

Pharmacologic Treatment of Heroin-Dependent Patients

Patrick G. O'Connor, MD, MPH, and David A. Fiellin, MD

Patients with heroin dependence frequently present to internists and other physicians for heroin-related medical, psychiatric, and behavioral health problems and often seek help with reducing their heroin use. Thus, physicians should be familiar with the identification and diagnosis of heroin dependence in their patients and be able to initiate treatment of heroin dependence both directly and by referral. Recent research has provided much information concerning effective pharmacologically based treatment approaches for managing opioid withdrawal and helping patients

to remain abstinent. Methadone maintenance and newer approaches using L- α acetylmethadol and buprenorphine seem to be particularly effective in promoting relapse prevention. Although these treatments are currently provided in special drug treatment settings, recent and ongoing research indicates that the physician's office may be an effective alternative site for these treatments.

Ann Intern Med. 2000;133:40-54.

For author affiliations and current addresses, see end of text.

Illicit drug use is responsible for more than 25 000 deaths and \$100 billion in total economic costs annually in the United States (1). Recently, heroin has emerged as the major contributor to these societal problems and costs. Persons suffering from heroin abuse and dependence are an important patient population for general internists. Although patients may present with medical problems that relate directly to heroin or its route of administration (for example, injection), physicians are often unaware of the underlying drug abuse problems (2) and thus may miss the opportunity to offer drug treatment services. Over the past decade, research on heroin dependence has demonstrated that treatment is effective, and new pharmacologically based treatments show promise for the expansion of treatment options (3). Most recently, research has suggested that internists may have a direct role in the provision of drug treatment services for heroin-dependent persons in their offices (4). In this paper, we review the treatment of heroin dependence and emphasize recent developments in pharmacologically based treatment approaches.

Methods

All relevant English-language articles identified through the MEDLINE database from 1968 through January 2000 were systematically searched by using the following key words: *heroin*, *heroin dependence*, *narcotics*, *opioids*, *substance-related disorders*, *substance withdrawal syndrome*, and *narcotic antagonists*. Selected references from these articles and appropriate textbooks were also reviewed.

Definitions and Epidemiology

The most commonly used terms to describe the clinical phenomena of illicit drug use (as well as use of nonillicit

substances) are *substance abuse* and *substance dependence* (Table 1) (5). Thus, these criteria are used when diagnosing opioid abuse and opioid dependence. Heroin, a pure opioid agonist derived from morphine, was initially manufactured in the 1800s for use as an antitussive. Currently, illicit heroin is sold as a white or brownish powder in "bags" or "bundles" (10 bags) and is commonly mixed ("cut") with adulterants, such as sugar or quinine. The availability of increasingly pure heroin has been responsible for an increased incidence of heroin overdose in some locations (6). Increased purity and the risk for HIV infection have resulted in a shift from heroin injection to smoking (7). According to the 1997 National Household Survey on Drug Abuse, approximately 2.5 million Americans have used heroin and the number of persons reporting heroin use over the past month increased fivefold between 1993 and 1997 (8). In addition, data from the 1996 Drug Abuse Warning Network (DAWN) survey documented a 108% increase in heroin-related emergency department episodes between 1990 and 1996 (9).

Common Clinical Problems in Heroin-Dependent Patients

Heroin-dependent patients are at risk for a wide variety of medical, psychiatric, and behavioral health problems. Thus, patients should be routinely screened in clinical practice for heroin abuse and dependence, as well as other substance use disorders (2). Although well-accepted screening instruments (for example, the CAGE questionnaire) have been developed and tested for identifying patients with alcohol use disorders, no parallel instruments have been as rigorously tested for the identification of heroin

abuse and dependence (10). However, modifications of existing instruments (for example, the CAGE-D) have been developed and are under evaluation (2). In the meantime, routine inquiry about past and current use of heroin and other drugs should be performed in all patients. Additional questions on symptoms related to heroin use (such as overdose and withdrawal), routes of administration, and complications associated with heroin use should be asked if indicated.

The medical problems that may result from heroin use are numerous and have been discussed in detail elsewhere (11–14). Psychiatric comorbidity is also highly prevalent among persons who use drugs (15). In a study of 716 treatment-seeking opioid abusers, 47% were found to have psychiatric comorbid conditions (including personality disorders, depression, and anxiety disorders) and psychiatric problems were associated with more severe substance abuse problems (16, 17). Heroin users are also at high risk for abusing other substances, including benzodiazepines, alcohol, and cocaine (16, 18). The problem of dependence on multiple substances can be particularly vexing for patients, physicians, and drug treatment programs, given the complexity of multiple drug effects (for example, different patterns of dependence and withdrawal) seen in these patients. In addition, unlike with heroin, no pharmacologic agent has been demonstrated to effectively treat cocaine dependence (19). Thus, because many opioid-abusing patients concurrently use other drugs with heroin, such as cocaine and alcohol, physicians need to keep in mind that heroin detoxification and methadone maintenance do not necessarily effectively treat withdrawal or reduce the use of other drugs in these patients.

Other behavior-related problems, such as family dysfunction, unemployment, and legal problems, are highly prevalent among heroin-dependent patients (20). In addition, accidents and injuries, criminal behavior, and domestic violence are associated with illicit drug use (21–23).

Because of the wide variety of health problems experienced by heroin-dependent patients, internists are in a unique position to provide enhanced screening and preventive health services to these patients. This includes screening for medical conditions, such as HIV disease and hepatitis; provision of appropriate vaccinations; screening for psychiatric problems, including depression; and assessment for behavior-related problems, such as high-risk sexual activity or physical abuse (Table 2). Patients identified as having psychiatric, behavioral, or physical abuse problems

Table 1. Diagnostic and Statistical Manual of Mental Disorders-IV Criteria for Substance Abuse and Dependence*

Substance abuse: A maladaptive pattern of substance use leading to clinical impairment or distress in those who never met criteria for dependence in the past, manifested within a 12-month period by one or more of the following characteristics:
Recurrent use resulting in a failure to fulfill role obligations at work, school, or home
Recurrent use in physically hazardous situations, such as driving or operating machines
Recurrent substance-related legal problems (for example, arrests)
Continued use despite social or interpersonal problems (for example, physical fights, marital problems)
Substance dependence: A maladaptive pattern of substance use leading to clinical impairment or distress, manifested within a 12-month period by three or more of the following characteristics:
Tolerance, defined by increased amounts used to achieve intoxication or other desired effect or diminished effects with continued use of the same amount of the substance
Withdrawal, manifested by the characteristic withdrawal syndrome, or use of the substance to relieve or avoid withdrawal symptoms
Substance taken in larger amounts or over a longer period than intended
Persistent desire or unsuccessful attempts to cut down or control substance use
Great deal of time spent obtaining the substance, using the substance, or recovering from the effects of substance use
Important social, occupational, recreational activities given up or reduced
Substance use despite knowledge of associated physical or psychological problems

* Adapted from reference 5.

should be referred for appropriate services as indicated. Similarly, social complications should be addressed by referral to social work, family counseling, or other social service agencies if needed.

Treatment Approaches for Patients with Heroin Dependence

Heroin-dependent patients require a thoughtful management approach if they are to be successfully engaged in substance abuse treatment. Once such patients are identified, it is critical for the physician to assess patients' readiness to change their drug-using behaviors (24). Prochaska and DiClemente's six-stage model describing the stages of patients' readiness to change their behaviors has been widely accepted as useful for guiding physicians' initial treatment approach (24, 25). In the "precontemplation" stage, patients are not thinking of their substance use as problematic and are thus unlikely to see a need for treatment. Physicians must help patients overcome denial and move them into the "precontemplation," "contemplation," and "determination" stages rather than referring them to treatment that they believe they do not need (25). After a

Table 2. Routine Screening and Prevention Activities for Clinicians Caring for Drug Users*

Complication	Screening or Prevention Activity
Medical	
Bacterial infection	Pneumococcal vaccine
Viral infection	HIV counseling and testing HIV staging and therapy (if appropriate)
Sexually transmitted diseases	Screening for hepatitis A, B, and C Vaccination against hepatitis A and B Vaccination against influenza
Tuberculosis	Screening for syphilis, gonorrhea, and chlamydia
Malignant conditions	Screening for infection and active disease Screening for cervical cancer Screening for other cancer (as indicated)
Psychiatric	
Depression	Assessment for symptoms
Anxiety and other problems	Assessment for symptoms
Other substance abuse	CAGE questionnaire (alcohol problems) Assessment for use of other illicit drugs (for example, cocaine) Assessment for abuse of prescription drugs
Behavioral	
Accidents and injuries	Assessment for symptoms, signs
Physical or sexual abuse	Assessment for symptoms, signs
Social	
Unemployment, homelessness	Assessment of living situation
Lack of entitlements	Assessment of resources to support medical care

* CAGE = cut down, annoyed, guilty, eye-opener.

patient has entered the “action” phase, physician support for behavior change and treatment is crucial. Of interest, one study of primary care patients who screened positive for alcohol abuse and dependence determined that 63% of patients were in the “action” phase (26). This suggests that supporting relapse prevention is a very important role for physicians (27).

Once patients indicate an interest in treatment, their appropriateness for opioid detoxification or opioid agonist maintenance should be determined. We discuss these two aspects of treatment in detail and emphasize pharmacologic approaches to detoxification and maintenance.

Heroin Withdrawal: Diagnosis and Management The Opioid Withdrawal Syndrome

The opioid withdrawal syndrome consists of signs and symptoms that result in part from neurophysiologic rebound in the organ systems affected by opioids. These systems (and signs and symptoms) include the cardiovascular system (tachycardia, hypertension), central nervous

system (pupillary dilatation, restlessness, irritability, insomnia, craving), gastrointestinal system (nausea, vomiting, diarrhea), skin (piloerection), and mucous membranes (rhinorrhea, lacrimation). Although no widely accepted assessment instrument is available for managing opioid withdrawal, brief, easy-to-use assessment tools that may be useful in clinical practice have been developed (28). Unlike patients undergoing alcohol withdrawal, patients experiencing opioid withdrawal do not typically have such severe complications as seizures, arrhythmias, or delirium tremens. In opioid withdrawal, both subjective (for example, craving) and objective (for example, vomiting) phenomena, especially intense craving, frequently lead to relapse. Thus, the effective management of opioid withdrawal is a critical first step in treating patients. Subsequent referral of detoxified patients to ongoing drug treatment services is also essential for proper and effective management.

The time of onset, peak symptoms, and duration of opioid withdrawal vary, depending on the specific opioid drug being used. For example, symptoms of heroin withdrawal usually begin 4 to 6 hours after last use, peak within approximately 24 to 48 hours, and may last for 7 to 14 days. In contrast, symptoms of withdrawal from methadone, a longer-acting opioid, generally begin 24 to 36 hours after last use and can last for several days to a few weeks. The management of opioid withdrawal combines general supportive measures and pharmacologic treatments. Supportive measures include a safe environment, adequate nutrition, and careful monitoring. Pharmacologic therapies, including opioids and nonopioids, can be provided to alleviate withdrawal symptoms.

Detoxification Using Opioid Agonists

Opioid-based detoxification is based on the principle of cross-tolerance, in which one opioid is replaced with another that is slowly tapered. Methadone is used because it has a long half-life and can be administered once daily. Withdrawal from heroin is usually managed with initial dosages of methadone in the range of 15 to 30 mg per day (29, 30). Although this dosage is generally adequate to control symptoms in many heroin users over a 24-hour period, additional methadone can be given as required on the basis of clinical findings. In acute medical settings, this dosage should be maintained through the second or third day and then slowly tapered by approximately 10% to 15% per day. Longer-term opioid detoxification using

methadone is often available through drug treatment programs. Although a licensed physician can perform methadone detoxification in an inpatient medical setting, outpatient detoxification requires a specially licensed drug treatment program.

More recently, buprenorphine, a partial opioid agonist, has been studied as a treatment for opioid withdrawal. One study randomly assigned 45 heroin-dependent patients to buprenorphine (2 mg) or methadone (30 mg) for 3 weeks, followed by tapering over a 4-week period, and found both approaches to be equivalent (31). Another study that compared a gradual (36 days) to a more rapid (12 days) buprenorphine taper (initially 8 mg) found the gradual approach to be superior (32). A study that compared a 3-day course of buprenorphine (3 mg) to a 5-day course of clonidine reported that these approaches were equivalent (33), although another study found that a longer course of buprenorphine (10 days) was superior to clonidine (34).

Detoxification Using Nonopioid Medications

Nonopioid methods of opioid detoxification have focused primarily on clonidine, an α_2 -agonist, which diminishes norepinephrine activity during opioid withdrawal (35). Early studies demonstrated that clonidine diminished withdrawal symptoms in patients who were withdrawn from methadone (36, 37). Clonidine seems to be most effective in suppressing autonomic signs and symptoms of opioid withdrawal but is less effective for subjective withdrawal symptoms (38). Initial daily doses of up to 1.2 mg in divided doses are commonly suggested. For example, a regimen of 0.1 to 0.2 mg every 4 hours has been used in two clinical trials for heroin withdrawal, with careful monitoring of blood pressure (39, 40). Because it may be less effective in managing subjective withdrawal symptoms, adjuvant therapy (nonsteroidal anti-inflammatory drugs for myalgia, benzodiazepines for insomnia, and antiemetics) may be needed (39, 40).

Although methadone is most commonly used for opioid withdrawal in pregnancy, data from one study suggest that clonidine may be appropriate for some pregnant women with mild withdrawal (41). In addition, in a randomized trial that included 55 patients who received clonidine in a primary care setting, 65% of patients underwent successful detoxification (40). In another study that examined predictors of successful clonidine detoxification,

patients who completed detoxification were more likely to be heroin smokers (rather than intravenous users) and to have abstained from opioids for a longer time before presenting for treatment (42).

Lofexidine, a centrally acting α_2 -adrenergic agonist, has also been evaluated as a treatment for opioid withdrawal, although it has not yet been approved by the U.S. Food and Drug Administration (FDA) for this purpose. In a randomized trial that compared lofexidine to methadone in 86 opioid addicts, lofexidine-treated patients had more severe withdrawal symptoms from days 3 to 7 and again on day 10 but had similar symptoms thereafter. Rates of treatment completion did not significantly differ (43). In two randomized, double-blind trials that compared lofexidine with clonidine in patients dependent on methadone (44) and heroin (45), both agents effectively reduced withdrawal symptoms. Patients treated with lofexidine experienced fewer side effects, especially hypotension. Finally, one study suggested that a 5-day lofexidine regimen decreased symptoms of opioid withdrawal more rapidly than a 10-day regimen (46).

Rapid and Ultrarapid Opioid Detoxification

Because most opioid and nonopioid approaches to detoxification require a prolonged time frame of a week or more, “rapid” and “ultrarapid” opioid detoxification protocols have been developed (47). These protocols use an opioid antagonist (for example, naloxone or naltrexone) to cause an accelerated withdrawal response, with the goal of completing detoxification in time periods from 8 days to as little as a few hours. In addition to an opioid antagonist, both approaches use pharmacotherapies (for example, clonidine, sedation, and general anesthesia) to minimize the acute withdrawal symptoms experienced when opioid antagonists are administered. Because detoxification is completed more quickly, these approaches may have the advantage of minimizing the risk for relapse and allowing patients to enter postdetoxification treatments, such as naltrexone maintenance, more rapidly.

Rapid Opioid Detoxification

Rapid opioid detoxification was first described by Resnick and colleagues (48) in a cohort of 29 methadone-dependent patients who were given naloxone and began naltrexone maintenance within 48 hours in an inpatient setting. Rapid detoxification with naltrexone was first stud-

ied by Charney and coworkers (49) in 40 methadone-maintained patients who were also treated as inpatients. Kleber and coworkers (50) performed the first study of rapid detoxification in heroin-dependent patients in an outpatient substance abuse treatment unit. Most of the 14 participants in this study (86%) successfully began naltrexone maintenance (50).

O'Connor and colleagues examined rapid detoxification in a "primary care" setting in two studies that compared the procedure with clonidine (39, 40). In the first study, in which patients selected their treatment, 94% (60 of 64 patients) in the rapid detoxification group successfully completed detoxification compared with 42% (24 of 57 patients) in the clonidine group (39). In a subsequent randomized clinical trial of 162 patients that compared two methods of rapid detoxification with clonidine, more patients (81%) successfully completed detoxification in the two rapid detoxification groups than in the clonidine group (65%), although the difference did not achieve statistical significance (40). In addition, this study demonstrated that patients who were treated with a rapid detoxification protocol that used buprenorphine experienced less severe withdrawal than did patients in the other two groups (40).

Ultrarapid Opioid Detoxification

Ultrarapid detoxification was first described in a study of 12 opioid-dependent patients who were given naloxone while under general anesthesia (51). Subsequent studies of this technique (47, 52) have used various approaches to detoxification and to sedation or general anesthesia. These studies have generally been small and methodologically limited, have not compared ultrarapid detoxification to other methods, and have provided little long-term follow-up (47). In one study in which detoxified patients were followed up by telephone interview, only 10% continued naltrexone maintenance therapy for 7 months (53). Two studies have demonstrated that substantial withdrawal symptoms persist well beyond detoxification (52, 54). In addition, the expense of this procedure (up to \$7500), the additional risk associated with general anesthesia, and safety concerns (55, 56) limit its usefulness in clinical practice (47). In at least one instance, safety concerns led to the termination of a clinical program that provided ultrarapid detoxification (57). Thus, the widespread use of this procedure has been questioned (47), and some authors have

suggested that the procedure should be limited to clinical trials until its safety and efficacy can be further established (58).

Opioid Detoxification in Physician Offices

At this point, opioid detoxification using opioid agonists is impractical in primary care settings given the lack of research on its effectiveness and the legal restrictions on use of opioid agonists for detoxification to inpatient settings and licensed treatment programs. However, detoxification with clonidine can be effective for some patients and may be feasible in the medical office setting (40). This approach may be worth considering for highly motivated patients who have relatively low levels of dependence and who may not desire or need opioid agonist maintenance treatment. Although rapid opioid detoxification in primary care settings shows promise, more research is required before it can be generalized. Because this approach requires enhanced resources, it may be difficult for most physicians to perform. All patients who are being considered for detoxification should have a feasible and acceptable plan for immediate entry into postdetoxification substance abuse treatment.

Prevention of Relapse by Using Maintenance Medications

Although detoxification is a reasonable short-term approach designed to help selected patients achieve a drug-free state, long-term treatment is designed to prevent relapse to illicit drug use. Various pharmacologic therapies have been developed to promote abstinence from heroin, each designed to be administered in conjunction with counseling. The two pharmacologic strategies that have been developed are based on the use of an opioid antagonist or opioid agonists (Table 3).

Naltrexone

Opioid antagonists block opioid effects, thereby eliminating opioid-induced euphoria, diminishing the reinforcing effects of heroin (59), and potentially extinguishing the association between conditioned stimuli and opioid use (60). Opioid antagonists offer the advantage of treatment with medications that have no addictive potential or tolerance. Naltrexone, approved by the FDA in 1984, is the only opioid antagonist used for maintenance treatment of opioid dependence and is available in tablet form for use in

Table 3. Opioid Antagonists and Agonists Used To Treat Opioid Dependence

Medication	Action	Dose	Frequency	Availability
Naltrexone	Antagonist	50–100 mg orally	Daily or three times per week	Narcotic treatment program
Methadone	Agonist	20–100 mg orally	Daily	Narcotic treatment program
L- α acetylmethadol	Agonist	25–100 mg orally	Three times per week	Narcotic treatment program
Buprenorphine	Partial agonist	8–24 mg sublingually	Daily to three times per week	Pending approval by the Food and Drug Administration

detoxified patients. Naltrexone, a derivative of naloxone, displaces bound agonist (with receptor affinity 20 times that of morphine) (59) and blocks the effects of heroin administration (60). Peak plasma concentrations are achieved within 1 hour, and antagonist effects can last for up to 72 hours (60). For example, dosages of 50, 100, and 150 mg/d can block the effect of 25 mg of intravenous heroin for 24, 48, and 72 hours, respectively (60). Standard dosages of naltrexone are 50 mg/d or 100 mg on Monday and Wednesday and 150 mg on Friday (61). Naltrexone precipitates withdrawal in dependent patients who have not been abstinent for at least 7 days. In some patients, it may be necessary to document abstinence with urine toxicology or through a naloxone challenge. Potential side effects of naltrexone include epigastric pain, nausea, headache, dizziness, nervousness, fatigue, or insomnia. Large dosages (up to 300 mg/d) may be hepatotoxic.

Despite the appealing properties of naltrexone, its clinical usefulness has been limited (19, 59, 61–63). Because naltrexone therapy requires abstinence, induction can be difficult and early dropout is common. In one treatment program, for example, only 15 of approximately 300 patients chose naltrexone instead of detoxification or methadone maintenance; of these 15, only 3 continued receiving therapy for more than 2 months (62). In another program, only 40% of 242 patients remained in treatment over 4 weeks (64). Randomized trials have shown low retention rates (2%) (65) and no efficacy at reducing opioid use compared with placebo (66). Naltrexone has shown some efficacy in the treatment of selected populations (for example, health care professionals) (67) and in combination with fluoxetine and weekly drug counseling (68).

Methadone, L- α Acetylmethadol, and Buprenorphine

Recent research has demonstrated that repeated exposure to opioids, such as heroin, leads to changes in neurons in the locus ceruleus and mesolimbic areas of the brain and

results in the clinical phenomena of tolerance, dependence, craving (69), and reward (70). These neurobiological changes provide insight into the chronic and relapsing nature of heroin dependence and a rationale for opioid agonist maintenance to stabilize these complex systems.

The primary goal of maintenance therapy is to prevent withdrawal and stabilize brain neurochemistry. This is accomplished by replacing heroin, a short-acting, euphorogenic opioid that is characterized by rapidly changing serum levels, with a long-acting, noneuphorogenic opioid that has relative steady-state pharmacokinetics. Opioid agonist maintenance therapies have several advantages over heroin. First, their slower onset of action minimizes their euphoric effect. Second, by occupying brain opioid receptors, they can block the euphoria associated with administration of heroin (competitive antagonism). Third, they eliminate the risk for infection associated with intravenous drug injection (13). Finally, opioid agonist maintenance prevents withdrawal (cross-tolerance) and thereby allows patients to function at a level that permits attention to the psychosocial aspects of treatment.

Methadone

Methadone hydrochloride, a synthetic, long-acting μ -opioid receptor agonist, is available in tablets or as a solution for oral or parenteral use in detoxification, maintenance, and treatment of severe pain. Peak blood levels after oral ingestion occur at 2 to 6 hours. Because of significant protein binding (>90%), levels are constant over 24 hours. Methadone readily crosses the blood–brain barrier and undergoes extensive hepatic metabolism; urinary excretion is increased with acidification (71). Methadone blocks many of the euphoric effects of exogenously administered opioids (72). However, when injected, methadone has potential for abuse in persons who are less opioid-dependent. Long-term treatment with methadone results in tolerance to its analgesic, sedative, and euphoric effects (73), with minimal toxicity. Long-term side effects include

constipation, weight gain, decreased libido, and menstrual irregularities (resulting from hyperprolactinemia). Methadone interacts with medications metabolized by the cytochrome P450 pathway, and plasma levels can be increased by concomitant administration of such medications as cimetidine, erythromycin, ketoconazole, and fluvoxamine (74). Induction of hepatic microsomal enzymes leads to decreased plasma methadone levels and withdrawal due to interactions with alcohol, barbiturates, phenytoin, carbamazepine, isoniazid, rifampin (74, 75), retinovir (76), nevirapine (77), and possibly efavirenz (78). Methadone is a racemic compound, and the D-isomer is an *N*-methyl-D-aspartate (NMDA)-receptor antagonist. Because of this property, it may be useful in patients with a high tolerance to opioids and in the management of neuropathic pain (79–81).

Current federal regulations mandate that methadone can be prescribed for detoxification or maintenance only by physicians with a special registration from the U.S. Drug Enforcement Administration (DEA) (82). This DEA registration is separate from the standard registration required for the prescription of controlled substances and is contingent upon compliance with DEA security regulations and other regulatory processes resulting from the Narcotic Addict Treatment Act of 1974 (82).

The efficacy of methadone has been demonstrated empirically in several experimental and observational studies (83–88). In one clinical trial of 169 persons seeking treatment for opioid dependence, opioid-positive results on urine toxicology tests decreased from 63% to 29% at 1-month follow-up in those randomly assigned to receive methadone. In contrast, a control group that remained on a waiting list for treatment had no change in their rate of opioid-positive urine test results (62% compared with 60% at 1 month) (89). An analysis of methadone maintenance by Ball and Ross (85) involved 633 patients in six methadone treatment programs in New York, New York; Philadelphia, Pennsylvania; and Baltimore, Maryland. The prevalence of intravenous drug use decreased from 81% at admission to 29% at 4 years for the 388 patients who continued to receive treatment (85). Among the 105 patients who discontinued treatment, 82% resumed intravenous drug use by 12 months (85). These findings were recently replicated in the Drug Abuse Treatment Outcome Study (DATOS). In 727 patients who started methadone treatment, weekly heroin use dropped from 89% before treatment to 28% at 1 year (90).

In addition to decreasing heroin use, methadone maintenance has demonstrated other benefits (88). In one study, criminal behavior measured as “crime days” per year decreased from a mean of 238 days before treatment to 32 days at 4 years of treatment (85). Similarly, the DATOS study showed a decrease in the number of patients who reported illegal activity (29% before treatment to 14% at 1-year follow-up [90]). Methadone maintenance treatment has also been shown to reduce risk behavior for HIV infection and seroconversion in injection-drug users (91–94). For example, Metzger and colleagues demonstrated that HIV seroconversion occurred in 22% of 103 out-of-treatment patients compared with 3.5% of 152 patients receiving methadone maintenance (92).

As seen with other medications, methadone dose can have a profound effect on therapeutic efficacy. The original study by Dole and Nyswander that demonstrated the efficacy of methadone in decreasing heroin use was conducted with daily doses ranging from 50 to 150 mg (86). Subsequently, several studies have demonstrated that higher doses of methadone (>50 mg) are associated with better treatment retention and decreased illicit drug use (95–98). A recent trial noted lower rates of opioid-positive urine samples (53% compared with 62%; $P < 0.05$) in patients receiving 80 to 100 mg of methadone compared with those receiving 40 to 50 mg (96). However, because of misconceptions about the role of methadone dose (99), many programs are reluctant to prescribe and patients are reluctant to take optimal doses. Thus, treatment practices and outcomes vary considerably (100).

Methadone has been almost exclusively provided through narcotic treatment programs since 1972, when the FDA created regulations that specified the types and amount of treatment services to be provided (85). More than 900 programs currently exist in the United States, most in large cities. These programs usually have multidisciplinary staff who take a multilevel approach to determine frequency of program contact (daily compared with weekly) on the basis of federal regulations, duration of treatment, urine toxicology tests, patient compliance, and evidence of social stability.

Patient progress toward abstinence is monitored by patient self-report and assessment of results of urine toxicology tests. Continued illicit drug use is met with various strategies, including loss of privileges for take-home medication, increased frequency of clinic visits, and changes in medication dosage to combat withdrawal symptoms. Al-

though evaluations of programs demonstrate continued illicit drug use in the overall client populations (85, 100), persistent drug use that does not respond to contingency management usually results in detoxification and program dismissal (85, 100, 101).

L- α Acetylmethadol

L- α acetylmethadol (LAAM) is a long-acting derivative of methadone that was approved by the FDA for maintenance treatment in 1993. It is available in oral and parenteral form and is metabolized to more potent metabolites that have a prolonged duration of action. Peak blood levels are seen 4 to 8 hours after oral administration, and opioid withdrawal can be prevented for up to 72 hours (102, 103). This long duration of action makes it possible for patients to receive doses every 2 to 3 days, instead of daily as with methadone. Infrequent side effects noted with LAAM are similar to those seen with methadone.

Early work (104) helped to establish that LAAM was efficacious in preventing opioid withdrawal, and subsequent research provided evidence supporting the use of LAAM for opioid maintenance. These comparisons have demonstrated similar rates of retention in treatment (105–108) and opioid-positive results on urine tests (106–110) in patients receiving methadone and LAAM. A recent meta-analysis of 14 randomized controlled trials comparing LAAM with methadone maintenance noted slightly greater treatment retention for methadone but a trend toward a greater decrease in illicit drug use with LAAM (111). Recent trials have demonstrated a dose-related decrease in heroin use in patients treated with LAAM (112, 113). For example, in one study, 180 patients were randomly assigned to receive LAAM three times per week: Monday, Wednesday, and Friday at 25, 25, and 35 mg; 50, 50, and 70 mg; and 100, 100, and 140 mg, respectively. Patients who received higher doses experienced more abstinence (112).

Despite the advantages of LAAM, including more steady and sustained agonist activity than methadone, dosing three times per week, reduced dispensing costs, and decreased risk for diversion due to lack of “take-home” doses, a relatively small proportion of patients enrolled in opioid agonist maintenance receive it. In 1996, a survey found that only 62 of 750 treatment programs offered LAAM (114). Reasons given for this slow acceptance were the additional state and local regulatory processes that are

required, the reluctance of narcotic treatment programs to adopt new procedures, and the delay in insurance reimbursement (114).

Buprenorphine

Buprenorphine hydrochloride, an investigational maintenance drug with unique pharmacologic properties, has not yet been approved for use as a maintenance medication but is being considered for approval by the FDA. If approved, buprenorphine, unlike methadone and LAAM, may be available outside of regulated narcotic treatment programs (115). Buprenorphine is a partial rather than full agonist at the μ -opioid receptor and a weak antagonist at the κ -receptor; thus, it may cause fewer withdrawal symptoms and have less potential for abuse, respiratory depression, and overdose (31, 116, 117). In addition, buprenorphine has a slow rate of dissociation from opioid receptors, which results in a long duration of action.

Buprenorphine exists in parenteral form, a tablet for sublingual administration, and a new sublingual tablet that combines buprenorphine with naloxone. Buprenorphine is poorly absorbed through the gastrointestinal tract; however, sublingual administration results in plasma concentrations that are 60% to 70% of parenteral doses (118). Constipation was the only significant side effect noted in a recent dose-ranging study of buprenorphine (115). Buprenorphine is metabolized by the cytochrome P450 pathway, and preliminary data suggest that potential drug–drug interactions exist between buprenorphine and benzodiazepines (119), fluoxetine, fluvoxamine (120), and ritonavir (76).

Jasinski and coworkers (116) established the opioid agonist effects of buprenorphine and its ability to block the effects of exogenous morphine administration. Subsequent research established its ability to suppress self-administration of heroin (121). Clinical trials have demonstrated the efficacy of buprenorphine over placebo in decreasing illicit opioid use (122) and have helped establish the safety and efficacy of dosages ranging from 8 to 16 mg/d (115). In addition, it has been shown that daily and alternate-day buprenorphine dosing have equivalent effects on opioid withdrawal symptoms (123–125) and illicit opioid use (125). Administration three times per week also seems to be effective (4).

Clinical trials have shown that buprenorphine and low doses of methadone (20 to 30 mg) have similar effects on retention and illicit opioid use (126, 127). Comparisons

with higher doses of methadone (35 to 90 mg) have yielded inconclusive results; one trial demonstrated improved efficacy (128) and another demonstrated reduced efficacy (129). Dose-ranging studies with buprenorphine have reported improved treatment outcomes with dosages of 6 to 16 mg/d compared with dosages of 1 to 4 mg/d (115, 129).

Nonpharmacologic Services for Opioid Agonist Maintenance

Nonpharmacologic or psychosocial counseling services are key components of the successful use of medications for opioid agonist maintenance. Psychosocial counseling services can vary by program and therapist (85, 100, 101). Common components of individual counseling services include 1) addressing motivation for treatment, 2) teaching coping skills, 3) changing reinforcement contingencies, 4) fostering management of painful effects, 5) improving interpersonal functioning, and 6) fostering compliance with and retention in pharmacotherapy (130). Although individual sessions are the hallmark of these services, narcotic treatment programs are often structured to provide other ancillary services, including group and family therapy, vocational counseling, case management, social service liaison, and education classes (85).

McLellan and colleagues (131) demonstrated the importance of psychosocial counseling and ancillary services on treatment outcomes in methadone maintenance in a 6-month trial. New patients were randomly assigned to receive one of three levels of care: 1) methadone alone, 2) methadone plus standard counseling services, or 3) methadone and standard counseling services, plus on-site medical and psychiatric care, employment counseling, and family therapy services (131). A dose-response effect was observed, and patients who received the standard or enhanced services had higher treatment retention rates than patients who received methadone alone. In addition, patients in the enhanced group had the fewest opiate-positive results on urine tests (131). A cost-effectiveness analysis of these patients after 1 year showed that the annual cost per abstinent client was \$16 485 for low levels of support, \$9804 for intermediate levels of support, and \$11 818 for high levels of support (132).

The duration of opioid agonist maintenance varies substantially according to patient characteristics. A recent national survey of methadone treatment programs demon-

strated that 58% of programs encouraged their clients to undergo detoxification within 3 to 12 months of admission and that the average length of treatment was 20 months (100). However, on the basis of the high rates of relapse observed in detoxified patients (85, 95) and the risk for complications resulting from relapse (11), some authorities advocate a policy of providing treatment as long as treatment is clinically indicated and the patient continues to benefit from treatment, wishes to remain in treatment, remains at risk for relapse to heroin use, and has no significant side effects (133).

Opioid Maintenance in Physician Offices

Because of the success of long-term methadone treatment of opioid-dependent patients and growing evidence that primary care physicians can play a major role in treating alcohol problems (134) and possibly heroin dependence (4), interest has increased in providing ongoing opioid maintenance therapy from physicians' offices (82, 135, 136). "Medical maintenance" is defined by Novick and colleagues (135) as the treatment by primary care physicians of rehabilitated methadone maintenance recipients who are stable and employed, are not abusing drugs, and do not need supportive services. The potential advantages of medical maintenance include the ability to expand opioid maintenance treatment capacity and a recognition of the view that for some patients, opioid dependence is a chronic disease with a persistent neurochemical disorder (137). In addition, there is a desire to allocate traditional drug treatment services more appropriately and to increase the number of practicing physicians involved in the care of opioid-dependent patients (82, 88). Finally, the physician's office may provide treatment in a setting that minimizes the stigma of drug treatment programs and limits contact with drug-using patients.

Published reports of two successful medical maintenance programs support the idea of transferring the care of stabilized, methadone-maintained patients to these settings (135, 136, 138). One program in New York City reported 85% retention at 3 years in 100 patients whose care was transferred from conventional methadone maintenance treatment to medical maintenance (136). A randomized clinical trial compared medical maintenance with maintenance in a methadone program and reported 1-year retention rates of 73% for patients in both groups (138). Of interest, a recent clinical trial showed improved retention

and decreased illicit opioid use when buprenorphine was administered three times per week in a primary care setting compared with thrice-weekly buprenorphine maintenance in a formal drug treatment program (4).

An important unanswered question about medical maintenance is patient selection. Previous programs (135, 136, 138) have used patient factors—including longer duration of methadone maintenance without relapse, stable means of financial support, absence of concurrent substance abuse or dependence, absence of substantial untreated comorbid psychiatric disease, and patient motivation to participate—to identify successful patients for medical maintenance. Of note, the duration of ongoing methadone maintenance required before eligibility for medical maintenance has varied between 5 years (135, 136) and 1 year (138). In contrast, in a study that examined the efficacy of buprenorphine in a primary care setting, some enrolled patients were not receiving any treatment at the time of enrollment (4).

Medical maintenance pilot programs are under way in Connecticut, Maryland, New York, and Washington State. Results from these efforts are expected to inform decisions regarding types of patients, physician training, and the role of the treatment program. In these programs, the traditional treatment program serves as the “hub” and the physician’s offices represent “spokes” of a wheel. Therefore, patients receiving medical maintenance remain registered in their treatment program and the medical maintenance physicians are enrolled as medical staff in that program; this can facilitate transfer of the patient to the “hub” program in the event of a substantial relapse. The success of the early models of medical maintenance has resulted in a call for the expansion of these programs. A recent survey found that 30 state authorities favored off-site physician linkages with methadone programs as an adjunct to traditional methadone maintenance treatment (139). Until the models for these programs are fully developed and the legal restrictions on them are changed, office-based opioid maintenance will not be feasible. However, recent initiatives in office-based maintenance are promising and may be feasible soon.

Matching Pharmacologic Approaches to Patients with Heroin Dependence

The choice between detoxification and opioid agonist therapy for pharmacologic management of heroin-depen-

dent patients can be difficult, and no clear guidelines exist. Federal requirements have evolved from the fairly restrictive criteria that were in place when methadone was introduced in the 1960s (140). Initially, candidates for methadone maintenance were required to be 21 to 40 years of age, to have been addicted to heroin for at least 4 years, to have evidence of relapse with previous attempts at detoxification, and to have no major medical or psychiatric problems or polysubstance abuse. Pregnant women were not eligible. Current criteria for maintenance with methadone or LAAM specify that patients must be at least 18 years of age and have at least a 1-year history of opioid addiction and evidence of physiologic dependence (140). Medical, psychiatric, or comorbid substance use disorders do not indicate obligatory exclusion, and pregnant women can be admitted under modified criteria (for example, heroin dependence less than 1 year with current use) (140).

These regulations notwithstanding, the decision to institute opioid agonist maintenance involves a careful consideration of clinical characteristics and an evaluation of the risks and benefits for an individual patient. For example, an attempt at detoxification would be an appropriate first choice of treatment for a patient with a low level of heroin use, few symptoms of dependence, and no substantial risk for acquiring or transmitting bloodborne infections (for example, through intranasal heroin use). However, for patients with a long history of dependence, previous failed attempts at detoxification, high levels of heroin use, and substantial risk for infectious complications (for example, injection drug use or seropositive HIV status), opioid agonist or partial agonist maintenance is likely to be more effective in reducing the harm associated with heroin use and in promoting abstinence. Clearly, further research on the differential roles of detoxification and maintenance therapies is needed to identify the most appropriate strategies to match patient to treatment.

Summary: The Roles of Physicians in the Management of Heroin-Dependent Patients

Patients who are dependent on heroin or other illicit drugs provide unique challenges for physicians. Because heroin dependence has major medical sequelae, patients are likely to interact with various aspects of the health care system, including the emergency department, hospital, and physician’s office. Physicians in these settings therefore need to be able to take an active role in the identification

Table 4. Additional Resources for Treatment of Opioid Dependence

A Guide to Substance Abuse Services for Primary Care Clinicians. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment; 1997. Treatment Improvement Protocol Series, no. 24

Effective Medical Treatment of Opiate Addiction. National Institutes of Health Consensus Statement. 1997;15:1-41

The National Institute on Drug Abuse (<http://www.nida.nih.gov>)

and management of patients with drug problems if they are to provide effective and efficient health care.

The major roles for physicians in managing heroin-dependent patients and patients who use other substances include universal screening for substance use, assessing patients for health and behavioral problems related to substance use, and providing appropriate preventive health services. In addition, physicians should be able to provide an appropriate level of advice and counseling and refer patients to appropriate specialty services for treatment of drug dependence. Because these patients often present with a diverse set of needs, careful coordination with physicians and professionals from other disciplines is usually necessary. Despite these complexities, internists and other primary care physicians are well suited to provide longitudinal care for heroin-dependent patients. Additional resources on treatment of opioid dependence can be found in **Table 4**.

Ongoing and future research promises to further unravel the mysteries of drug dependence and provide new insights into patient management. New treatment approaches are constantly being evaluated and developed. Opioid maintenance treatment has been particularly successful in this regard, and new approaches to patient-treatment matching are under evaluation. Office-based treatment strategies may increase access to maintenance treatment while greatly expanding the role of internists and other physicians in patient management. Although prevention of drug abuse is a new science that holds promise for the future, recognition and treatment of drug abuse are essential given the impact of opioid dependence on individual persons and on society.

From Yale University School of Medicine and Yale–New Haven Hospital Primary Care Center, New Haven, Connecticut.

Grant Support: Dr. Fiellin is supported by the National Institute on Drug Abuse Physician Scientist Award (K12 DA00167).

Requests for Single Reprints: Patrick O'Connor, MD, MPH, Yale University School of Medicine, 333 Cedar Street, Box 208025, New Haven, CT 06520.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Drs. O'Connor and Fiellin: Yale University School of Medicine, 333 Cedar Street, Box 208025, New Haven, CT 06520.

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Congratulations to Susan Rakley, MD, of Northbrook, Illinois, winner of the 1999 *Annals* Poetry Prize. Dr. Rakley's poem was published in the 19 October 1999 issues of *Annals* (vol. 131, no. 8) and is reprinted here.

On Rounds, 7 a.m.

**Yes, I have something in my eye,
I have
death
in my eye.
Curious that an ordinarily inert substance
like death
can cause such a reaction
when deposited in an unaccustomed place
like an eye.**

Susan Rakley, MD
Northbrook, IL 60062