treatment for opiate dependence to all who need it. Accomplishing that goal will require:

- Making treatment as cost-effective as possible without sacrificing quality.
- Increasing the availability and variety of treatment services.
- Including and ensuring wider participation by physicians trained in substance abuse who will oversee the medical care.
Providing additional funding for opiate dependence treatments and coordinating these services with other necessary social services and medical care.

**Training Physicians and Other Health Care Professionals**

One barrier to availability of MMT is the shortage of physicians and other health care professionals prepared to provide treatment for opiate dependence. Practitioners of all primary care medical specialties (including general practice, internal medicine, family practice, obstetrics and gynecology, geriatrics, pediatrics, and adolescent medicine) should be taught the principles of diagnosing and treating patients with opiate dependence. Nurses, social workers, psychologists, physician assistants, and other health care professionals should also be trained in these areas. The greater the number of trained physicians and other health care professionals, the greater the supply not only of professionals who can competently treat the opiate dependent but also of members of the community who are equipped to provide leadership and public education on these issues.

**Reducing Unnecessary Regulation**

Of critical importance in improving MMT of opiate dependence is the recognition that, as in every other area of medicine, treatment must be tailored to the needs of the individual patient. Current Federal regulations make this difficult if not impossible. By prescribing MMT procedures in minute detail, FDA’s regulations limit the flexibility and responsiveness of the programs, require unproductive paperwork, and impose administrative and oversight costs greater than those necessary for many patients. Yet these regulations seem to have little if any effect on quality of MMT care. We know of no other area where the Federal Government intrudes so deeply and coercively into the practice of medicine. For example, although providing a therapeutic dose is central to effective treatment and the therapeutic dose is now known to be higher than had previously been understood, FDA’s regulations discourage such higher doses. However well intended the FDA’s
treatment regulations were written in 1972, they are no longer helpful. We recommend that these regulations be eliminated. Alternative means, such as accreditation, for improving quality of MMT programs should be instituted. The U.S. Department of Health and Human Services can more effectively, less coercively, and much less expensively discharge its statutory obligation to provide treatment guidance to MMT programs, physicians, and staff by means of publications, seminars, Web sites, continuing medical education, and the like.

We also believe current laws and regulations should be revised to eliminate the extra level of regulation on methadone compared with other Schedule II narcotics. Currently, methadone can be dispensed only from facilities that obtain an extra license and comply with extensive extra regulatory requirements. These extra requirements are unnecessary for a medication that is not often diverted to individuals for recreational or casual use but rather to individuals with opiate dependence who lack access to MMT programs.

If extra levels of regulation were eliminated, many more physicians and pharmacies could prescribe and dispense methadone, making treatment available in many more locations than is now the case. Not every physician will choose to treat opiate-dependent persons, and not every methadone-treated person will prefer to receive services from an individual physician rather than to receive MMT in a clinic setting. But if some additional physicians and groups treat a few patients each, aggregate access to MMT would be expanded.

We also believe that State and local regulations and enforcement efforts should be coordinated. We see little reason for separate State and Federal inspections of MMT programs. State and Federal regulators should coordinate their efforts, agree about which programs each will inspect to avoid duplication, and target “poor performers” for the most intensive scrutiny while reducing scrutiny for MMT programs that consistently perform well. The States should address the
problem of slow approval (at the State level) of FDA-approved medications. LAAM, for example, has not yet been approved by many States. States should harmonize their requirements with those of the Federal Government.

We would expect these changes in the current regulatory system to reduce unnecessary costs both to MMT programs and to enforcement agencies at all levels. The savings could be used to treat more patients.

In the end, an infusion of additional funding will be needed—funding sufficient to provide access to treatment for all who require treatment. We strongly recommend that legislators and regulators recognize that providing MMT is both cost-effective and compassionate and that it constitutes a health benefit that should be a component of public and private health care.
What Are the Future Research Areas and Recommendations for Improving Opiate Agonist Treatment and Improving Access?

- What initiates opiate use?
- Define genetic predispositions.
- Do some individuals take opiates to treat a preexisting disorder?
- Which of the multiple psychological, sociological, and economic factors believed to predispose individuals to try opiates are most important as causative factors?
- If the above are known, can one prevent opiate dependence?
- What are the changes in the human brain that result in dependence when individuals repeatedly use opiates?
- What are the underlying anatomical and neurophysiological substrates of craving?
- What are the differences between individuals who can successfully terminate opiate dependence and those who cannot?
- A scientifically credible national epidemiological study of the prevalence of opiate dependence in the United States is strongly recommended.
- Rigorous study of the economic costs of opiate dependence in the United States and the cost-effectiveness of methadone maintenance therapy is also needed.
- Longer term followup studies of patients who complete rapid detoxification are necessary.
- The feasibility of alternative routes of administration for agonist and antagonist therapy should be explored.
● Systematic pharmacokinetic studies of methadone during MMT maintenance therapy are essential.

● Physiologic factors that may influence adequate methadone dose in pregnant women need to be defined.

● The effects of reduction of entitlement programs for those patients on MMT must be assessed.

● The effects of the early and systematic introduction of rehabilitation services in MMT should be evaluated.

● Variables that determine barriers must be defined.

● Research on changing attitudes of the public, of health professionals, and of legislators is needed.

● Research on improving educational methods for health professionals should be performed.

● Research on prevention methods is necessary.

● Research on efficacy of other opiate agonists/antagonists should be compared with that of methadone.
Conclusions and Recommendations

- Vigorous and effective leadership is needed within the Office of National Drug Control Policy (ONDCP) (and related Federal and State agencies) to inform the public that dependence is a medical disorder that can be effectively treated with significant benefits for the patient and society.

- Society must make a commitment to offering effective treatment for opiate dependence to all who need it.

- The panel calls attention to the need for opiate-dependent persons under legal supervision to have access to MMT. The ONDCP and the U.S. Department of Justice should implement this recommendation.

- The panel recommends improved training of physicians and other health care professionals in diagnosis and treatment of opiate dependence. For example, we encourage the National Institute on Drug Abuse and other agencies to provide funds to improve training for diagnosis and treatment of opiate dependence in medical schools.

- The panel recommends that unnecessary regulation of MMT and all long-acting agonist treatment programs be reduced.

- Funding for MMT should be increased.

- We advocate MMT as a benefit in public and private insurance programs, with parity of coverage for all medical and mental disorders.

- We recommend targeting opiate-dependent pregnant women for MMT.

- MMT must be culturally sensitive to enhance a favorable outcome for participating African American and Hispanic persons.

- Patients, underrepresented minorities, and consumers should be included in bodies charged with policy development guiding opiate dependence treatment.

- We recommend expanding the availability of opiate agonist treatment in those States and programs where this treatment option is currently unavailable.
Consensus Development Panel

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“The Natural History of Opiate Addiction”
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“Transmission of Bloodborne Viruses Among Heroin Injectors”
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David P. Desmond, M.S.W.
“Deaths Among Heroin Users In and Out of Methadone Maintenance”
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Rose Etheridge, Ph.D.
“Factors Related to Retention and Posttreatment Outcomes in Methadone Treatment: Replicated Findings Across Two Eras of Treatment”
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“Methadone Maintenance and Regional Cerebral Glucose Metabolism in Opiate Abusers: A Positron Emission Tomographic Study”
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“Diversion of Methadone: Expanding Access While Reducing Abuse”
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Michael Gossop, Ph.D.
“Methadone Substitution Treatment in the United Kingdom: Outcome Among Patients Treated in Drug Clinics and General Practice Settings”
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“Behavioral Therapies: A Treatment Element for Opiate Dependence”
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Henrick J. Harwood
“Societal Costs of Heroin Addiction”
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“The History and Current Status of Opiate Agonist Treatment”
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“Access to Narcotic Addiction Treatment and Medical Care”
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“Narcotic Agonist Treatment as a Benefit Under Managed Care”
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“Problem-Service Matching in Methadone Maintenance Treatment: Policy Suggestions From Two Prospective Studies”
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“Impact of Methadone Maintenance on HIV Seroconversion and Related Costs”
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“Neurobiological Substrates for Opiate Addiction”
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“Narcotic Drugs and Crime: Addict Behavior While Addicted Versus Nonaddicted”
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“Legal, Regulatory, and Funding Barriers to Good Practice and Associated Consequences”
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“Genetic and Other Risk Factors in Opiate Addiction”
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“Prenatal Care and Antiretroviral Use Associated With Methadone Treatment of HIV-Infected Pregnant Women”
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Bibliography

The speakers listed above identified the following key references in developing their presentations for the consensus conference. A more complete bibliography prepared by the National Library of Medicine at NIH, along with the references below, was provided to the consensus panel for their consideration. The full NLM bibliography is available at the following Web site: http://www.nlm.nih.gov/pubs/cbm/heroin_addiction.html.

Overview and Natural History


Dole, VP. Hazards of process regulations: the example of methadone maintenance. JAMA 1992;267:2234-5.


Molecular Neurobiology and Pathogenesis of Opiate Addiction


Consequences of Untreated Opiate Addiction


Current Opiate Addiction Treatment Modalities


Predictors of Treatment Outcome


National evaluations of drug abuse treatment outcomes. Psych Addict Behav [Special Issue]. In press.


**Barriers to Effective Use and Availability of Opiate Agonist Treatment**


Effective Medical Treatment of Opiate Addiction
A Continuing Medical Education Activity Sponsored by the National Institutes of Health/Foundation for Advanced Education in the Sciences

OBJECTIVE
The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Effective Medical Treatment of Opiate Addiction. The statement provides state-of-the-art information regarding effective treatments for opiate addiction and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. Upon completing this educational activity, the reader should possess a clear working clinical knowledge of the state of the art regarding this topic.

ACCREDITATION
The National Institutes of Health/Foundation for Advanced Education in the Sciences is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The National Institutes of Health/Foundation for Advanced Education in the Sciences designates this continuing medical education activity for 1 credit hour in Category I of the Physician’s Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

EXPIRATION
This form must be completed and postmarked by November 19, 2000, for eligibility to receive continuing medical education credit for this continuing medical education activity. The expiration date for this test may be extended beyond November 19, 2000. Beginning November 20, 2000, please check the NIH Consensus Development Program Web site (http://consensus.nih.gov) or call the NIH Office of Medical Applications of Research at 301-496-1144 for information regarding an extended expiration date for this continuing medical education activity.

INSTRUCTIONS
The consensus statement contains the correct answers to the following 12 questions. Select your answer(s) to each question and write the corresponding letter(s) in the answer space provided. Mail the completed test by the expiration date shown above to CME Program, Office of Medical Applications of Research, National Institutes of Health, Building 31, Room 1B03, 31 Center Drive MSC 2082, Bethesda, MD 20892-2082. You will receive notification of your test results within 2 to 3 weeks. If you have successfully completed the test (nine or more correct answers), you will receive a certificate for 1 hour of continuing education credit along with your test results. The estimated time to complete this educational activity is 1 hour. Photocopies of this form are acceptable. There is no fee for participating in this continuing education activity.
1. **The evidence to support opiate addiction as a medical disorder includes:**
   *(You must indicate all that are true.)*
   a. A consistency in the medical history, signs, and symptoms of opiate addiction irrespective of culture, ethnicity, and socioeconomic backgrounds.
   b. Pathophysiologica changes in the brain.
   c. A strong tendency to relapse after long periods of abstinence.
   d. None of the above.
   
   **ANSWER:** ______________________________________________________

2. **The consequences of an untreated opiate addiction include:**
   *(You must indicate all that are true.)*
   a. Increased mortality rates.
   b. Decreased use of routine medical services.
   c. Increased prevalence of infectious diseases.
   d. Increased joblessness and criminal activity.
   e. None of the above.
   
   **ANSWER:** ______________________________________________________

3. **Which of the following are true regarding opiate addiction:**
   *(You must indicate all that are true.)*
   a. It is an increasing problem among young people.
   b. It is a major cause in the spread of HIV.
   c. A majority of opiate addicts are not in treatment.
   d. None of the above.
   
   **ANSWER:** ______________________________________________________

4. **The current recommended duration of narcotic maintenance therapy is:**
   a. Less than 6 months.
   b. Between 1 and 2 years.
   c. Indefinitely.
   d. None of the above.
   
   **ANSWER:** ______________________________________________________

5. **Which of the following narcotics are currently approved by FDA and available for opiate maintenance therapy?** *(You must indicate all that are true.)*
   a. Methadone
   b. Buprenorphine
   c. LAAM
   d. Clonidine
   
   **ANSWER:** ______________________________________________________

6. **With regard to the use of methadone during pregnancy, which of the following is true?** *(You must indicate all that are true.)*
   a. HIV-infected women who receive methadone are more likely to be treated with zidovudine.
   b. The use of methadone during the third trimester should be avoided if possible.
   c. Babies whose mothers are treated with methadone during pregnancy have a greater likelihood of lower birth weight especially in contrast with babies whose mothers used heroin during pregnancy.
   d. Use of methadone during pregnancy, in conjunction with prenatal care, has been shown to decrease obstetrical and fetal complications.
   
   **ANSWER:** ______________________________________________________

7. **Which of the following has been demonstrated to affect the outcome of narcotic maintenance treatment?** *(You must indicate all that are true.)*
   a. Adequate medication dosage.
   b. Psychosocial services.
   c. Duration and continuity of treatment.
   d. None of the above.
   
   **ANSWER:** ______________________________________________________
8. Which of the following are true regarding medically supervised opioid withdrawal? (You must indicate all that are true.)
   a. Various opioid and non-opioid medications had been demonstrated to be effective.
   b. The duration of the withdrawal process is directly proportional to the duration of subsequent sustained abstinence.
   c. Ultra-rapid anesthesia-aided withdrawal has been demonstrated in controlled studies to be a superior method for sustaining opioid abstinence.
   d. Relatively few opioid-addicted patients sustain abstinence after opioid withdrawal if other treatments are not initiated.
   ANSWER: _____________________________________________________

9. Some of the common misconceptions concerning opiate addiction and opioid maintenance treatment include: (You must indicate all that are true.)
   a. Opiate addiction treatment is effective.
   b. Relapse after treatment is an indication of ineffective treatment.
   c. Opiate addiction is a medical illness.
   d. Opiate addiction is primarily limited to the mentally and socially impoverished.
   ANSWER: _____________________________________________________

10. Important barriers to treatment include: (You must indicate all that are true.)
    a. Stigma.
    b. Inadequate treatment facilities.
    c. Federal, State, and local laws and regulations.
    d. Inadequate public and private funding.
    e. None of the above.
    ANSWER: _____________________________________________________

11. Which of the following are true regarding molecular neurobiology and pathogenesis of opiate addiction? (You must indicate all that are true.)
    a. Twin, family, and adoption studies show that drug abuse vulnerability may be partially inherited.
    b. Cross-fostering adoption studies have identified several genetic pathways to drug abuse/dependence.
    c. Controlled family studies report significantly increased relative risk for substance abuse.
    d. None of the above.
    ANSWER: _____________________________________________________

12. Which of the following are true with regard to the diagnosis of opiate addiction? (You must indicate all that are true.)
    a. Addiction is defined as a cluster of cognitive, behavioral, and physiological symptoms that are continued despite significant opiate-induced problems.
    b. The absence of opioids in saliva and urine is an important finding and indication that the individual is not addicted to opiates.
    c. Opiate dependence is characterized by repeated self-administration that often results in tolerance, withdrawal symptoms, and compulsive drug-taking.
    d. None of the above.
    ANSWER: _____________________________________________________
Your response to the following four questions is optional and will have no effect on the grading results of this test.

To what extent did this CME activity meet the stated objectives?

a. not at all  

b. very little  
c. somewhat  
d. considerably  
e. completely

ANSWER: ____________________________________________________

To what extent will participation in this CME activity enhance your professional effectiveness?

a. not at all  

b. very little  
c. somewhat  
d. considerably  
e. completely  
f. does not apply

ANSWER: ____________________________________________________

Do you have additional comments you think would enhance the utility or impact of this NIH Consensus Statement?

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

Are there new topics you would like to have covered in a similar or related NIH Consensus Development Conference or Statement?

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

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