105

CURRENT AND EXPERIMENTAL THERAPEUTICS FOR THE TREATMENT OF OPIOID ADDICTION

PAUL J. FUDALA GEORGE E. WOODY

Currently, numerous effective pharmacologic and behavioral therapies are available for the treatment of opioid addiction, and these two types of therapies often are combined to optimize patient management. Newer therapeutic options may take various forms. For example, methadone maintenance is an established treatment modality, whereas the use of buprenorphine and naloxone in an office-based setting represents a new variation on that theme. Clonidine has been used extensively to ameliorate opioid withdrawal signs, whereas lofexidine is a structural analogue that appears to have less hypotensive and sedating effects. The depot dosage form of naltrexone, currently under development, may increase compliance with a medication that has been an effective opioid antagonist but that has been underused secondary to patient nonacceptance. In almost every treatment episode using pharmacotherapy, it is combined with some type of psychosocial or behavioral treatment. Recent research has documented the value of these additional treatments and has provided insight into the ones that are the most effective. This chapter reviews current and experimental treatments for opioid addiction with an emphasis on some of the newer, more promising, and interesting therapies.

TREATMENT PARADIGMS

Long-Term, Short-Term, Rapid, and Ultrarapid Opioid Detoxification

Detoxification from opioids, for most patients, is only the first phase of a longer treatment process. Most patients seek-

Paul J. Fudala: Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania; Department of Behavioral Health Service, Veterans Affairs Medical Center, Philadelphia, Pennsylvania.

George E. Woody: Substance Abuse Treatment Unit, VA Medical Center, Philadelphia, Pennsylvania.

ing treatment have been addicted to heroin or other opioids for 2 to 3 years, some for 30 years or more. Thus, treatment usually involves changes in patients' lifestyles. Although generally ineffective in producing sustained remission unless combined with long-term pharmacologic, psychosocial, or behavioral therapies, detoxification alone continues to be widely used and studied. It is sometimes the only option available for patients who do not meet United States Food and Drug Administration (FDA) criteria for, do not desire, or do not have access to agonist medications such as methadone or methadyl acetate (L- α -acetylmethadol or LAAM).

The detoxification process may include use of opioid agonists (e.g., methadone), partial agonists (e.g., buprenorphine), antagonists (e.g., naloxone, naltrexone), or nonopioid alternatives such as clonidine, benzodiazepines, or nonsteroidal antiinflammatory agents. In many cases, one or more medications are combined, such as naloxone with clonidine and a benzodiazepine. The choice of detoxification medication and the duration of the process depend on numerous factors including patient preference, clinician expertise and experience, type of treatment facility, licensing, and available resources. Ultimately, however, the goal of detoxification is the achievement (and maintenance) of a drug-free state while minimizing withdrawal. Unfortunately, however, detoxification for some patients appears to be used in a punitive manner or as an expedient means to achieve a drug-free state rapidly with no follow-up pharmacologic or behavioral therapy.

Opioid detoxification paradigms are frequently categorized according to their nominal duration: long-term (typically 180 days), short-term (up to 30 days), rapid (typically 3 to 10 days), and ultrarapid (1 to 2 days). These temporal modifiers provide only a coarse description of the paradigm; they do not provide other important information such as the medications used or whether postdetoxification pharmacologic (e.g., naltrexone maintenance), psychosocial, or behavioral therapy is provided. However, some general guidelines typically apply.

The most common detoxification protocols, and those for which the most data are available, are the long-term (typically 180 days) and short-term (up to 30 days) paradigms involving the use of methadone. Unfortunately, these strategies have not generally been associated with acceptable treatment response using relapse to opioid use as an outcome criterion. For example, one study reported that more than half the patients participating in a 180-day detoxification program were using opioids illicitly during the medication-taper phase of the protocol (1). Six-month follow-up indicated that 38.5% of the urine samples (n = 26) tested negative for illicit opioids, only three of 31 patients reported remaining free of illicit opioids for the entire 6 months before follow-up, and 22 participated in some other form of treatment (2). Results from more rapid detoxification evaluations using short- or even intermediate-term (up to 70 days) medication-tapering protocols are even less encouraging and have an unfortunately low success rate. However, provision of additional services such as counseling, behavioral therapy, treatment of underlying psychopathologies, job skills training, and family therapy to address concomitant treatment needs can improve outcome, although success rates remain low, even with these services (3).

1508

Rapid detoxification involves the use an opioid antagonist, typically naltrexone or naloxone, in combination with other medications (such as clonidine and benzodiazepines) to mitigate the precipitated withdrawal syndrome. The procedure is intended to expedite and compress the withdrawal process to minimize discomfort and to decrease treatment time. Ultrarapid detoxification also uses other medications, along with an opioid antagonist, to moderate withdrawal effects. However, rather than being awake as they are during the rapid detoxification process, patients are placed under general anesthesia or, alternatively, are deeply sedated. A comprehensive review of the rapid and ultrarapid detoxification literature (identifying 12 and 9 of each type study, respectively) has been published (4). Rapid detoxification studies were conducted in inpatient facilities, outpatient substance abuse treatment settings, and outpatient primary care facilities; ultrarapid ones were confined to inpatient settings. Patients included those who were heroin dependent as well as those in methadone maintenance treatment.

Only four of the studies reviewed provided follow-up beyond the initial detoxification. Retention on postdetoxification naltrexone maintenance in one rapid detoxification study was 53% at 1 month and 82% in another at 3 months. Only one of the ultrarapid detoxification studies provided follow-up information indicating that all patients (11 of 11) were taking naltrexone 30 days after detoxification (5). A more recently published study (6), in which ultrarapid detoxification was followed by naltrexone maintenance and supportive psychotherapy, indicated that 49 of 72 patients were opioid abstinent 12 months after detoxification. All these studies involved self-selected patients; thus, it is impos-

sible to know the overall effectiveness of this type of intervention

A major concern regarding ultrarapid detoxification in particular is the occurrence of potentially serious adverse effects, such as respiratory distress (7), or other pulmonary and renal complications (8), during or immediately after the procedure. A high frequency of vomiting has also been reported (9). The degree to which serious adverse effects occur has not yet been determined; however, there have been press reports of sudden death occurring shortly after the procedure that were not caused by relapse to opioid use and overdose.

In spite of the emerging evidence about serious adverse effects, ultrarapid detoxification may be appropriate for highly selected patients based on considerations of previous treatment history, economic factors, and patient choice. However, patients seeking this treatment must be thoroughly informed that serious adverse effects, including sudden unexpected deaths, have occurred in association with this procedure, and its use should probably be limited to inpatient settings where monitoring by anesthesiologists and other highly trained staff is available.

Buprenorphine, a μ -opioid partial agonist, has also been used as a detoxification agent. Results from inpatient (10–12) and outpatient (13,14) studies have shown that it is safe and well tolerated, and it mitigates opioid withdrawal signs and symptoms over a range of doses and detoxification schedules. Clonidine, an α_2 -adrenergic agonist, has been shown to suppress many of the autonomic signs and symptoms of opioid withdrawal. It can cause pronounced sedation and hypotension but has been used with few problems when appropriate monitoring is available. It does not suppress the subjective discomfort of withdrawal, and probably for that reason, it is not well accepted by most opioid addicts.

Other α_2 -adrenergic agonists have also been evaluated to find agents that are equally or more effective, but produce less sedation and hypotension than clonidine. Lofexidine, a medication that was originally promoted as an antihypertensive, has been the most thoroughly studied. When compared with clonidine, it was found to suppress autonomic signs and symptoms of opioid withdrawal equally, but with less sedation and hypotension (15-17). When compared with methadone dose tapering, lofexidine detoxification was associated with opioid withdrawal effects that peaked sooner, but resolved to negligible levels more rapidly (18). In another study (19), an accelerated 5-day lofexidine treatment regimen attenuated opioid withdrawal symptoms more rapidly than 10 days of either lofexidine or methadone, with similar blood pressure responses observed for the two lofexidine groups. Data regarding the potential effectiveness of guanabenz and guanfacine have also been reported, but further studies are required to assess the potential utility of these medications for detoxification treatment. In summary, recent studies have shown that lofexidine is

likely to be a useful opioid detoxification agent whose efficacy approximates that of clonidine but with fewer side effects.

Opioid Agonist Pharmacotherapy

Methadone maintenance was developed by Dole and Nyswander and has become the most commonly used pharmacotherapy for opioid dependence (20). Methadone acts as the μ -opioid receptor, and its ability to suppress opioid withdrawal for 24 to 36 hours after a single oral dose makes it an ideal medication for this purpose. Another μ-opioid agonist, LAAM, received FDA approval for maintenance treatment in 1993. LAAM is a long-acting congener of methadone that suppresses withdrawal for 48 to 72 hours and thus has the advantage of requiring less frequent clinic visits than methadone, which must be taken daily. A third medication, buprenorphine, is far advanced in the FDA approval process. It was mentioned earlier as a detoxification agent and is discussed later and in more detail because it has unique properties that are likely to result in its being used with fewer regulatory controls than methadone and LAAM.

Both methadone and LAAM are Schedule II controlled substances and can be used only for maintenance and detoxification in programs that are licensed and regulated by the FDA and the Drug Enforcement Administration (DEA). The regulations specify who is eligible for treatment, procedures that are required for its administration, the number of take-home doses permitted, and the type of medication storage security needed. Treatment programs have been inspected approximately every 3 years for the past 30 years, and violations have resulted in sanctions ranging from administrative citations to criminal prosecution.

The combination of FDA and DEA regulations has resulted in a treatment system that is separated from the mainstream of other medical care and that consists almost entirely of specially licensed and inspected clinics. Clinics are often located in old buildings that have been converted to comply with regulations but that were never intended for medical use. At the present time, it is estimated that approximately 179,000 patients are being maintained on methadone or LAAM at 940 or more sites, and this number represents only about 20% of the opioid addicts in the United States (21).

This treatment-program regulatory system has been under increasing criticism since the early 1990s. Criticism has come from both patients and treatment providers who believe that the current regulations impose unnecessary burdens and expenses, have done little to improve the quality of treatment, and impede access to care. The importance of these criticisms has been underlined by the recent increase in heroin addiction (22), by evidence that methadone maintenance reduces the incidence of hepatitis and HIV infection, and by the lack of coverage for agonist maintenance

by most health insurance plans. The overall effect has been a widening gap between treatment need and availability, and lost treatment opportunities.

As a result, the Institute of Medicine and the National Institutes of Health each made recommendations for regulatory reform (23,24). Many of these recommendations are in the process of being carried out and include an overall reduction in regulations and transfer of oversight to accreditation bodies that are approved by the Center for Substance Abuse Treatment, rather than the FDA. Other recommendations include allowing long-term, stable patients to be treated in settings other than methadone clinics where they can receive up to 30 days of take-home medications (medical maintenance), allowing take-home doses for LAAM, and allowing more clinical judgment in determining dosages and take-home schedules. Procedures to prevent diversion include careful screening of patients who receive medical maintenance, return to directly observed medication administration if illicit drug use or diversion is detected, random urine testing, and call-back procedures in which patients will be required to report to the medical treatment setting and to produce the remaining, unused take-home containers.

The appropriate agonist medication dosage has been a subject of both federal and state regulations, although there has been a gradual shift toward allowing more clinical judgment in its determination. Numerous studies have been conducted since the mid-1970s to determine the optimal dose, and, although it is clear that some patients do well on low doses of methadone or LAAM (about 20 to 50 mg), studies have consistently shown that most patients need higher doses if they are to achieve maximum benefit from agonist treatment (25). The results of these methadone dose comparison studies are generally supportive of the guidelines originally proposed by Dole and Nyswander, who recommended doses in the 80- to 120-mg per day range (20). Clear relationships between methadone blood levels and clinical response have not been observed consistently. One study found significant correlations between oral dose and methadone concentration, but only among patients who complained of low dosing (26). These findings suggest that some patients may be more sensitive to dosage changes and that clinical response, including subjective complaints, is a more important guide to adequate dose levels than specific blood levels. No controlled studies have been done examining doses higher than 120 mg; thus, the upper limits of dosing effectiveness are not well understood.

Perhaps the most important pending regulatory change is to amend the Controlled Substances Act with respect to registration requirements for practitioners using drugs approved for detoxification or maintenance that are in Schedules III, IV, and V (27). Physicians who choose to treat persons with opioid dependence under the new regulations will need to notify the Secretary of Health and Human Services in writing of their intent and to show that they

1510

are qualified to provide addiction treatment by virtue of certification or experience. No physician would be allowed to treat more than 30 patients at one time without special approval, according to the legislation as it is now proposed.

This change in the regulations will be especially important for buprenorphine and the buprenorphine-naloxone combination (discussed later), because it will provide better access to treatment for persons who are unwilling or unable to be treated in the current methadone or LAAM system. The overall intent of the proposed regulatory reform is to better integrate maintenance treatment into the mainstream of medical care, to make it more readily available, and to improve its quality.

As mentioned earlier, these changes are likely to influence the ways in which buprenorphine is used in opioid addiction treatment. Buprenorphine is marketed internationally as an analgesic (both without naloxone and with naloxone to deter abuse) and as a treatment for opioid addiction. The most widespread use of buprenorphine is in France, where it was approved for the latter indication in 1996. In the United States, buprenorphine is currently approved only as an analgesic for parenteral administration; approval for opioid addiction treatment is pending. Buprenorphine has been used almost exclusively sublingually in addiction treatment because of its poor oral bioavailability. Most of the early clinical trials used a sublingual solution of buprenorphine formulated in a hydroethanolic vehicle, although a more commercially suitable sublingual tablet formulation is now used.

The greatest advantage of buprenorphine compared with full agonists such as methadone and LAAM is the plateau effect of µ-agonist activity. Parenteral doses as high as 12 mg intravenously (28) have been given to opioid-intolerant patients with only limited adverse effects (e.g. sedation, irritability, nausea, itching). Numerous large trials have confirmed the utility of buprenorphine for agonist maintenance therapy. These studies have included comparisons of buprenorphine with placebo (29,30), a buprenorphine-naloxone combination with placebo (30), and a multiple-dose comparison study (31). In one of the most recent trials (32), buprenorphine (given three times weekly) was compared with LAAM (given three times weekly) and methadone (given daily) in a 17-week study. Mean retention in treatment was higher for buprenorphine, LAAM, and high-dose methadone groups compared with low-dose methadone and for high-dose methadone compared with LAAM. Opioidpositive urine samples decreased most for the LAAM-treated group and least for low-dose methadone. Patient self-reports of opioid use did not differ among the groups, but they showed decreases of about 90% over the course of the study.

Buprenorphine has the potential to be abused and can produce addiction. However, most persons who abuse buprenorphine initiated opioid use with other drugs. Abuse may take the form of using greater than prescribed dosages for analgesia, using buprenorphine in place of a more desired but less available opioid such as heroin, or using bu-

prenorphine for its own positive subjective effects (33,34). Only one study published to date has characterized the behavioral and physiologic effects of a wide range of buprenorphine analysesic doses in nonusers of opioids (35). The results indicated that buprenorphine, given intravenously, has a low abuse liability in this population.

Buprenorphine, in combination with naloxone, has less potential for abuse than buprenorphine alone (36,37). The therapeutic utility of combining naloxone with buprenorphine derives from the low sublingual bioavailability of naloxone compared with buprenorphine. Parenteral misuse of the combination by persons addicted to opioids would be expected to produce antagonist-like effects; thus, most opioid addicts would not be likely to inject the combination more than once. The use of the buprenorphine-naloxone combination product in an office-based setting represents an innovative alternative to the restrictive methadone or LAAM maintenance paradigm described previously. The use of this new drug combination should expand the availability of agonist maintenance treatment with a relatively low risk for abuse or diversion. In addition, the partial agonist activity of buprenorphine results in a much lower risk of overdose death than is the case with methadone or LAAM.

Antagonist Maintenance

Naltrexone is the prototypical opioid antagonist used in abstinence maintenance therapy; this drug blocks the effects of heroin and other opioids through competitive receptor inhibition. Naltrexone has no opioid agonist effects and is a competitive opioid antagonist. It is orally effective and can block opioid effects for 24 hours when administered as a single daily dose of 50 to 60 mg. Higher doses usually will not block opioid effects for 48 to 72 hours though they will provide more cross tolerance to heroin and other opioids during the 24-hour dosing period (38). Despite a favorable adverse event profile (nausea is typically the most common side effect), naltrexone is generally not favored by opioid addicts because, unlike opioid agonists and partial agonists, it produces no positive, reinforcing effects. Furthermore, it may be associated with the precipitation of an opioid withdrawal syndrome if it is used too soon after opioid use stops, an effect that can be minimized by administering a naloxone challenge test before giving naltrexone.

Although the literature on naltrexone treatment spans more than 25 years, work continues on increasing medication compliance and improving outcomes. Some of these more recent efforts include work to develop a depot form that will block opioid effects for 14 to 28 days. This dosage form is currently in phase II clinical trials. At present, a patient treated with naltrexone has only to stop the medication for 1 to 3 days to experience the full effects of subsequent opioid use. A depot dosage form of naltrexone would provide more time for patients to overcome ambivalence about stopping opioid use and could result in more long-term success than has currently been the case. Another var-

iant on antagonist treatment is nalmefene, an orally effective but somewhat longer-acting (about 48 hours at dosages of 50 to 100 mg per day) opioid antagonist that has been effective for alcohol treatment that may have advantages over naltrexone due to its longer duration of action. The problem will be that addicts may not take it, as has generally been the case with naltrexone (39,40).

Psychosocial and Behavioral Treatment

Research has called attention to the finding that, as in other substance use disorders, most patients with opioid dependence and abuse are ambivalent about stopping drug use (41,42). This ambivalence presents a therapeutic challenge because it contributes to varying levels of motivation to enter and remain in treatment, to early dropout, and to partial or (in some cases) nontreatment response. Studies have emphasized that treatment providers must be aware of this "normal" ambivalence and make reasonable efforts to resolve it in favor of treatment participation and cessation of drug use (42). Suggestions have been made regarding initial steps to maximize the chances for engagement in treatment and cessation of drug use. These include avoiding unnecessary delays in entering treatment, expressing a hopeful and nonjudgmental attitude, performing a comprehensive evaluation, and developing a treatment plan that is responsive to patients' self-identified goals (41).

In addition to challenges related to ambivalence, patients often have serious problems with nonopioid substance abuse or with medical, psychiatric, legal, employment, and family or social issues that preexist or result from the addiction. Research has found that addressing these additional problems can be helpful, but they are complex and require coordination between agonist pharmacotherapy staff and other medical and psychosocial services (43,44).

The most common type of psychosocial service in opioid agonist treatment is individual drug counseling. Counselors are typically persons at the masters level or below who deliver a behaviorally focused treatment aimed to identify specific problems, to help the patient access services that may not be provided in the clinic (e.g., medical, psychiatric, legal, family or social), to stop substance use, and to improve overall adjustment. Functions that counselors perform include monitoring methadone and LAAM doses and requesting changes when needed, reviewing urine test results, responding to requests for take-homes doses, assisting with family problems, assessing and responding to crises, writing letters for court or social welfare agencies, recommending inpatient treatment when necessary, and providing support and encouragement for a drug-free lifestyle.

Counseling usually addresses both opioid and nonopioid use. Although nicotine (tobacco) use is not always included, the increased emphasis on adverse health effects of smoking has resulted in more attention to stop smoking at all levels, including drug counseling. Counselors and patients typically have weekly, 30- to 60-minute sessions during the first

weeks or months of treatment with reductions in frequency to biweekly or monthly depending on progress. The frequency of counseling can vary widely depending on the severity of the patient's problems, clinic requirements, and counselor workload.

The importance of regular counseling was clearly demonstrated in a study by McLellan and co-workers (43), in which patients were randomly assigned to minimal counseling (one 5- to 10- minute session per month), standard counseling (one 45-minute session per week), or enhanced counseling (standard plus on-site referral to psychiatric, medical, and family or social services). Results showed a dose–response relationship with the minimal condition doing significantly worse than standard and enhanced counseling doing the best overall; however, about 30% of patients did well in the minimal counseling condition. This study clearly demonstrated the positive benefits achieved by drug counseling and showed that, for most patients, counseling is necessary to bring out the maximum benefits of agonist maintenance.

Most counseling is individual, one on one, but some programs use group therapy exclusively. However, most programs use groups only for selected patients with focal problems such as HIV disease, posttraumatic stress disorder, homelessness, loss of close personal relationships, or not at all. Many programs encourage patients to participate in self-help groups, but ask them to be careful to select a group that accepts persons who are receiving opioid agonist maintenance treatment. Some programs have self-help groups that meet regularly on site. Counselors, like psychotherapists, can vary widely in the results they achieve (45). This variability seems more related to the ability to form a positive, helping relationship with the patient than to specific techniques (46).

Contingency management techniques are always included in drug counseling, if for nothing else than to fulfill regulations about requiring progress in treatment as a condition of providing take-home doses, and studies have shown that they can be very helpful. For example, an opportunity to receive take-home medications in return for drug-free urine tests is a powerful motivator for many patients (47). Such a contingency strategy is an example of research with a clear use in general clinical practice because it is easily applied and costs little or nothing beyond standard program costs. More flexibility in dispensing take-home doses as contingencies for positive behaviors could be a positive effect of the regulatory reforms described earlier.

Another contingency that is easily applicable and that some programs have used with positive results is requiring a negative alcohol breath test before dispensing the daily dose of methadone or LAAM. This contingency can be especially useful for patients with alcohol abuse or dependence. Maintenance, counseling, and contingency management are often combined in complex ways, as seen in the following vignette:

A 42-year-old man presented for his sixth episode of

methadone maintenance. He had a long history of alcoholism and was using cocaine regularly. He had done fairly well on methadone as far as illicit opioid use was concerned, but his clinic attendance and ability to comply with clinic rules, especially regarding take-home doses, were severely compromised by alcohol use. In the past, he would remain in treatment for about a year, then become angry over his inability to obtain take-home doses because of positive breathalyzer tests, drop out, and have a relapse to opioid use. He had frequently been offered inpatient detoxification for alcoholism but always refused because "alcohol's not my problem, heroin's the problem," and he could not take time off from work (as a stockperson in a liquor store). When he presented for treatment most recently, he was unemployed (secondary to alcohol problems) and living with his parents, who were threatening to put him out because of drug use. He agreed that, as part of his treatment plan, he would go into the hospital for alcohol detoxification and stabilization on methadone and then be discharged to maintenance therapy. After inpatient discharge, he attended AA-style counseling, requested daily alcohol breath tests, and turned down an offer to return to his job at the liquor store. He remained stable for 3 years on 65 mg per day of methadone with no urine samples positive for opioids (but occasionally positive for cocaine), and he enrolled (and continued) in school.

It is clear that in such a complex but relatively typical case, a single intervention was not enough. Rather, a series of coordinated steps was necessary to achieve a positive treatment response. Although not demonstrated in this vignette, family therapy is another intervention that can be combined with agonist therapy and other psychosocial interventions, and studies have shown that it can be useful as well (48).

Although counseling and other services are effective enhancements of agonist treatment, adherence is often an issue, and clinics vary in the way they respond to this problem. Some remind patients of appointments, others do not permit patients to be medicated unless they keep appointments, and others suspend patients who miss appointments. For nonadherent patients, a very powerful contingency is requiring certain behaviors for patients to remain on the program, a procedure that is often formalized in a treatment contract. Here, the patient is given an option of stopping unprescribed drug use, keeping regular counseling appointments, looking for work, or correcting other behaviors that need improvement as a condition for remaining in treatment. Patients who fail are administratively detoxified, suspended for months to years, and referred to another program, although the referrals are not always successful.

The long-term effects of this form of contingency management have not been well studied. For example, relatively little is known about negative effects on patients who may have improved with methadone and counseling, but not to the degree required by the contingency, and who are subsequently discharged for failing to adhere to a treatment

contract. One study done in Philadelphia (49) found that among 110 patients who were administratively discharged or dropped out of a Veterans Affairs (VA) maintenance program, 8.2% (nine of 110) died within the following year as compared with only 1% (four of 397) who remained in treatment. Among the 43 patients (from among the 110) who were discharged for failing to adhere to a treatment contract, five (11.6%) died within a year. None of these five patients were in treatment at the time of death, and all died as a result of overdoses. No overdose deaths occurred among patients remaining in treatment, and, interestingly, there were no deaths in those patients who were suspended for violating program rules (mainly drug dealing or giving a false urine specimen). These results are consistent with data from New South Wales, Australia, where there has been a sharp rise in heroin-related deaths. Although it is estimated that 20% to 30% of the heroin addicts in New South Wales are receiving methadone maintenance, only 3% of the 953 heroin-related fatalities occurred among patients receiving methadone maintenance (50). These data emphasize the fine line between contingencies maintained in programs and the dangers associated with program dismissal.

The foregoing data, when considered along with studies showing a protective effect of maintenance on acquiring HIV infection (51), have made some clinicians increasingly hesitant to suspend patients from maintenance treatment for positive urine test results alone. This caution may be especially relevant in environments where the potency of heroin is high, such as Philadelphia, where the average "bag" of heroin is now 71% pure (22).

Therapeutic communities are another psychosocial approach that is often useful for opioid addicts who have a long history of addiction and a strong motivation to become drug free. These programs are very selective, self-governing, long-term (6 to 18 months) residential settings where patients share responsibilities for maintaining the treatment milieu (cleaning, cooking, and leading group therapy). Confrontation of denial and behaviors such as lying and "conning," combined with group support for healthy, positive change, is used to restructure character and the addictive lifestyle. Medications such as methadone, LAAM, or naltrexone are rarely used; however, medications for specific psychiatric or medical conditions are usually available after careful screening and evaluation. Patients who enter therapeutic communities are often referred by the criminal justice system. Some patients have tried, but not responded, to agonist maintenance on repeated occasions. Although dropout rates are high, studies have shown that more than 80% of patients who complete a course of treatment in a therapeutic community have a sustained remission and demonstrate significant improvement in psychiatric symptoms, employment, and criminal behavior (52,53).

Addressing Comorbidity

Patients seeking treatment for opioid dependence are typically dependent on one or more other substances (cocaine, alcohol, benzodiazepines, amphetamines, marijuana, nicotine), and have additional problems in the psychiatric, medical, family or social, employment, or legal areas. In fact, it is rare to find a person with only opioid dependence and no other substance abuse or without a psychiatric, medical, or family or social problem. The presence of these problems, perhaps with the exception of nicotine dependence, tends to magnify the severity of the opioid dependence and makes the patient more difficult to treat.

Among the psychiatric disorders seen in persons with opioid dependence, antisocial personality disorder is one of the most common (54). Diagnostic studies of persons with opioid dependence have typically found rates of antisocial personality disorder ranging from 20% to 50%, as compared with less than 5% in the general population. Posttraumatic stress disorder is also seen with increased frequency.

Opioid-dependent persons are especially at risk for the development of brief depressive symptoms and for episodes of mild to moderate depression that meet symptomatic and duration criteria for major depressive disorder or dysthymia. These syndromes represent both substance-induced mood disorders as well as independent depressive illnesses. Brief periods of depression are especially common during chronic intoxication or withdrawal or in association with psychosocial stressors that are related to the dependence. Insomnia is common, especially during withdrawal; sexual dysfunction, especially impotence, is common during intoxication. Delirium or brief, psychotic-like symptoms are occasionally seen during opioid intoxication (54).

The data on psychiatric comorbidity among opioid addicts and its negative effect on outcome (55) have stimulated research on the effect of combining psychiatric and substance abuse treatment. Several studies have now shown that tricyclic antidepressants can be useful for chronically depressed opioid addicts who are treated with methadone maintenance (56). Two studies have shown that professional psychotherapy can be useful for psychiatrically impaired, methadone-maintained opioid addicts, although another study found no psychotherapy effect (57–59). The main result in most pharmacotherapy and psychotherapy studies with methadone-maintained addicts has usually been a reduction in psychiatric symptoms such as depression, although some studies have shown reductions in substance use as well (56,57).

Fewer than 5% of persons with opioid dependence have psychotic disorders such as bipolar illness or schizophrenia; however, these patients can present special problems because programs typically have few psychiatric staff members. As a result, these patients are sometimes excluded from methadone treatment because of the severity of their psychotic

disorders. Others are treated with methadone, counseling, and the same antipsychotic or antimanic medications used for nonaddicted patients with similar disorders. Although studies evaluating the outcome of combining opioid agonist treatment with antipsychotic or antimanic medications have not been done, there is little controversy that these medications are useful for opioid addicts with psychotic disorders, and most programs use them with little hesitation.

Women opioid addicts can present special challenges because many have been sexually abused as children, have other psychiatric disorders, and are involved in difficult family or social situations (60). Abusive relationships with addicted men are common, sometimes characterized by situations in which the man exerts control by providing drugs. These complex psychiatric and relationship issues have emphasized the need for comprehensive psychosocial services that include psychiatric assessment and treatment and access to other medical, family, and social services.

Medical comorbidity is a major problem among opioid addicts; HIV infection, AIDS, and hepatitis B and C have become some of the most common illnesses. Sharing injection equipment, including "cookers" and rinse water, and engaging in high-risk sexual behavior are the main routes of infection. Sexual transmission appears to be a more common route for HIV transmission among women than men because the HIV virus is spread more readily from men to women than from women to men. Females patients who are intravenous drug users and who also engage in prostitution or other forms of high-risk sexual behavior are at extremely high risk of HIV infection (60). Cocaine use has been found to be a significant risk factor as a single drug of abuse or when used in combination with heroin or other opioids (61).

As mentioned earlier, mortality is high, and studies have found annual death rates of approximately 10 per 1,000 or greater, which is substantially higher than demographically matched samples in the general population (62). Common causes of death are overdose, accidents, injuries, and medical complications such as cellulitis, hepatitis, AIDS, tuberculosis, and endocarditis. The cocaine and alcohol dependence that is often seen among opioid-dependent persons contributes to medical morbidity by cirrhosis, cardiomyopathy, myocardial infarction, or serious cardiac arrhythmias.

Tuberculosis has become a particularly serious problem among intravenous drug users, especially heroin addicts. In most cases, infection is asymptomatic and is evident only by the presence of a positive tuberculin skin test. However, many cases of active tuberculosis have also been found, especially among those who are infected with HIV who may have a newly acquired infection or reactivation of a prior infection as a result of impaired immune function.

After rising rapidly in the late 1970s and early 1980s, the incidence of new HIV infections among intravenous drug users, of whom opioid-dependent persons constitute a large proportion, decreased (63). However, as a result of high levels of needle sharing and other risky behavior in the early phases of the epidemic, the prevalence of HIV infection among heroin addicts reached as high as 50% in some areas of the United States (64). Because of the long incubation period before the development of AIDS, it is expected that future years will continue to see high levels of morbidity and mortality associated with HIV infection, although the advent of new pharmacotherapies for HIV has extended many lives.

Studies done over the last several years have identified several important interactions between methadone and drugs used to treat HIV infection. Information is not complete, however, and more studies are needed to map out the extent of these interactions completely. One important interaction is that methadone increases plasma levels of zidovudine; the associated symptoms resemble methadone withdrawal. There have been instances in which methadone doses have been increased in response to complaints of withdrawal, with increasing doses compounding the problem. Another important interaction involves decreased methadone blood levels secondary to nevirapine administration that may be associated with mild to moderate withdrawal. This interaction can be important if the patient discontinues either of these two drugs while taking methadone, because the result may be a sudden rise in methadone blood levels with signs and symptoms of overmedication (65,66).

Other medical complications of heroin dependence are seen in children born to opioid-dependent women. Perhaps the most serious is premature delivery and low birth weight, a problem that can be reduced if the mother is receiving methadone maintenance and prenatal care (67). Another is physiologic dependence on opioids, seen in about half the infants born to women maintained on methadone or dependent on heroin or other opioids. Effective treatments for neonatal withdrawal are available, and long-term adverse effects of opioid withdrawal have not been demonstrated. Adverse neonatal effects associated with LAAM or buprenorphine have not been observed, but few studies have been done because neither medication is approved for use in pregnancy.

The possibility that breast-feeding may cause adverse effects in infants of methadone-maintained mothers was studied. It was found that methadone was present in the breast milk of women maintained on doses as high as 180 mg, but the concentration was very low, and no adverse effects were observed in the infants (68). HIV infection is seen in about one-third of infants born to HIV-positive mothers, but this incidence can be reduced to about 10% if HIV-positive pregnant women are given zidovudine before delivery (69). HIV can also be transmitted by breast-feeding, and thus infant formula feeding is recommended for babies of HIV-positive mothers, except in some developing countries, where formula is unavailable or unaffordable. Thorough washing of infants born to HIV-infected mothers im-

mediately after delivery also appears to reduce the incidence of HIV infection.

An important line of research resulting from the data on comorbidity has been studies on the effects of integrating psychiatric and medical care within agonist and other substance abuse treatment programs (70). Clinical experience and National Institute on Drug Abuse demonstration projects have shown that integration of these services with agonist maintenance can be done, and with very positive results, because patients are seen frequently and treatment retention is high (44). Related to this line of research are studies that have shown improved compliance with directly observed antituberculosis pharmacotherapy (71). These findings have important implications for tuberculosis control policies in methadone programs because intravenous drug users are at very high risk of tuberculosis infection and because maintenance programs provide settings in which directly observed therapy can be easily applied. Similar principles apply to administration of psychotropic medication in noncompliant patients with schizophrenia or other major axis I disorders.

Harm Reduction

Harm reduction is concerned with minimizing various negative consequences of addiction. As such, the focus is shifted away from drug use to the consequences of use and its attendant behaviors (72). Examples of harm reduction include needle exchange programs, efforts directed at reducing druguse-associated behaviors that may result in the transmission of HIV, and making changes in policies (including increasing treatment availability) that reduce heroin use and the criminal behavior associated with drug procurement. Harm reduction refers to reducing harm not only to the individual addict, but also to family, friends, and society generally. Other terms sometimes used synonymously with harm reduction include harm minimization, risk reduction, and risk minimization (73).

Some authors have identified the limitations of harm reduction when it is used as a sole strategy to combat the adverse effects of addiction. For example, Reuter and Caulkins pointed out the benefit of integrating drug use reduction and harm reduction components into a single framework (74), because total harm may be lowered by reducing either component. Roche and colleagues proposed a model for an integrated addiction treatment strategy that incorporates harm reduction and use reduction with abstinence and nonuse (75), in addition to other critical elements such as factors related to culture and gender. Additionally, MacCoun provided a template for integrating harm reduction with prevalence reduction (discouraging the engagement in drug use) and quantity reduction (encouraging the reduction in frequency or extent of drug use) (76).

With regard to opioids, much of the health-related harm from their improper or illicit use is secondary to elements other than the substances themselves (77). Sequelae of unhygienic methods of administration and poor injection technique are typically more serious than the constipation or other side effects of the drugs themselves, acute overdoses notwithstanding. With regard to opioid addiction treatment, medications such as methadone, LAAM, and buprenorphine, among others (including supervised heroin substitution) used for maintenance agonist treatment, may be considered harm reduction measures. All have the potential to reduce morbidity, mortality, and crime associated with the addict lifestyle. However, in this sense they are no different from other medical therapies such as those used for the treatment of hypertension, diabetes, or asthma.

Needle or syringe exchange represents one of the most controversial strategies in harm reduction. Research indicates that these types of programs may have beneficial effects in numerous areas, including a reduction in the spread of blood-borne infectious disease such as hepatitis and HIV, and acting as a conduit to more comprehensive drug-abuse treatment services (78). In one study (79), the initiation and continuation of syringe exchange program participation among high-risk injection drug users were independently associated with a cessation of syringe sharing. In another study (80), participation in a needle exchange program was associated with patients' entering detoxification treatment for both HIV-infected and noninfected groups. Not all findings have been positive, however. In a study designed to assess the association between risk behaviors and HIV seroprevalence and incidence among injection drug users, risk elevations for HIV associated with needle exchange programs were substantial and consistent despite adjustment for confounding factors (81). However, an examination of potential bias in nonrandomized comparisons (82) suggested that injection drug users participating in needle exchange programs at a given point may include a high proportion of persons whose pattern of drug use puts them at greater risk for blood-borne viral infections. Further, a prospective cohort study found no evidence of a causal association between needle exchange program participation and transmission of HIV (83).

Harm reduction related to psychoactive substance abuse has gone through numerous stages. The current phase has been described as the development of an integrated public health perspective for all drugs in which a multifaceted, strategic approach is taken (84). The direction of this approach will be guided, in part, by whether biases against a harm reduction philosophy can be overcome by those who see it as synonymous with acceptance of drug abuse or legalization, and how harm reduction objectives relate to an overall strategy to improve public health.

IMPACT OF MANAGED CARE

Efforts to control costs by managed care have resulted in a marked reduction in use of inpatient or residential treat-

ment programs in many locations. Funds saved from these cost reductions have often not been invested in outpatient treatment. A good example is the VA, which administers the largest network of substance abuse treatment programs in the United States. Since the application of managed care policies, the overall amount spent on substance abuse treatment declined by 41%, from \$597 million in 1993 to \$351 million in 1999. Measured as a percentage of overall VA health care costs, specialized substance abuse care decreased from 4.2% in 1993 to 2.3% in 1999. In contrast, overall VA health care expenditures increased 10% between 1993 and 1999 (85). Most of these reductions were achieved by reducing inpatient beds, with the funds saved allocated to other areas but not to reinvestment in other substance abuse treatment services. The result has been an overall reduction in the total number of veteran patients treated and in the amount of drug counseling provided. As a result, no new methadone programs were opened in the VA despite the recent increase in heroin addiction, evidence of waiting lists for methadone treatment, and cities (such as Portland, Oregon) with serious heroin problems but no agonist maintenance programs in spite of recent increases in heroin overdose deaths.

A focused review of substance abuse programs by the United States Senate Committee on Veterans Affairs found that changes in resource allocation have caused programs to become vulnerable to service disruptions, poor morale, burnout, and reduced motivation and quality of performance and characterized by failures to maintain service levels in accord with the mandates of law (86).

Managed care strategies have also made it very difficult to integrate medical and psychiatric services into agonist maintenance programs. Thus, both old and new pharmacotherapies for opioid addiction described earlier are underused in the VA, the largest substance abuse treatment system. There is every indication that penetration of these new treatments into the opiate treatment field at large has also been slow.

SUMMARY

New pharmacotherapies, behavioral therapies, and treatment strategies are being developed for opioid addiction. This continued development is important, because more treatment options will encourage treatments that are more individualized and balanced across important dimensions such as patient response, adverse effects, treatment costs, comorbidity, living situations, and overall adjustment. As described earlier, various treatments can be combined to produce better patient outcomes. However, the overall effect of these developments on addiction treatment and public health is very dependent on funding support, which has become a serious problem. Parity legislation may help to

solve funding problems and result in the expansion of treatment to meet patient needs, but the details of how and when more investment in substance treatment may occur are unclear as of this writing.

REFERENCES

- Banys P, Tusel DJ, See KL, et al. Low (40mg) versus high (80mg) dose methadone in a 180-day heroin detoxification program. J Subst Abuse Treat 1994;11:225–232.
- 2. Reilly PM, Banys P, Tusel DJ, et al. Methadone transition treatment: a treatment model for 180–day methadone detoxification. *Int J Addict* 1995;30:387–402.
- Kleber HD. Opioids: detoxification. In: Galanter M, Kleber HD, eds. Textbook of substance abuse treatment, second ed. Washington, DC: American Psychiatric Association, 1999:251–269.
- O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. JAMA 1998;279:229–234.
- Legarda JJ, Gossop M. A 24-h inpatient detoxification treatment for heroin addicts: a preliminary investigation. *Drug Alcohol De*pend 1994;35:91-93.
- Hensel M, Kox WJ. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anesthesia: a prospective study in methadone, heroin, codeine, and morphine addicts. *Acta Anaesthesiol Scand* 2000;44: 3226–3233.
- 7. San L, Puig M, Bulbena A, et al. High risk of ultrashort noninvasive opiate detoxification. *Am J Psychiatry* 1995;152:956.
- Pfab Ř, Hirtl C, Zilker T. Opiate detoxification under anesthesia: no apparent benefit but suppression of thyroid hormones and risk of pulmonary and renal failure. *J Toxicol Clin Toxicol* 1999; 37:43–50.
- Cucchia AT, Monnat M, Spagnoli J, et al. Ultra-rapid opiate detoxification using deep sedation with or midazolam: short- and long-term results. *Drug Alcohol Depend* 1998;52:243–250.
- Cheskin LJ, Fudala PJ, Johnson, RE. A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. *Drug Alcohol Depend* 1994;36:115–121.
- 11. Parran TV Jr, Adelman CL, Jasinski DR. A buprenorphine stabilization and rapid-taper protocol for the detoxification of opioid dependent patients. *Am J Addict* 1994;3:306–313.
- Vignau J. Preliminary assessment of a 10-day rapid detoxification programme using high dosage buprenorphine. Eur Addict Res 1998;4:29-31.
- 13. O'Connor PG, Carroll KM, Shi JM, et al. Three methods of opioid detoxification in a primary care setting: a randomized trial. *Ann Intern Med* 1997;127:526–530.
- Diamant K, Fischer G, Schneider C, et al. Outpatient opiate detoxification treatment with buprenorphine: preliminary investigation. *Eur Addict Res* 1998;4:198–202.
- Kahn A, Mumford JP, Rogers GA, et al. Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. *Drug Alcohol Depend* 1997;44:57–61.
- Lin SK, Strang J, Su LW, et al. Double blind randomized controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. *Drug Alcohol Depend* 1997;48:127–133.
- Carnwath T, Hardman J. Randomised double-blind comparison of lofexidine and clonidine in the out-patient treatment of opiate withdrawal. *Drug Alcohol Depend* 1998;50:251–254.
- Bearn J, Gossop M, Strang J. Randomized double-blind comparison of lofexidine and methadone in the in-patient treatment of opiate withdrawal. *Drug Alcohol Depend* 1996;43:87–89.

- Bearn J, Gossop M, Strang J. Accelerated lofexidine treatment regimen compared with conventional lofexidine and methadone treatment for in-patient opiate detoxification. *Drug Alcohol De*pend 1998;50:227–232.
- 20. Dole VP, Nyswander M. Successful treatment of 750 criminal addicts. *JAMA* 1968;26:2708–2710.
- 21. Addict Treat Forum 2000;9:2.
- Community Epidemiology Work Group. Epidemiologic trends in drug abuse: advance report. Washington, DC: NIDA, Dept. of Health and Human Services, 1999.
- Fulco DR, Liverman CT, Earley LE, eds. The development of medications for the treatment of opiate and cocaine addictions: issues for the government and private sector. Washington, DC: Institute of Medicine, National Academy Press, 1995.
- NIH Consensus Statement. Effective medical treatment of opiate addiction. Rockville, MD: National Institutes of Health, 1997
- 25. Ball JC, Ross A. The effectiveness of methadone maintenance treatment. New York: Springer-Verlag, 1991.
- Hiltunen AJ, Beck O, Hjemdahl P, et al. Rated well-being in relation to plasma concentrations of l- and d-methadone in satisfied and dissatisfied patients on methadone maintenance treatment. *Psychopharmacology* 1999;143:385–393.
- House Resolution 2634. United States House of Representatives, 2000.
- Umbricht-Schneiter A, Huestis MA, Cone EJ, et al. Safety of buprenorphine: ceiling for cardio-respiratory effects at high IV doses. NIDA Res Monogr 1998;179:225.
- Johnson RE, Eissenberg T, Stitzer ML, et al. A placebo controlled trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995;40:17–25.
- Fudala PJ, Bridge TP, Herbert S et al. A multisite efficacy evaluation of a buprenorphine/ naloxone product for opiate dependence treatment. NIDA Res Monogr 1998;179:105.
- Ling W, Charuvastra C, Collins JC, et al. Buprenorphine maintenance treatment for opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475–486.
- Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone as treatments for opioid dependence. N Engl J Med 2000;343: 1290–1297.
- Baumevieille M, Haramburu F, Bégaud B. Abuse of prescription medicines in southwestern France. *Ann Pharmacother* 1997;31: 847–850.
- 34. Dore GM, Hargreaves G, Niven BE, et al. Dependent opioid users assessed for methadone treatment in Otago: patterns of drug use. *NZ Med J* 1997;110:162–165.
- Zacny JP, Conley K, Galinkin J. Comparing the subjective, psychomotor and physiological effects of intravenous buprenorphine and morphine in healthy volunteers. *J Pharmacol Exp Ther* 1997; 282:1187–1197.
- Fudala PJ, Yu E, Macfadden W, et al. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend* 1998b;50:1–8.
- Mendelson J, Jones RT, Welm S, et al. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphinestabilized, opiate-dependent volunteers. *Psychopharmacology* 1999;141:37–46.
- Lee MC, Wagner HN, Tanada S, et al. Duration of occupancy of opiate receptors by naltrexone. J Nucl Med 1988;29:1207– 1211.
- Mason BJ, Ritvo EC, Morgan, RO, et al. A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp* Res 1994;18:1162–1167.

- Jones HE, Johnson RE, Fudala PJ, et al. Nalmefene: blockade of intravenous morphine challenge effects in opioid abusing humans. *Drug Alcohol Depend* 2000;60:29–37.
- Miller WR, Rollnick S. Motivational interviewing: preparing people to change addictive behavior. New York: Guilford, 1991.
- 42. Rollnick S, Mason P, Butler C. Health behavior change: a guide for practitioners. New York: Churchhill Livingstone, 1999.
- McLellan AT, Arndt IO, Metzger DS, et al. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993;269: 1953–1959.
- 44. Umbricht-Schneiter A, Ginn DH, Pabst KM, et al. Providing medical care to methadone clinic patients: referral vs on-site care. *Am J Public Health* 1994;84:207–210.
- 45. McLellan AT, Woody GE, Luborsky L, et al. Is the counselor an "active ingredient" in substance abuse treatment? *J Nerv Ment Dis* 1988;176:423–430.
- 46. Luborsky L, McLellan AT, Woody GE, et al. Therapist success and its determinants. *Arch Gen Psychiatry* 1985;42:602–611.
- Iguchi, MY, Lamb, RJ, Belding, MA, et al. Contingent reinforcement of group participation versus abstinence in a methadone maintenance program. *Exp Clin Psychopharmacol* 1996;4: 315–321.
- 48. Stanton MD, Todd T. *The family therapy of drug abuse and addiction.* New York: Guilford, 1982.
- Zanis DA, Woody GE. One-year mortality rates following methadone treatment discharge. *Drug Alcohol Depend* 1998;52: 257–260.
- Darke S, Ross J, Zador D, et al. Heroin-related deaths in New South Wales, Australia, 1992–1996. *Drug Alcohol Depend* 2000; 60:141–15.
- 51. Metzger DS, Navaline H, Woody GE. Drug abuse treatment as AIDS prevention. *Public Health Rep* 1998;113S:97–106.
- Inciardi JA, Martin SS, Butzin CA, et al. An effective model of prison-based treatment for drug-involved offenders. J Drug Issues 1997;27:261–278.
- DeLeon G. Therapeutic communities. In: Galanter M, Kleber HD, eds. *Textbook of substance abuse treatment*. Washington, DC: American Psychiatric Association, 1999:447–462.
- First MB, Pincus HA, eds. *Diagnostic and statistical manual of mental disorders*, fourth ed (text revision: DSM-IV-TR). Washington, DC: American Psychiatric Association, 1999.
- McLellan AT, Luborsky L, Woody GE, et al. Predicting response to alcohol and drug abuse treatments: role of psychiatric severity. *Arch Gen Psychiatry* 1983;40:620–625.
- Nunes EV, Quitkin FM, Donovan S, et al. Imipramine treatment of opiate dependent patients with depressive disorders: a placebocontrolled trial. *Arch Gen Psychiatry* 1998;55:153–160.
- Woody GE, McLellan AT, Luborsky L, et al. Psychiatric severity as a predictor of benefits from psychotherapy the Penn-VA study. Am J Psychiatry 1984;141:1172–1177.
- Woody GE, Mercer DE. Individual psychotherapy for substance use disorders. In: Gabbard GO, ed. *Treatments of psychiatric disor*ders, third ed. Washington, DC: American Psychiatric Association, 2001:849–861.
- Rounsaville BJ, Glazer W, Wilber CH, et al. Short-term interpersonal psychotherapy in methadone maintained opiate addicts. *Arch Gen Psychiatry* 1982;39:161–166.
- Blume SB. Addiction in women. In: Galanter M, Kleber HD, eds. Textbook of substance abuse treatment. Washington, DC: American Psychiatric Association, 1999:485–494.
- Booth RE, Kwiatkowski CF, Chitwood DD. Sex related HIV risk behaviors: differential risks among injection drug users, crack smokers, and injection drug users who smoke crack. *Drug Alcohol Depend* 2000;58:219–226.
- 62. Gronbladh L, Ohlund LS, Gunne LM. Mortality in heroin addic-

- tion: impact of methadone treatment. *Acta Psychiatr Scand* 1990; 82:223–227.
- 63. Seage G, Holte SE, Metzger DS, et al. Are US populations appropriate for HIV vaccine trials? The HIVNET Vaccine Preparedness Study *Am J Epidemiol* 2001;153:619–627.
- 64. DesJarlais D, Marmor M, Friedmann P, et al. HIV Incidence among injection drug users in New York City, 1992–1997: evidence for a declining epidemic. *Am J Public Health* 2000;90: 352–359.
- Altice FL, Friedland GH, Cooney EL. Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadone. AIDS 1999;13:957–962.
- Otero, MJ, Fuentes, A, Sanchez, R, et al. Nevirapine-induced withdrawal symptoms in HIV patients on methadone maintenance programme; an alert. AIDS 1999;13:1004–1005.
- 67. Finnegan, LP. Treatment issues for opioid-dependent women during the perinatal period. *J Psychoactive Drugs* 1991;23: 191–201.
- 68. McCarthy JJ, Posey BL. Methadone levels in human milk. *J Hum Lactation* 2000;16:115–120.
- Connor, EM, Sperling, RS, Gelber R, et. al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173– 1180.
- Kessler RC, Nelson CB, McGonagle KA, et al. The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *Am J Orthopsychiatry* 1996; 66:17–31.
- 71. Chaulk CP, Moore-Rice K, Rizzo R, et al. Eleven years of community-based directly observed therapy for tuberculosis. *JAMA* 1995;274:945–951.
- 72. Marlatt GA. Harm reduction: come as you are. *Addict Behav* 1996;21:779–788.
- 73. Riley D, Sawka E, Conley P, et al. Harm reduction: concepts and practice. A policy discussion paper. *Subst Use Misuse* 1999; 34:9–24.
- Reuter P, Caulkins JP. Redefining the goals of national drug policy: recommendations from a working group. Am J Public Health 1995;85:1059–1063.
- 75. Roche AM, Evans KR, Stanton WR. Harm reduction: roads less travelled to the Holy Grail. *Addiction* 1997;92:1207–1212.
- MacCoun RJ. Toward a psychology of harm reduction. Am Psychologist 1998;53:1199–1208.
- 77. Kalant H. Differentiating drugs by harm potential: the rational versus the feasible. *Subst Use Misuse* 1999;34:25–34.
- Normand J, Vlahov D, Moses L, eds. Preventing HIV transmission: the role of sterile needles and bleach. Washington, DC: National Research Council, Institute of Medicine. National Academy Press, 1995.
- Bluthenthal RN, Kral AH, Gee L, et al. The effect of syringe exchange use on high-risk injection drug users: a cohort study. AIDS 2000;14:605–611.
- 80. Strathdee SA, Celentano DD, Shah N, et al. Needle-exchange attendance and health care utilization promote entry into detoxification. *J Urban Health* 1999;76:448–460.
- Bruneau J, Lamothe F, Franco E, et al. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study. *Am J Epidemiol* 1997;146:994–1002.
- 82. Hagan H, McGough JP, Thiede H, et al. Volunteer bias in nonrandomized evaluations of the efficacy of needle-exchange programs. *J Urban Health* 2000;77:103–112.
- 83. Schechter MT, Strathdee SA, Cornelisse PG, et al. Do needle exchange programmes increase the spread of HIV among injec-

- tion drug users? An investigation of the Vancouver outbreak. *AIDS* 1999;13:F45–F51.
- 84. Erickson PG. Introduction: the three phases of harm reduction. An examination of emerging concepts, methodologies, and critiques. *Subst Use Misuse* 1999;34:1–7
- 85. Chen S, Wagner TH, et al. Expenditures for substance abuse
- treatment in the Department of Veterans Affairs. 1993–1999: report from the Health Economics Resource Center and the Center for Health Care Evaluation. Menlo Park, CA: VA Palo Alto Health Care System, 2000.
- 86. Rockefeller JD. Minority staff review of VA programs for veterans with special needs. United States Senate, 1999.