

Treating Opioid Dependence

Growing Implications for Primary Care

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Almost 3 million Americans have abused heroin. The most effective treatment for this concerning epidemic is opioid replacement therapy. Although, from a historical perspective, acceptance of this therapy has been slow, growing evidence supports its efficacy. There are 3 approved medications for opioid maintenance therapy: methadone hydrochloride, levomethadyl acetate, and buprenorphine hydrochloride. Each has unique characteristics that determine its suitability for an individual patient. Cardiac arrhythmias have been reported with methadone and levomethadyl, but not with buprenorphine. Due to concerns about cardiac risk, levomethadyl use has declined and the product may ultimately be discontinued. These recent safety concerns, specifics about opioid detoxification and maintenance, and new federal initiatives were studied. Opioid detoxification has a role in both preventing acute withdrawal and maintaining long-term abstinence. Although only a minority of eligible patients are engaged in treatment, opioid maintenance therapy appears to offer the greatest public health benefits. There is growing interest in expanding treatment into primary care, allowing opioid addiction to be managed like other chronic illnesses. This model has gained wide acceptance in Europe and is now being implemented in the United States. The recent Drug Addiction Treatment Act enables qualified physicians to treat opioid-dependent patients with buprenorphine in an office-based setting. Mainstreaming opioid addiction treatment has many advantages; its success will depend on resolution of ethical and delivery system issues as well as improved and expanded training of physicians in addiction medicine.

Arch Intern Med. 2004;164:277-288

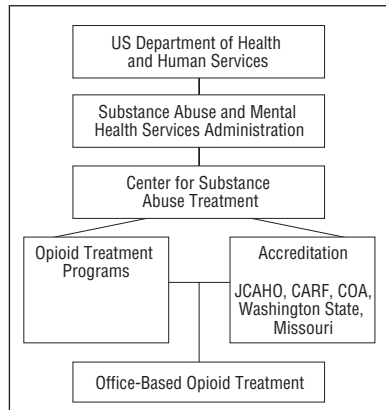
The lifetime prevalence of heroin use has again increased in the past decade; almost 3 million Americans have used heroin.¹ The most effective treatment appears to be opioid replacement therapy, currently serving more than 200 000 patients in the United States.² There are more than 1000 opioid treatment programs (OTPs) in operation, although services are not currently available in Montana, Mississippi, Wyoming, and the Dakotas. Primary care providers should become increasingly familiar with opioid addiction because these specially licensed programs currently reach only an estimated 14% of opioid-dependent patients.³ A potentially important way to narrow this gap

is to mainstream the treatment of opioid dependence into primary care.

SCOPE OF THE PROBLEM

It is estimated that intravenous drug abuse and all of its sequelae have a health care cost of close to \$100 billion annually.⁴ The risk of fatal overdose and the infectious complications of intravenous drug abuse are substantial. The prevalence of hepatitis C in heroin users enrolled in OTPs is estimated at 90%.⁵⁻⁷ This subgroup of 150 000 patients with hepatitis C are potential interferon and liver transplantation applicants.^{8,9} Moreover, heroin abuse accounts for nearly half of the annual total number of cases of human immunodeficiency virus (HIV) infection in the United States.¹⁰⁻¹² Acute bacterial infections lead-

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Post-Food and Drug Administration regulatory oversight of opioid agonist therapy for addiction. JCAHO indicates Joint Commission on Accreditation of Healthcare Organizations; CARF, Commission on Accreditation of Rehabilitation Facilities; and COA, Council on Accreditation for Children and Family Services. Washington State and Missouri refer to the Divisions of Alcohol and Substance Abuse in those states.

ing to costly hospitalizations are common in this population, and many of these episodes are attributable to acute bacterial endocarditis.^{13,14} The magnitude of the problem is illustrated by the fact that 5% of primary care patients report current substance abuse.¹⁵

Heroin abusers frequently have psychiatric comorbidities, which play an important role in their poor outcome.¹⁶⁻¹⁸ Antisocial personality disorder is one of the most common disorders, along with major depression and anxiety disorders.¹⁹⁻²² Opioid-dependent patients with Axis I psychiatric comorbidity often need significantly higher methadone doses. In addition, there is an eating disorder-opioid abuse connection in bulimic patients.²³ Complicating matters, entrants to methadone treatment are often dually addicted to heroin and cocaine.²⁴ Most users of illicit opioids also smoke cigarettes²⁵ and suffer a devastatingly high tobacco-related mortality.^{26,27}

HISTORICAL PERSPECTIVE

In the early part of the 20th century, physicians faced with persons addicted to narcotic drugs prescribed heroin and morphine. In 1914 the Harrison Act was passed, and as a result addiction was viewed primarily as a criminal problem rather than a medical concern. The Harrison Act resulted in significant trepidation

among physicians treating narcotic addicts. Treatment for addiction was essentially unavailable until 1935 when US Public Health Services started a hospital in Lexington, Ky. The treatments were entirely detoxification-based. Interest in narcotic management began to rise again with the 1955 publication of a position paper by the New York Academy of Medicine.²⁸ In 1963, the New York Academy of Sciences recommended that clinics be established to dispense narcotics to opioid-dependent patients.²⁸

During the 1960s, heroin addiction was the leading cause of death in African American men in New York City.²⁹ In response to this growing epidemic, Vincent Dole, MD, and Marie Nyswander, MD, from the Rockefeller Institute, New York, pioneered the use of the synthetic opioid methadone for treating heroin addicts. They found oral morphine to be unsuccessful because patients alternated between feelings of intoxication and withdrawal. Methadone, because of its long half-life, could avert this problem if given once daily.³⁰ The initial efforts of these two physicians guided development of the methadone maintenance treatment paradigm.³¹

In 1972, the US Food and Drug Administration created stringent regulations governing methadone. This reduced the amount of flexibility for practitioners caring for opioid-dependent patients. The 1974 Narcotic Treatment Act established guidelines that limited methadone to opioid addicts. States added their own rules, which further complicated care delivery. Some experts have suggested that the current system emphasizes regulatory process more than medical judgment.³² In part because of these restrictions, many heroin addicts had limited access to methadone maintenance, resulting in a significant treatment gap nationwide.

The Office of National Drug Control Policy subsequently made changes in the 1995 Federal Regulations of Methadone Treatment to encourage the development of a less restrictive approach³³ and give physicians more latitude in prescribing methadone.³⁴ In 1997 a National Institutes of Health consensus conference published its support for methadone and recommended the

medicalization of treatment.³⁵ The new accreditation process is no longer administered by the Food and Drug Administration; the Department of Health and Human Services will oversee the 2-year period in which the nation's OTPs have to achieve accreditation.³⁶ This new regulatory structure is depicted in the **Figure**. Recent evidence suggests that the accreditation process improves adherence to guidelines for optimal dosing practices.³⁷ The accreditation process, it is hoped, will enhance access to quality care and integrate narcotic treatment into traditional medical practice.

SCIENTIFIC BASIS OF OPIOID MAINTENANCE

The shift toward less restrictive access to care is predicated not only on the aforementioned treatment gap but also on strong scientific evidence supporting the efficacy of opioid replacement therapy. There appears to be a specific neurologic basis for the compulsive use of heroin. Chronic heroin abusers end up with an endogenous opioid deficiency because of down-regulation of opioid production. This creates an overwhelming craving, which necessitates effective treatments that shift the addicted patient's interests from obsessive preoccupation with the timing and dose of an illicit substance to more ordinary topics and less dangerous behaviors.³⁸

The early observations of Dole and Kreek³⁹ were sentinel in this regard, namely that the essential feature of successful maintenance treatment is patient stabilization through opioid receptor occupation. Previous attempts using morphine maintenance had failed because the narcotic receptor did not remain continuously occupied. In addition, neuroendocrine studies have shown normalization of stress hormone responses after several months of stabilization with methadone. Similarly, positron emission tomography has demonstrated that only 25% to 35% of brain opioid receptors are occupied during steady-state methadone maintenance. This suggests that these unoccupied opioid receptors, which were disrupted during cycles of opioid abuse, could normalize dur-

ing methadone maintenance.⁴⁰ Moreover, minimal euphoria is realized from illicit heroin abuse if the long-acting opioid is bound to the receptors and blocks heroin's reinforcing nature. Thus, the steady-state perfusion of the synthetic opioid at the specific μ -opioid receptors, which prevents abstinence symptoms and eliminates craving, in concert with classic deconditioning due to the lack of euphoric effects of heroin, are the basis for the effectiveness of opioid agonists in decreasing abuse.

Long-term opioid agonist treatment also appears to have an important positive impact on public health. Before the introduction of methadone maintenance, the annual death rate from opioid dependence was 21 per 1000. After the introduction of methadone, the death rate decreased to 13 per 1000. Similarly, the death rate for opioid-dependent persons in methadone treatment has consistently been 30% less than for those not in treatment.⁴¹ Studies have also demonstrated that treatment with opioid agonists reduces the rate of criminal activity.^{42,43}

Hepatitis C is the most common cause of chronic hepatitis in the United States⁴⁴ and is endemic in patients undergoing methadone maintenance.⁴⁵ Most heroin injectors contract hepatitis C early in their injection drug use.⁴⁶ The presumption is that since hepatitis C is spread by the same percutaneous route as HIV, methadone might represent an effective way of preventing this disease.

Methadone treatment has assumed particular importance in view of the HIV epidemic.⁴⁷ In 1996, the total number of AIDS cases reported to the Centers for Disease Control and Prevention was 513 000; of those, 184 000 (36%) were associated with injection drug use.⁴⁸ Methadone maintenance dramatically reduces the frequency of injection drug use and has also been shown to decrease sexually related high-risk behaviors.⁴⁹⁻⁵¹ Consequently, there are much lower HIV seroprevalence rates in those enrolled in methadone treatment and for those with longer amounts of time in treatment compared with untreated addicts.⁵²⁻⁵⁵ Methadone maintenance has also been found to be a cost-effective intervention, with a cost of \$8200 per quality-adjusted life-

year gained.⁵⁶ It is estimated that the 6-month costs are about \$21 000 for an untreated drug abuser, \$20 000 for an incarcerated drug abuser, and \$1750 for a patient enrolled in a methadone maintenance program.⁵⁷

OPIOID AGONIST PHARMACOTHERAPY

Heroin-dependent patients have 3 major approaches available to treat their addiction: opioid detoxification, agonist maintenance, and antagonist maintenance. Naltrexone is the only available antagonist agent; in contrast to opioid agonist therapy, naltrexone has been relatively unsuccessful in treatment retention and in reduction of illicit substance abuse.⁵⁸ This may be due to dysphoria related to blockade of endogenous opioids with naltrexone.⁵⁹ Currently, there are 3 approved opioid agonist therapies: methadone hydrochloride, levomethadyl acetate, and buprenorphine hydrochloride.

Methadone

Methadone is a long-acting μ -opioid receptor agonist, introduced in the 1960s, after being developed in Germany at the end of World War II.⁶⁰ It has an onset of action within 30 minutes⁶¹⁻⁶³ and an average duration of action of 24 to 36 hours. Its oral bioavailability is excellent and approaches 90%. These unique pharmacologic properties ideally lend themselves to once-daily dosing for maintenance therapy, although, when used to treat chronic pain, methadone is generally dosed 3 times daily. When the dosage is judiciously titrated, methadone-treated patients generally do not experience euphoria or sedation, nor do they suffer impairment in the ability to perform mental tasks. One of the most important advantages of methadone is that it relieves narcotic craving, which is the primary reason for relapse. Similarly, methadone blocks many of the narcotic effects of heroin,⁶⁴ which helps reinforce abstinence. Once a therapeutic dose is achieved, patients frequently can be maintained for many years with the same dose.⁶⁵

Methadone hydrochloride is available in 5- and 10-mg tablets as

Table 1. Adverse Effects of Methadone

Common
Constipation
Sweating
Diminished libido
Mild nausea
Less common
Flushing of the face
Pruritus
Euphoria/dysphoria
Insomnia
Urinary retention or hesitancy
Bradycardia
Rare
Biliary spasm
Urticaria
Syncope
Death from overdose
Torsade de pointes

well as a 40-mg dispersible wafer. However, it is most frequently used for maintenance in a 10-mg/mL liquid concentrate. An intravenous solution is also available but has been linked with bradycardia when administered for sedation.⁶⁶ Methadone is metabolized extensively in the liver,⁶⁷ and its excretion rate can be accelerated by urinary acidification.⁶⁸ Elimination is slower in women.⁶⁹ Mild adverse effects observed include sweating, decreased libido, weight gain, constipation, and irregular menstrual periods. Most adverse effects occur during the initial stabilization process (**Table 1**). As with any potent narcotic, serious consequences such as debilitating sedation and fatal overdose may occur. Tolerance to the narcotic properties of methadone, such as sedation, develop within 4 weeks, but tolerance to its autonomic effects such as constipation may take longer, and many patients continue to experience chronic constipation. Doses as low as 20 mg may improve treatment retention, but higher doses are often necessary to suppress illicit drug use.⁷⁰ The minimal effective dose is usually 50 mg, but some individuals need much larger doses.^{71,72} Because methadone is metabolized via the cytochrome P450 pathway, phenytoin, carbamazepine, barbiturates, isoniazid, and certain HIV protease inhibitor medications can reduce plasma methadone levels.⁷³⁻⁷⁵ Conversely, medications such as cimetidine, erythromycin, and fluvox-

amine maleate will increase levels. Opioid agonist-antagonist medications such as pentazocine will cause withdrawal symptoms in patients receiving methadone maintenance and should be avoided. The medications that most commonly interact with methadone are listed in **Table 2**. Liver disease may increase the half-life of methadone, but renal failure does not.⁷⁶

There have been rare cases of torsade de pointes in patients receiving very-high-dose methadone hydrochloride therapy (mean dosage, approximately 400 mg/d; range, 60-1000 mg/d) for opioid dependency and chronic pain.⁷⁷ It is important to emphasize that most cases occurred with methadone doses higher than those often encountered in clinical practice. Furthermore, these cases frequently oc-

curred in the setting of additional proarrhythmic factors such as hypokalemia. Preliminary data suggest that this ventricular arrhythmia may be mediated through inhibition of the rapidly activating component of the delayed rectifier potassium current in cardiac tissue.⁷⁸ Blockade of this ion channel has been shown to be an important mediator of drug-related torsade de pointes.^{79,80}

Levomethadyl

Development of new opioid substitution pharmacotherapies, designed to build on the strengths and improve on the weakness of methadone, has resulted in 2 alternative opioid agonist agents, levomethadyl and buprenorphine. Levomethadyl, a more potent derivative of

methadone, actually has very little opioid effect in its parent form and is functionally a "prodrug." It is extensively metabolized by the liver into 4 major metabolites.⁸¹ Nor-levomethadyl and dinor-levomethadyl are the major active metabolites.⁸² Nor-levomethadyl is most active, being about 100 times more potent in vitro and 10 times more potent in vivo than its parent compound.^{83,84} Like methadone, levomethadyl is metabolized primarily by the hepatic P450 isozyme CYP3A4.⁸⁵ In addition, methadone and levomethadyl share the same protein binding sites in plasma.⁸⁶ Because of this, methadone and levomethadyl when taken concurrently may have additive effects. Therefore, patients generally receive one or the other agent, but not a combination, for maintenance therapy.

Levomethadyl is a synthetic μ -opioid receptor agonist that is commercially available in a liquid suspension. It is rapidly absorbed from the gastrointestinal tract, although its oral bioavailability is somewhat lower than that of methadone.⁸⁷ Because of these properties, the opioid effect of levomethadyl is somewhat slower in onset than that of methadone (90 minutes), but it has a much longer duration of action (48-72 hours) and is therefore able to be dispensed 3 times per week. The comparative pharmacologic effects of levomethadyl, methadone, and buprenorphine are outlined in **Table 3**. Other potential advantages of levomethadyl's longer duration of action include reduced dispensing time and less opportunity for illegal diversion. Similar to methadone, it suppresses symptoms of withdrawal and produces cross-tolerance. Adverse effects of levomethadyl are infrequent

Table 2. Selected Methadone Drug Interactions

Medication	Description
Contraindicated (precipitates opioid withdrawal)*	
Naltrexone	Opioid antagonist
Naloxone hydrochloride	Opioid antagonist
Buprenorphine hydrochloride	Mixed opioid agonist-antagonist
Pentazocine	Mixed opioid agonist-antagonist
Tramadol hydrochloride	Analgesic, may have opioid antagonist properties
Decreases plasma methadone concentration†	
Phenobarbital	Sedative-hypnotic
Carbamazepine	Antiepileptic
Phenytoin	Antiepileptic
Ethanol	Causes interaction with long-term abuse
Rifampin	Antituberculosis agent
Increases plasma methadone concentration‡	
Ciprofloxacin	Antibiotic
Cimetidine	Histamine ₂ receptor antagonist
Ketoconazole	Antifungal
Amitriptyline hydrochloride	Antidepressant
Fluvoxamine maleate	Obsessive-compulsive disorder therapy

*Direct antagonism of methadone action at the opioid receptor site.

†Through induction of hepatic cytochrome P450 activity.

‡Through inhibition of hepatic cytochrome P450 activity.

Table 3. Pharmacotherapy of Heroin Addiction

Drug	Classification (DEA Schedule)	Route of Administration	Duration of Action, h	Withdrawal; Symptoms	Frequency of Administration
Heroin	Substance of abuse (I)	Intravenous, intranasal, inhalational	3-6	After 3-6 h; intense	Often multiple times daily
Methadone hydrochloride	Opioid agonist (II)	Oral (pill and liquid) and parenteral	24-36	After 24 h; intense	Once daily
Levomethadyl acetate	Opioid agonist (II)	Oral suspension	48-72	After 48 h; intense	3 Times weekly
Buprenorphine hydrochloride	Partial opioid agonist-antagonist (III)	Sublingual and parenteral	72-96	After 72 h; mild	Once daily to 3 times weekly
Naltrexone	Opioid antagonist (IV)	Oral	24	None	Daily or 3 times weekly

*Abbreviation: DEA, Drug Enforcement Agency.

and, when they occur, are the same as those for methadone. The average daily dose is 75 to 115 mg given 3 times per week. Treatment centers that are not open 7 d/wk dispense a larger dosage of levomethadyl before the 48-hour weekend period.

As with methadone, there have been a small number of reported cases of torsade de pointes in patients receiving levomethadyl.^{88,89} Because of this, the manufacturer has recommended that a baseline electrocardiogram be obtained to exclude significant prolongation of the QT segment before levomethadyl therapy is initiated.⁹⁰ A follow-up electrocardiogram should be obtained between 2 and 4 weeks after initiation, when steady-state dosing has been attained.

Buprenorphine

Buprenorphine is a long-acting partial opioid agonist^{91,92} that is classified as a Schedule III narcotic, in contrast to methadone and levomethadyl, which are Schedule II. Its potential advantages include a higher degree of safety than with methadone, coupled with an ameliorated withdrawal syndrome. This is due to its partial agonist property at the μ -receptor along with its being a weak antagonist at the κ -receptor.⁹³⁻⁹⁵ It is available in a tablet form for sublingual administration and in parenteral form. Buprenorphine is metabolized through the cytochrome P450 pathway.^{96,97} The brand name for the buprenorphine monotablet is Subutex, and the combination buprenorphine hydrochloride–naloxone hydrochloride tablet is Suboxone (both Reckitt Benckiser Pharmaceuticals, Richmond, Va). Both formulations come in strengths of 2 and 8 mg. The combination product contains 0.5 mg of the opioid antagonist naloxone hydrochloride and is designed to decrease the potential for abuse. Suboxone is also likely to have limited “street value,” reducing its diversion potential. Because buprenorphine has minimal oral bioavailability, sublingual administration is the primary route of delivery for treating opioid dependence. The average daily dose is 8 to 16 mg. Issues of cost and comparative efficacy will determine whether buprenorphine will

play a central role in maintenance therapy in OTPs, although it will likely have a significant impact on office-based addiction treatment.

OPIOID AGONIST MAINTENANCE

The central goal of opioid dependency treatment is to reduce illicit drug use and its attendant health risks. Other targeted outcomes for maintenance treatment include a reduction in unsafe sexual practices, improvement in vocational and psychosocial functioning, and an enhanced quality of life. The types and intensity of available substance abuse treatments cover a wide range of services including office-based therapy, intensive outpatient services, and inpatient rehabilitation. Presently, successful opioid treatment is most often achieved through long-term maintenance programs that prescribe methadone, levomethadyl, or buprenorphine.

Methadone Maintenance

Methadone is the most inexpensive and well-validated agent for opioid maintenance, which leads to 1-year treatment retention rates of 80% with concomitant reductions in illicit opioid use.⁹⁸ One study randomly assigned 179 opioid-dependent patients to either methadone maintenance or a psychosocially enriched detoxification program, and it showed that methadone maintenance resulted in greater treatment retention and lower rates of illicit heroin use than did detoxification.⁹⁹ Many additional studies have corroborated the efficacy of methadone maintenance,¹⁰⁰ including the Drug Abuse Treatment Outcome Study, which showed a decline from 89% to 28% in illicit heroin abuse.¹⁰¹

Treatment is initiated with 25 to 30 mg of methadone hydrochloride once daily. A lower starting dose may be prudent in patients with less severe opioid habits and those with significant hepatic or pulmonary disease. The dose is gradually titrated in 5- to 10-mg increments per day to a dose range of 60 to 120 mg, which provides relief from abstinence symptoms, usually without perceptible sedation effects. There is

no arbitrary ceiling dose. The issue of adequate methadone dosing is very pertinent because low-dose treatment has been associated with worse outcomes. Moreover, as heroin availability and purity increase, the issue of optimal methadone dose is more important. A recent trial examined moderate-dose (40-50 mg) vs high-dose (80-100 mg) methadone treatment and found both doses to be effective for retention of patients in treatment, but the higher-dose group had less illicit opioid use.¹⁰² Previously, these authors had shown that low-dose methadone maintenance (20 mg) was associated with both more illicit drug use and less treatment retention compared with a moderate dose (50 mg).¹⁰³ Other studies have corroborated the increased efficacy of high-dose methadone maintenance.¹⁰⁴ Accordingly, the Center for Substance Abuse Treatment has defined the therapeutic dosage for methadone maintenance treatment as being between 80 and 120 mg/d.

There has been some interest in correlating the daily methadone dose and serum concentration to predict optimal doses.¹⁰⁵ In general, a trough serum methadone concentration of 400 ng/mL is considered an effective target in methadone maintenance, although there is no compelling evidence that serum monitoring is superior to “symptom-guided” dose titration.¹⁰⁶ As a rule, there has been inconsistent correlation between serum methadone concentration and clinical stability; the best and most cost-effective solution therefore remains individualized therapeutic monitoring.

The question of what type and intensity of ancillary services are optimal for methadone maintenance programs remains open. Individual and group counseling are the main ancillary therapies provided in most treatment programs. In addition, several psychotherapeutic methods including cognitive-behavioral and supportive-expressive techniques may be useful adjuncts in opioid-dependent patients. These services require the availability of a trained psychologist or psychiatrist. Some studies have suggested that “more is better,” with more intensive psychosocial services hav-

ing better outcomes.¹⁰⁷ Others have questioned the effectiveness of these enhanced programs.¹⁰⁸ It may be that only patients identified as being the most difficult to treat need to be referred for intensive services. A more intensive approach with daily staff contact is often invoked for patients with persistent illicit heroin use. Ultimately, detoxification leading to termination from a program may be pursued if the OTP staff believes that there has been no positive response to methadone or other opioid agonist therapy. Program termination should be used as a last resort given the significant harm reduction afforded by methadone maintenance therapy.

Levomethadyl Maintenance

Although methadone maintenance programs have been effective, clinical experience has demonstrated some shortcomings. Daily clinic visits for supervised medications may impact employment opportunities. The provision of take-home medications to reduce clinic visits may promote illegal methadone diversion and result in community dissatisfaction. Moreover, the fact that only a minority of heroin addicts are enrolled in OTPs may in part reflect patient displeasure with methadone treatment. Therefore, there has been a need to develop new substitution pharmacotherapies. Levomethadyl, approved in 1993, has been demonstrated to be effective in retention of patients in maintenance programs as well as in reducing illicit heroin use. In controlled clinical trials, long-term treatment with levomethadyl was comparable to methadone with respect to these 2 measures.¹⁰⁹ Levomethadyl acetate dosages in the range of 60 to 100 mg 3 times a week have been shown to reduce opioid use comparably to therapy with 50 to 100 mg of methadone hydrochloride daily.¹¹⁰ Seventy-five milligrams of levomethadyl acetate provides opioid blockade and withdrawal suppression for up to 96 hours.¹¹¹ A recent meta-analysis also found levomethadyl and methadone maintenance to be comparable with regard to ongoing illicit drug use.¹¹²

From a practical standpoint, levomethadyl's niche may be in pa-

tients perceived by clinicians to benefit from reduced frequency of visits, whereas methadone might be more appropriate for patients in need of the intensive support from daily clinic visits. In addition, persons with transportation or scheduling problems, those with a history of previous methadone failure, and those with a desire to avoid methadone maintenance because of either social stigma or negative myths may find levomethadyl useful. Some patients receiving maintenance treatment believe that levomethadyl stabilizes opioid cravings better than methadone¹¹³ and has less perceptible opioid-agonist effects, allowing them to feel more normal. Patients can be inducted directly into levomethadyl treatment from either methadone or heroin. In general, an initial dose of 30 mg suffices; if the patient is switching from methadone, the recommended initial dose of levomethadyl acetate is 1.2 to 1.3 times the methadone dose.

Yet, despite all of the aforementioned potential advantages plus its minimal street value, levomethadyl is currently available in less than 10% of opioid agonist treatment centers.¹¹⁴ Levomethadyl has had very limited availability in OTPs because of its higher cost and requirement for electrocardiogram monitoring. Heightened concerns regarding arrhythmia risk and subsequent underutilization have led the manufacturer of levomethadyl to begin phasing it out of production during 2004.¹¹⁵ Opioid treatment programs should consider transitioning levomethadyl patients to methadone therapy. The daily methadone dose should be approximately 80% that of the prior levomethadyl dose and should be administered no sooner than 48 hours after the patient's last levomethadyl dose.

Buprenorphine Maintenance

Buprenorphine has some advantages over methadone, including milder withdrawal symptoms after abrupt cessation, lower risk of overdose, and a longer duration of action, which allows alternate-day dosing.¹¹⁶ Patients with a less chronic form of heroin addiction might be

better served with buprenorphine than by a full opioid agonist like methadone or levomethadyl. Alternatively, patients with very high levels of physical dependence may be more optimally treated initially with methadone or levomethadyl. Ideal candidates for buprenorphine would be those who are motivated to comply with treatment and willing to follow safety precautions given the limited oversight inherent in office-based opioid maintenance.

One maintenance study found less illicit heroin use with buprenorphine compared with methadone, although a better retention rate was noted in the methadone group.¹¹⁷ Another study showed high-dose methadone to be more efficacious than 8 mg of buprenorphine hydrochloride concerning retention and ongoing opioid use.¹¹⁸ A recent double-blind randomized trial using an average dose of buprenorphine (10 mg/d) vs methadone (70 mg/d) demonstrated a higher retention rate with methadone, but equal efficacy in reducing illicit usage of heroin.¹¹⁹ Another report demonstrated the utility of buprenorphine in opioid-dependent patients with concurrent cocaine abuse.¹²⁰ Most studies of buprenorphine have been based on daily doses. Johnson et al¹⁰² recently reported a trial of buprenorphine administered 3 times weekly and found it to be similar to levomethadyl in terms of retention and similar to methadone in terms of reducing heroin use. These studies support buprenorphine as a viable alternative for opioid maintenance therapy.

There are a number of logistic considerations for buprenorphine induction and maintenance. In contrast to methadone and levomethadyl, buprenorphine is a mixed agonist antagonist and may precipitate opioid withdrawal. Because of this potential, patients transferring from short-acting opioids, such as heroin, should be instructed to abstain from illicit opioid use a minimum of 4 hours and preferably 12 to 24 hours before administering the first buprenorphine dose. If there is any question about the accuracy of the patient's drug history, or if there are any signs of acute opioid use, the first dose should be delayed until the

patient manifests signs of withdrawal or reports abstinence symptoms. Induction into buprenorphine treatment from long-acting opioids such as methadone and levomethadyl presents a challenge because of their long half-lives.

Defining the specific subgroup that may benefit more from buprenorphine, levomethadyl, or methadone maintenance therapy has not been fully elucidated. However, it is clear that not all opioid abusers are alike. Therefore, the concept of matching patients to the most appropriate maintenance treatment should be attempted in clinical practice to optimize outcomes.

MEDICALLY SUPERVISED OPIOID WITHDRAWAL (DETOXIFICATION)

The third approach available to treat opioid addiction is detoxification. "Medically supervised withdrawal" is the preferred phrase to describe the process of tapering opioid-dependent patients from agonist therapy, but it may be used interchangeably with "detoxification." This critical process must be exercised slowly and cautiously to avoid a marked abstinence syndrome. Although untreated alcohol withdrawal is potentially more dangerous, opioid withdrawal causes intensely disturbing symptoms. Withdrawal symptoms begin 3 to 6 hours after the last use of heroin, but they may not begin for a number of days after abrupt discontinuation of methadone, levomethadyl, or buprenorphine, given their longer half-lives. Symptoms include gastrointestinal distress (diarrhea and cramping), marked anxiety, irritability, insomnia, pathognomonic skin piloerection, and an influenza-like syndrome characterized by rhinorrhea, lacrimation, and myalgias. This syndrome may last 5 to 10 days and must be carefully managed to prevent immediate heroin relapse. In addition, a protracted abstinence phase may last for months and is characterized by asthenia, depression, and hypotension.¹²¹

There are 3 main treatment modalities used for detoxification during the initial treatment of opioid-dependent patients: (1) those using

opioid agonists, (2) those using non-opioid medications, and (3) the newest modalities of rapid and ultrarapid opioid detoxification. For opioid-based detoxification, methadone is frequently used because it can be given once daily. Initially, methadone hydrochloride is given in a dosage range of 10 to 30 mg/d, depending on the size of the opioid habit.¹²² Additional methadone may be necessary if signs of abstinence appear. The methadone dose is then tapered by 10% to 20% per day for inpatients after an initial day or two of stabilization.¹²³ For outpatients, the dose is tapered 5% to 10% per week.¹²⁴ A slower rate of reduction may be associated with decreased illicit opioid use.¹²⁵ Although these regimens result in successful detoxification in 80% of inpatients and 40% of outpatients, long-term recidivism rates after detoxification remain high. Outpatient detoxification can be performed only through specially licensed OTPs, although any licensed physician can coordinate this in the inpatient setting. Some OTPs are licensed for 21- and 180-day detoxification protocols for patients with less extensive addiction histories, while others provide only maintenance services. Buprenorphine has also been used in several experimental studies of opioid withdrawal. Most studies have found it to be equivalent to methadone when tapered over 4 to 6 weeks.^{126,127}

Non-opioid-based detoxification using clonidine was described in the late 1970s.¹²⁸ The purported explanation was that clonidine blocked activation of the noradrenergic locus ceruleus nucleus, which is involved with opioid withdrawal. Clonidine in initial dosages of 0.1 to 0.2 mg every 4 hours with careful monitoring of blood pressure eliminates most commonly reported withdrawal symptoms.¹²⁹⁻¹³¹ Some withdrawal symptoms such as anxiety and myalgias are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory agents may be necessary adjuncts to treat these symptoms. Clonidine may be preferable for outpatient detoxification because it is not a controlled substance and is therefore more widely available than methadone, and it may shorten the detoxification period to 1 to 2 weeks.¹³²

Clonidine has been combined with the opioid antagonist naltrexone, in a dose of 12.5 to 50 mg, as a successful detoxification regimen of even shorter duration.¹³³ Lofexidine, another α_2 -adrenergic agonist, has been used experimentally with some success.¹³⁴

During the past several years, there has been a proliferation of protocols encompassed by the expression "rapid opioid detoxification."^{135,136} Its development is attributable to the prolonged period currently needed for opioid and nonopioid detoxification approaches. The rapid approach shortens the detoxification process to 3 to 5 days by precipitating withdrawal through the administration of opioid antagonists such as naloxone or naltrexone.¹³⁷ Ultrarapid detoxification is a variant that is performed with the patient under general anesthesia over 24 hours.¹³⁸ Because the patient is anesthetized during the acute phase of withdrawal, he or she does not consciously experience the unpleasant acute opioid withdrawal syndrome. Most of the rapid protocols use clonidine along with an opioid antagonist, as well as adjuvant benzodiazepines and antiemetics to treat the withdrawal syndrome.¹³⁹ Many of these protocols maintain the rapidly detoxified patients with naltrexone.¹⁴⁰ Specific details of this emerging science are beyond the intended scope of this review, but physicians should be aware of its potential utility for individuals who have been unsuccessful with traditional opioid tapered programs,¹⁴¹ and in highly motivated patients without extensive histories of opioid abuse. Issues related to long-term effectiveness remain unresolved. One disadvantage of ultrarapid opioid detoxification is its inability to adequately address the psychological aspects of opioid dependency. More integration of counseling and relapse prevention strategies may enhance the effectiveness of these protocols.

Regardless of the method used for detoxification, maintenance of abstinence is essential to the overall treatment strategy. While drug-free substance abuse treatment for detoxified opioid-dependent patients is still a possibility, the lessons from the early part of the 20th

century indicate that this will often be unsuccessful. This is especially so for those with unstable social situations and those in whom detoxification treatments have previously failed; for this large majority, opioid maintenance remains the preferred method of treatment. There is little research supporting the long-term efficacy of detoxification-based protocols followed by a treatment geared to result in the discontinuation of all opioid use. Although some have criticized the practice of methadone and levomethadyl maintenance, wherein there is substitution of one opioid for another, the clinical benefits strongly support this paradigm.

THE EXPANDING ROLE OF THE PRIMARY CARE PROVIDER

Because of both the success of opioid agonist therapy and the small number of OTPs compared with the number of opioid addicts, there is growing interest in expanding treatment into primary care physicians' offices. Prescribing opioid agonist maintenance therapy is one of the most scrutinized areas of medicine. As opposed to other Schedule II narcotics, methadone (when used to treat addiction) can only be dispensed from facilities that have an OTP license issued by the Drug Enforcement Agency and must comply with numerous regulatory requirements. In response, the 1998 National Consensus Panel for Opiate Addiction strongly endorsed the need to repeal unnecessary regulations and expand the availability of treatment.¹⁴² Cogent arguments that would allow use of levomethadyl and methadone in office-based, primary care addiction treatment have been articulated.¹⁴³ At the same time, there have been many articles published that urge primary care providers to take a more proactive role in treating substance abuse.^{144,145}

Methadone maintenance has already been extended into primary care settings outside of the United States. In Scotland, 70% of primary care providers prescribe methadone,¹⁴⁶ and 60% of injection drug users are enrolled in methadone treatment through these providers.¹⁴⁷ Australia and Switzerland have also

expanded access to treatment.^{148,149} A less restrictive approach to opioid-dependence treatment has been adopted by the Canadian government, which has increased the number of patients receiving methadone maintenance by 200% between 1993 and 1997.¹⁵⁰

This medical maintenance model has also been tested in the United States. A first report of outcomes, from a group of patients receiving methadone maintenance in general practice settings in New York City, showed an 82% retention rate.¹⁵¹ A follow-up report showed that office-based treatment was highly beneficial compared with methadone maintenance.¹⁵² Similarly, the care of a cohort of former heroin addicts treated with methadone maintenance was successfully transitioned to primary care physicians.¹⁵³ As this process continues to evolve, there are a variety of important philosophical, ethical, and system issues that must be addressed, not the least of which is ensuring adequate patient safety.¹⁵⁴

In addition to improved access, shifting the treatment of opioid addiction into physicians' offices has the potential to enhance health care provision. Intravenous drug users are less likely to be offered and to receive appropriate HIV treatment than other HIV-infected patients.^{155,156} The requirements for medical care of HIV-infected drug users have increased with the use of antiretroviral therapies.^{157,158} Moreover, creating linkages between primary care and addiction medicine should improve the receipt of preventive care by these individuals.¹⁵⁹ Without this improved access, there is increased reliance on emergency services.^{160,161} Primary care-based opioid treatment might therefore improve access to comprehensive medical care for these vulnerable patients.

With the passage of the Drug Abuse Treatment Act of 2000, buprenorphine has become available to treat opioid addiction in a physician's office without requiring participation in OTPs.¹⁶² Primary care physicians interested in treating opioid-dependent patients can qualify by submitting a notification of intent to the Substance Abuse and

Mental Health Services Administration, which will then provide a waiver. Qualified physicians must have active state and Drug Enforcement Agency licenses, agree to treat no more than 30 patients, and have the capacity to provide or refer patients for ancillary psychosocial services. Physicians must complete 8 hours of training (through the American Society of Addiction Medicine, the American Medical Association, the American Osteopathic Association, or the American Psychiatric Association). Those with board certification in addiction medicine or who have participated in clinical trials of narcotic treatment may be exempt from this training requirement. In general, physicians are expected to keep a supply of buprenorphine in a locked compartment with limited access and maintain a dispensing record. Alternatively, patients may fill prescriptions by using a coupon and return to the office for induction. Initial results with buprenorphine in a private practice setting have been very encouraging^{163,164} and, it is hoped, will be supported by longer-term data.

When providing opioid maintenance therapy in the primary care setting, clinicians should recognize that a supervening illness or injury might necessitate the use of additional analgesics. In treating acute pain in patients receiving buprenorphine maintenance, nonopioid analgesics are preferred. Because patients develop tolerance to long-acting opioids, analgesia is not realized from their regular opioid dose. Therefore, relief of acute pain is dependent on both maintaining their baseline long-acting opioid and providing additional analgesics. For severe acute pain, it may be appropriate to use opioids, although the dose of short-acting opioid analgesic may need to be increased because of cross-tolerance.

Drug addiction is a chronic disease. Mainstreaming addiction treatment will help eliminate some of the damaging stigma associated with opioid maintenance.¹⁶⁵ The advantages of office-based treatment include being more conducive to employment, enhancing patient privacy, and providing ready access to medical care. Combining regular outpatient

medical care and drug abuse care reduces the rate of subsequent hospitalization.¹⁶⁶ Treating opioid dependence as part of a medical practice may also eliminate some of the isolation addicted patients believe is inherent in our nation's OTPs. The recent success in France with buprenorphine should serve as an impetus for more active participation of US primary care physicians in opioid-dependency treatment.¹⁶⁷ With generalization of maintenance treatments in France, there was an increase in the number of opioid-dependent patients undergoing maintenance and a reduction in the number of intravenous users. Further evidence that integration of addiction treatment into primary care is feasible is based on the fact that medical maintenance programs in Washington and Connecticut were recently granted exemptions from key Food and Drug Administration regulations.¹⁶⁸ The movement to expand opioid treatment into primary care practice now appears to be gaining momentum.¹⁶⁹

An integral part of this medicalization effort is improved and expanded training of physicians in the treatment of opioid dependence. A fundamental understanding of the pharmacology of opioid agonist therapy will enable primary care physicians to safely and effectively treat a growing population of patients. Unfortunately, the current level of physician training in the United States concerning addiction medicine leaves much to be desired.^{170,171} Only 8% of US medical schools offer a required course in substance abuse.^{172,173} A recent national survey demonstrated that most primary care physicians inadequately screen for or intervene in diagnosed cases of substance abuse.¹⁷⁴

In conclusion, illicit heroin abuse causes a number of complex health care needs. Opioid agonist therapy has been shown to offer substantial public health, medical, social, and economic benefits. A national effort is under way to promote improved access to opioid treatment. The primary care provider will likely have a major role to play in optimizing the health of opioid-dependent patients. Future initiatives to promote primary care physician education and involve-

ment with illicit drug abuse treatment, coupled with the recent reorganization of federal regulations, should improve outcomes in this vulnerable population.

Accepted for publication March 31, 2003.

We thank William Baker, MD, for reviewing the manuscript; Leslie Amass, PhD, for helpful suggestions; and Adriana Padgett for administrative assistance.

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Announcement

New Editor and New Address for Editorial Correspondence

Effective January 2004, Philip Greenland, MD, succeeded James E. Dalen, MD, MPH, as Editor of the ARCHIVES. Editorial correspondence should be sent to the new address: Philip Greenland, MD, Editor, *Archives of Internal Medicine*, 680 N Lake Shore Dr, Suite 1102, Chicago, IL 60611; phone: 312-503-5387; fax: 312-503-5388; e-mail: archinternmed@jama-archives.org. Manuscript submissions should be sent to Dr Greenland's attention via e-mail attachment to archinternmed@jama-archives.org.