Treating Opioid Dependence

Growing Implications for Primary Care

Mori J. Krantz, MD; Philip S. Mehler, MD

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.

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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effective treatments that shift

among physicians treating narcotic

treatment for addiction was essen-

narcotics to opioid-dependent

HISTORICAL PERSPECTIVE

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addicts. Treatment for addiction was

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The Office of National Drug

Post–Food and Drug Administration regu-

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Societal and Human Services. Washington State

Opioid Treatment

Office-Based Opioid Treatment

JCAHO, CARF, COA, Washington State, Missouri

Accreditation

Opioid Treatment Programs

Center for Substance Abuse Treatment

Substance Abuse and Mental Health Services Administration

US Department of Health and Human Services

Figure. Recent evidence suggests

SCIENTIFIC BASIS

OF OPIOID MAINTENANCE

The Office of National Drug Control

Post–Food and Drug Administration regulatory

of opioid agonist therapy for addiction. JCAHO

HISTORICAL PERSPECTIVE

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addicts. Treatment for addiction was

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the use of the synthetic opioid metha-

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The Office of National Drug

The Office of National Drug

the 1955 publication of a position

interest in narcotic

TENANCE TREATMENT PARADIGM. 31

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The Office of National Drug

Figure. Recent evidence suggests

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resulted in significant trepidation

The Office of National Drug

The early observations of Dole

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The early observations of Dole

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ing methadone maintenance. 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. Studies have also demonstrated that treatment with opioid agonists reduces the rate of criminal activity. 

Hepatitis C is the most common cause of chronic hepatitis in the United States and is endemic in patients undergoing methadone maintenance. Most heroin injectors contract hepatitis C early in their injection drug use. 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. 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. Methadone maintenance dramatically reduces the frequency of injection drug use and has also been shown to decrease sexually related high-risk behaviors. Consequentially, 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. Methadone maintenance has also been found to be a cost-effective intervention, with a cost of $8200 per quality-adjusted life-year gained. 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.

**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. This may be due to dysphoria related to blockade of endogenous opioids with naltrexone. Currently, there are 3 approved opioid agonists 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. It has an onset of action within 30 minutes 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, which helps reinforce abstinence. Once a therapeutic dose is achieved, patients frequently can be maintained for many years with the same dose.

Methadone hydrochloride is available in 5- and 10-mg tablets as 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. Methadone is metabolized extensively in the liver, and its excretion rate can be accelerated by urinary acidification. Elimination is slower in women. 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. The minimal effective dose is usually 50 mg, but some individuals need much larger doses. Because methadone is metabolized via the cytochrome P450 pathway, phenytoin, carbamazepine, barbiturates, isoniazid, and certain HIV protease inhibitor medications can reduce plasma methadone levels. 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 occurred 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 weaknesses 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 Norlevomethadyl 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

<table>
<thead>
<tr>
<th>Medication Description</th>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>Contraindicated (precipitates opioid withdrawal)*</td>
<td>Naloxone hydrochloride</td>
</tr>
<tr>
<td>Contraindicated (precipitates opioid withdrawal)*</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>Contraindicated (precipitates opioid withdrawal)*</td>
<td>Naloxone hydrochloride</td>
</tr>
<tr>
<td>Decreases plasma methadone concentration†</td>
<td>Carbamazepine</td>
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<tr>
<td>Decreases plasma methadone concentration†</td>
<td>Phenobarbital</td>
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<tr>
<td>Decreases plasma methadone concentration†</td>
<td>Cimetidine</td>
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<tr>
<td>Decreases plasma methadone concentration†</td>
<td>Ethanol</td>
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<tr>
<td>Decreases plasma methadone concentration†</td>
<td>Ketaconazole</td>
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<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Ciprofloxacin</td>
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<td>Increases plasma methadone concentration‡</td>
<td>Clomipramine</td>
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<td>Increases plasma methadone concentration‡</td>
<td>Fluvoxamine maleate</td>
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<td>Increases plasma methadone concentration‡</td>
<td>Fluoxetine</td>
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<td>Increases plasma methadone concentration‡</td>
<td>Haloperidol</td>
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<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Hydroxyzine</td>
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<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Meperidine</td>
</tr>
<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Naloxone hydrochloride</td>
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<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Norbuprenorphine</td>
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<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Pentazocine</td>
</tr>
<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Rifampin</td>
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<tr>
<td>Increases plasma methadone concentration‡</td>
<td>Tramadol hydrochloride</td>
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<td>Increases plasma methadone concentration‡</td>
<td>Carbamazepine</td>
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<td>Rifampin</td>
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<td>Phenytoin</td>
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*Direct antagonism of methadone action at the opioid receptor site.
†Through inhibition of hepatic cytochrome P450 activity.
‡Through induction of hepatic cytochrome P450 activity.

Table 3. Pharmacotherapy of Heroin Addiction

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

*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.90,91 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 agonist93-95 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 monobase 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. Others have questioned the effectiveness of these enhanced programs. 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. 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. Seventy-five milligrams of levomethadyl acetate provides opioid blockade and withdrawal suppression for up to 96 hours. A recent meta-analysis also found levomethadyl and methadone maintenance to be comparable with regard to ongoing illicit drug use.

From a practical standpoint, levomethadyl’s niche may be in patients 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 methadone 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. 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. 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. 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. Another study showed high-dose methadone to be more efficacious than 8 mg of buprenorphine hydrochloride concerning retention and ongoing opioid use. 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. Another report demonstrated the utility of buprenorphine in opioid-dependent patients with concurrent cocaine abuse. Most studies of buprenorphine have been based on daily doses. Johnson et al 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...
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.122

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 ultra-rapid 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.122 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 relapse 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 α2-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


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.162 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.160 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 encouraging163,164 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 analgesics 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 involvement with illicit drug abuse treatment, coupled with the recent reorganization of federal regulations, should improve outcomes in this vulnerable population.

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