

## Clinical Practice

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

## OFFICE-BASED TREATMENT OF OPIOID-DEPENDENT PATIENTS

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A 30-year-old man reports a two-year history of heroin use. For the past year, he has been using intranasal heroin every day. He has undergone detoxification twice at a local opioid treatment program but began using heroin within two days after discharge each time. He has heard of methadone but fears that he will lose his business if he is recognized attending the local program. How should this patient be treated?

### THE CLINICAL PROBLEM

#### Diagnosis

Opioid dependence is characterized by repeated self-administration of opioids and encompasses physiologic dependence and addictive behavior.<sup>1</sup> Exposure to opioids causes neural changes that produce tolerance, dependence, and withdrawal. One set of criteria for this diagnosis is shown in Table 1.<sup>2</sup>

#### Epidemiology of Opioid Dependence

There are an estimated 800,000 opioid-dependent persons in the United States and 410,000 persons who began using heroin between 1996 and 1998.<sup>3,4</sup> Increased purity of heroin has resulted in higher rates of intranasal use, and only 37 percent of new users have injected heroin.<sup>3</sup> Of patients entering treatment for heroin dependence in 1998, 50 percent were non-Hispanic white, 25 percent were Hispanic, and 22 percent were non-Hispanic black. Sixty-two percent had at least a 12th-grade education, and 36 percent had health insurance.<sup>5</sup> Almost half the patients beginning

**TABLE 1. CRITERIA FOR A DIAGNOSIS OF SUBSTANCE DEPENDENCE.\***

Substance dependence is a maladaptive pattern of substance use leading to clinical impairment or distress, manifested within a 12-mo period by 3 or more of the following:
Tolerance defined by either 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 by the use of the substance to relieve or avoid withdrawal symptoms
Taking of the substance in larger amounts or over a longer period than intended
Persistent desire or unsuccessful attempts to cut down or control substance use
A great deal of time spent in 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 awareness of physical and psychological problems

\*Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.<sup>2</sup>

methadone maintenance therapy had coexisting psychiatric conditions.<sup>6</sup>

Abuse of prescription opiates is common among patients entering treatment programs for opioid dependence.<sup>5</sup> Reports of abuse of oxycodone and hydrocodone increased 68 and 31 percent, respectively, from 1999 to 2000.<sup>7</sup>

Despite the increased prevalence of opioid dependence, only 180,000 opioid-dependent persons in the United States currently receive the most effective treatment — opioid-agonist maintenance therapy with methadone or levomethadyl acetate — through opioid treatment programs, and five states do not have such services.<sup>1,4,8</sup> This disparity has resulted in calls for expanded treatment services.<sup>1,4</sup>

#### Opioid Treatment Programs as Compared with Office-Based Care

Treatment for opioid dependence has traditionally been provided in federally regulated programs with limited involvement by physicians. (There is geographic variation in the availability of these treatments, and there is a Web site to help locate treatment facilities.<sup>9</sup>) In contrast, office-based treatment of opioid dependence is a new model of care that involves the coordination of services by a physician's office.

Advantages of providing office-based treatment include increasing the availability of treatment, the ability to tailor services to the needs of patients, minimization of the potential stigma associated with treatment, and limiting patients' contact with drug-abus-

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ing patients. Challenges to implementing office-based treatment include the need for physicians to acquire clinical experience with a new population of patients and the provision of appropriate psychosocial services. In addition, logistic considerations, such as those related to the toxicologic testing of urine specimens, must be addressed, and systems must be developed to minimize inappropriate prescribing and diversion of medication by patients to others and to ensure confidentiality.<sup>10</sup>

#### Federal Initiatives Regarding Office-Based Treatment

Recent federal initiatives make office-based treatment more feasible in the United States. New rules have transferred administrative responsibility for the use of opioid medications in the treatment of opioid dependence from the Food and Drug Administration (FDA) to the Substance Abuse and Mental Health Services Administration.<sup>11</sup> The Center for Substance Abuse Treatment can provide program-wide exemptions from regulatory requirements to opioid treatment programs that work with allied physicians who wish to provide office-based methadone treatment.<sup>12,13</sup>

The Drug Addiction Treatment Act<sup>14</sup> allows qualified physicians to prescribe to opioid-dependent patients Schedule III, IV, and V medications that are approved for treatment of opioid dependence. Although there are currently no medications that meet these criteria, the Drug Enforcement Agency has proposed that buprenorphine be listed as a Schedule III medication, and this medication is currently under review for FDA approval.<sup>15</sup> The act stipulates that qualified physicians be licensed and hold an addiction-related certification from the American Board of Medical Specialties, the American Osteopathic Association, or the American Society of Addiction Medicine. Alternatively, physicians may qualify if they receive at least eight hours of training, provided by designated medical societies, in the care of opioid-dependent patients.<sup>14,16-20</sup> The act stipulates that physicians must have the capacity to refer patients for counseling and ancillary services, although it does not prescribe what these services should entail. Each physician or practice is allowed to treat a maximum of 30 such patients simultaneously.

To date, training to meet the requirements of the Drug Addiction Treatment Act has followed a curriculum developed with funding from the Center for Substance Abuse Treatment that covers opioid pharmacology, common coexisting medical and psychiatric conditions, logistic considerations for the office, the prescribing of medication, and patient confidentiality.<sup>21</sup> Training is offered in conjunction with meetings of medical societies, including the American Society of Addiction Medicine and the American Academy of Addiction Psychiatry,<sup>16,17</sup> and on-line programs are

available.<sup>17,20</sup> The requisite eight-hour training represents the minimal requirement, and physicians will benefit from additional training, experience, and collaboration with opioid-treatment programs.

#### STRATEGIES AND EVIDENCE

Outpatient treatments for opioid dependence include nonpharmacologic and pharmacologic therapies. Pharmacologic treatments include opioid agonists (methadone, levomethadyl acetate, and if it is approved, buprenorphine) and an opioid antagonist (naltrexone); these are discussed in the following sections. Both therapy with naltrexone and nonpharmacologic therapy often begin with the initiation of abstinence by means of detoxification.

Nonpharmacologic therapy involves individual or group psychosocial treatments intended to prevent relapse. Although there is some variability among treatment programs, group counseling is generally provided on a weekly basis in such programs, with individual counseling on a monthly basis. Psychosocial counseling services are available to patients for the duration of pharmacotherapy. Although therapies vary, they tend to use one or more of the following tactics: addressing motivation, teaching coping skills, providing positive or negative reinforcement, helping patients deal with painful emotions, improving interpersonal functioning, and when appropriate, fostering compliance with pharmacotherapy.<sup>22</sup>

The extent of psychosocial counseling and ancillary services has an effect on outcomes in patients receiving pharmacologic treatment, with increases in number and duration of services producing improved outcomes. One study has demonstrated higher retention in the treatment program and fewer opioid-positive urinalyses in patients receiving methadone and psychosocial and other services than in patients receiving methadone alone.<sup>23</sup>

#### Detoxification

Detoxification involves the pharmacologic management of the opioid abstinence syndrome. The opioid abstinence syndrome is often a motivation for abstinent patients to reinstitute drug use. Symptoms include arthralgias, myalgias, nausea, irritability, and insomnia. Signs include tachycardia, hypertension, mydriasis, rhinorrhea, piloerection, and diaphoresis.

The manifestations of the opioid abstinence syndrome can be ameliorated or managed by the following approaches to detoxification: reduction of the dose of opioids with the use of opioid agonists; use of  $\alpha_2$ -adrenergic agonists (e.g., clonidine); and rapid or ultrarapid detoxification with the use of an opioid antagonist and other medications (Table 2). Rapid detoxification and ultrarapid detoxification are designed to shorten the duration of the opioid abstinence syn-

TABLE 2. MEDICATION FOR THE TREATMENT OF OPIOID DEPENDENCE.\*

MEDICATION	INDICATION	ACTION	DOSE†	FREQUENCY	ADVERSE EFFECTS	CONTRAINDICATIONS
Methadone	Pharmacologic withdrawal and maintenance	Opioid agonist	20–100 mg orally	Daily	Constipation, respiratory depression, dizziness, sedation, nausea, diaphoresis	Hypersensitivity to methadone
Levomethadyl acetate	Maintenance	Opioid agonist	25–100 mg orally	Thrice weekly	QT prolongation, constipation, abdominal pain	Hypersensitivity to levomethadyl acetate, known or suspected QT prolongation, bradycardia, concomitant use of class I or II antiarrhythmic drugs or monoamine oxidase inhibitors, concomitant medications that induce activity of cytochrome P-450 3A4
Buprenorphine‡	Pharmacologic withdrawal and maintenance	Partial opioid agonist	8–24 mg sublingually	Daily to thrice weekly	Respiratory depression, constipation, headache§	Hypersensitivity to buprenorphine, concomitant large doses of opioid agonists
Clonidine	Pharmacologic withdrawal	$\alpha_2$ -Adrenergic agonist	0.1–0.3 mg orally	Every 6 hr	Bradycardia, hypotension, rebound hypertension, drowsiness, dry mouth	Hypersensitivity to clonidine
Naltrexone	Pharmacologic withdrawal and maintenance	Opioid antagonist	50–100 mg orally	Daily or thrice weekly	Anxiety, nausea, abdominal pain, myalgias, arthralgias	Sensitivity to naltrexone, acute hepatitis, hepatic failure, concomitant use of opioid analgesics

\*All medications except buprenorphine are currently available through opioid treatment programs and physicians' offices. For the use of methadone, a physician must have a relationship with an opioid treatment program that has received a special federal exemption to allow office-based care.

†Higher doses may be necessary and more effective. Each patient's dose should be gradually increased to achieve the optimal clinical response.

‡Active clinical studies are currently funded by the National Institute on Drug Abuse.

§Dizziness and nausea occur with intravenous administration.

drome and allow for the earlier initiation of treatment with naltrexone, psychosocial interventions, or both. Reduction of the dose of opioids with the use of opioid agonists usually involves the substitution of a medication for which there is cross-tolerance, such as methadone. Such reduction results in a syndrome that is less severe than that which usually follows cessation of heroin use. More gradual reductions with the substitution of methadone (e.g., 3 percent per week over the course of 30 weeks) are associated with higher rates of retention and lower rates of illicit-drug use than more accelerated reductions (e.g., 10 percent per week over the course of 10 weeks).<sup>24</sup> Although clonidine is not approved in the United States for the management of the opioid abstinence syndrome, it may be useful in doses of 0.1 to 0.2 mg every four hours.<sup>25,26</sup> Adjuvant medication for nausea and arthralgias should be provided during detoxification.

The long-term efficacy of detoxification is limited. One study involving 80 patients demonstrated a relapse to opioid use in 71 percent of patients within six weeks.<sup>27</sup> Approximately 85 percent of subjects who underwent a 180-day detoxification reported ongoing heroin use at 1 year, with drug use reported on 14 of the previous 30 days, on average.<sup>28</sup> The literature on rapid and ultrarapid detoxification is limited because there have been few controlled, randomized trials, and data are lacking on outcomes beyond two weeks.<sup>29</sup>

The risks associated with detoxification with the use of opioid agonists or clonidine are relatively minor and are related to the severity of withdrawal symptoms and side effects of the medications (Table 2). Judicious dosing and supervised distribution can prevent oversedation and respiratory depression. If oversedation occurs, it can be treated with naloxone. Hypotension resulting from clonidine use can be minimized with monitoring of vital signs and careful dosing. Rapid and ultrarapid detoxification should be managed only by physicians with extensive experience in the treatment of opioid-dependent patients and in the use of these particular techniques.

#### Office-Based Detoxification

Current federal restrictions prevent office-based physicians from undertaking detoxification with the use of methadone for more than three days.<sup>11</sup> Office-based physicians undertaking detoxification can currently choose between clonidine alone and, in very limited circumstances (e.g., only if they have previous experience with the method), rapid detoxification with clonidine and naltrexone. Buprenorphine, a partial mu-opioid agonist, if approved by the FDA, would provide a useful alternative. A study comparing these three therapies demonstrated successful detoxification in 36 of 55 of those receiving clonidine alone (65 percent), 44 of 54 of those receiving clonidine and nal-

trexone (81 percent), and 43 of 53 of those receiving buprenorphine (81 percent).<sup>25</sup> In comparison, success rates of 75 to 95 percent have been reported with detoxification in opioid-treatment programs.<sup>30</sup> Although rapid detoxification with clonidine and naltrexone may lead to improved short-term outcomes, it is unclear whether longer-term outcomes are superior to those achieved with clonidine alone.<sup>25,29</sup> Pending approval of buprenorphine, clonidine therapy is the most feasible office-based approach for physicians who have little experience in the treatment of opioid dependence.

Office-based physicians undertaking detoxification should monitor patients closely and use established treatment protocols. Physicians should interact with patients daily for the first three to five days of treatment in order to monitor symptoms and the response to treatment. Physicians must include a plan for the prevention of relapse and for the management of unsuccessful detoxification.

#### Opioid-Agonist Maintenance Therapy

Opioid-agonist maintenance therapy involves the replacement of short-acting opioids with long-acting opioids that have a slower onset of action. These medications block euphorogenic effects of opioids at mu-opioid receptors, thereby reducing their potential for reward. Oral medications also reduce the risk of infection associated with injection-drug use.<sup>31</sup>

Research supports the efficacy of opioid-agonist maintenance therapy in reducing illicit opioid use.<sup>1,8,28,32</sup> Among 388 patients receiving methadone, the rate of intravenous drug use declined from 81 percent at the initiation of methadone treatment to 29 percent at four years.<sup>8</sup> In another study, approximately 60 percent of subjects receiving methadone maintenance therapy reported heroin use at 1 year and reported having used heroin on approximately 5 of the previous 30 days.<sup>28</sup> Methadone maintenance therapy is also associated with a reduced frequency of criminal behavior and of human immunodeficiency virus seroconversion.<sup>8,32,33</sup>

Observed outcomes with methadone vary with variations in the dose of methadone; as compared with lower doses, doses of more than 50 mg are associated with less illicit-drug use and increased retention in treatment programs.<sup>34,35</sup> One study demonstrated lower rates of opioid use (53 percent vs. 62 percent) among patients receiving 80 to 100 mg of methadone than among those receiving 40 to 50 mg.<sup>35</sup> Clinical progress is followed with weekly to monthly urinalysis to supplement patients' reports of drug use or abstinence.<sup>36</sup>

Maintenance with levomethadyl acetate, a methadone derivative developed for thrice-weekly administration, is as effective as with methadone. However,

levomethadyl acetate should be reserved for patients in whom other treatments have failed, because it is associated with prolonged-QT syndrome and arrhythmias.<sup>37</sup>

Clinical characteristics and the availability of treatments should be considered in determining the appropriate duration of methadone treatment.<sup>34</sup> In one study, 82 percent of 105 patients who discontinued methadone treatment had relapses to intravenous drug use within 12 months.<sup>8</sup> Concern about high rates of relapse<sup>8,28</sup> has led authorities to advocate for the continuation of maintenance treatment as long as the patient continues to benefit, wishes to continue treatment, is at risk for relapse, and has no serious side effects and as long as the clinician believes such treatment is needed.<sup>38</sup> Older age, absence of criminal behavior, shorter duration of opioid use, less severe psychopathology, being employed, being married, less use of multiple substances, and greater expressed desire to obtain help with a drug problem are all associated with increased retention in treatment and decreased illicit-drug use with methadone therapy.<sup>39</sup>

Buprenorphine, if approved by the FDA, could also be useful as maintenance therapy in office-based treatment. A comparison of buprenorphine, levomethadyl acetate, higher-dose methadone (60 to 100 mg), and low-dose methadone (20 mg), found that buprenorphine, levomethadyl acetate, and higher-dose methadone all had greater efficacy than low-dose methadone. Twenty-six percent of 55 patients receiving buprenorphine maintenance therapy had 12 or more consecutive opioid-negative urinalyses.<sup>40</sup> Similar effects on opioid-withdrawal symptoms<sup>41-43</sup> and opioid use<sup>43</sup> have been demonstrated with daily and alternate-day administration of buprenorphine, and thrice-weekly administration also appears to be effective.<sup>44,45</sup> Agents used for opioid-agonist maintenance therapy are listed in Table 2.

#### Office-Based Opioid-Agonist Maintenance Therapy

Office-based treatment with opioid agonists is feasible with two populations of patients: patients who are already receiving treatment and patients who are just beginning treatment.<sup>4,45-49</sup> Patients demonstrating abstinence from opioid use with methadone therapy have been successfully transferred to office-based practices.<sup>46-49</sup> Eligibility criteria have included the receipt of methadone maintenance therapy for at least one<sup>46,48</sup> to five<sup>47,49</sup> years, the absence of recent evidence of drug use on urinalysis, the presence of stable means of financial support, the absence of involvement in illegal activity, and the absence of untreated psychiatric conditions. One program that has been in existence for 15 years demonstrated that 84 percent of patients treated in an office-based setting were compliant (adhered to the program's regulations) and were retained

in the program.<sup>47,50</sup> A six-month randomized trial involving 46 patients whose condition was clinically stable found similar rates of ongoing illicit-drug use (defined as two consecutive urinalyses showing evidence of opiates or cocaine) with office-based treatment and with continuation in a treatment program (18 percent vs. 21 percent).<sup>48</sup>

Office-based care of opioid-dependent patients who are just beginning treatment has been less well studied.<sup>45</sup> In a small, randomized trial, buprenorphine treatment in a primary care clinic resulted in significantly greater retention and significantly fewer opioid-positive urinalyses than it did in an opioid treatment program.<sup>45</sup> In Australia, Canada, France, and the United Kingdom, methadone or buprenorphine is provided through physicians' offices. In the United Kingdom, 40 percent of the methadone for treatment of opioid dependence is prescribed by general practitioners.<sup>51</sup> Studies of buprenorphine in France demonstrate similar rates of retention in general practitioners' offices and specialist settings.<sup>52</sup>

#### AREAS OF UNCERTAINTY

It is challenging to choose among detoxification, opioid-agonist maintenance therapy at an opioid treatment program, and such therapy through a physician's office. Clinical, demographic, pharmacologic, logistic, and regulatory variables, as well as the preferences of the patient, must be taken into account (Table 3). Given the limited long-term effectiveness of detoxification alone, this treatment may be best reserved for patients with high levels of motivation and social stability and low levels of opioid use and should be followed by relapse-prevention counseling and maintenance treatment with naltrexone.<sup>29</sup> However, maintenance treatment with naltrexone has limited clinical usefulness because its initiation requires abstinence from opioids and because retention in naltrexone treatment has been poor.<sup>53</sup>

Although there are established criteria for patients who can be transferred from a treatment program to treatment through a physician's office,<sup>46-50</sup> eligibility criteria for patients who are just beginning treatment through a physician's office are less clear. There is little empirical evidence on the economic effect of this model of care, and one projection estimates that office-based treatment may result in increased costs for medication and for care by physicians and nurses but reduced costs for dispensing of medication, toxicologic screening, counseling, and program administration, resulting in net savings.<sup>54</sup>

#### GUIDELINES

The 1997 National Institutes of Health consensus statement on treatment for opioid dependence recommended increased availability of treatment, reduced

**TABLE 3.** CHARACTERISTICS OF APPROPRIATE CANDIDATES FOR OPIOID TREATMENT PROGRAMS AND OFFICE-BASED CARE OF OPIOID DEPENDENCE.

##### Opioid treatment program\*

Age  $\geq 18$  yr or 2 documented unsuccessful attempts at short-term detoxification or drug-free treatment within a 12-mo period  
History of opioid dependence for  $\geq 1$  yr  
Exceptions to these criteria that allow treatment  
Release from penal institution  
Pregnancy  
History of previous treatment

##### Office-based care

Enrollment in maintenance program for 1-5 yr†  
Clinical stability as evidenced by 1 yr of illicit-drug-negative urine specimens†  
No evidence of dependence on cocaine, alcohol, or other drugs, except nicotine  
No untreated psychiatric conditions  
Presence of a stable source of financial support  
Presence of a stable source of coverage for medication and office visits  
Absence of involvement in illegal activities  
Compliance with treatment regimen  
No history of multiple relapses after treatment

\*Characteristics are according to federal criteria for admission to a program providing opioid-agonist maintenance therapy.<sup>11</sup>

†This is an additional criterion for transfer from an opioid treatment program to office-based care.

regulation of methadone, and increased training for physicians in the diagnosis and treatment of opioid dependence.<sup>1,55</sup> The American Society of Addiction Medicine places opioid maintenance therapy among its level I services — those that are appropriate for outpatient treatment.<sup>56</sup> A practice guideline has been developed for the Center for Substance Abuse Treatment for treatment with buprenorphine.<sup>13</sup>

#### CONCLUSIONS AND RECOMMENDATIONS

Although services for treating opioid dependence are typically offered in treatment programs, new federal initiatives will allow office-based care. Physicians can undertake detoxification with nonopioid medications or refer patients to a treatment program. Physicians currently can work with such treatment programs to obtain an exemption for office-based maintenance therapy in selected patients. The Drug Addiction Treatment Act creates the opportunity in the future for qualified physicians to prescribe Schedule III, IV, and V medications as they are approved for the treatment of opioid dependence.

Detoxification, even when coupled with counseling, often results in only a moderate, temporary decrease in opioid use. Opioid-agonist maintenance therapy is the most effective treatment, although often, it does not lead to the complete cessation of opioid use. For a patient such as the one described in the vignette, we would recommend high-dose methadone or, when

it becomes available, buprenorphine as the first-line agent; we would prescribe levomethadyl acetate only if the other treatments failed. Treatment should be continued indefinitely in most patients. Psychosocial services should also be provided routinely. Characteristics of the patient, the training and experience of the physician, and regulatory issues must be factored into decisions about whether office-based treatment is right for a given patient. For appropriate patients, this approach has the potential to improve the coordination of care and access to treatment.

Supported by the National Institute on Drug Abuse Physician Scientist Award (NIDA #K12 DA00167, to Dr. Fiellin). Dr. Fiellin is a Robert Wood Johnson Foundation Generalist Physician Faculty Scholar.

*We are indebted to Lynn E. Sullivan, M.D., for her critical review of earlier versions of this manuscript.*

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