HEALTH POLICY

Policy Progress for Physician Treatment of Opiate Addiction

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Medical treatment of heroin addiction with methadone and other pharmacotherapies has important benefits for individuals and society. However, regulatory policies have separated this treatment from the medical care system, limiting access to care and contributing to the social stigma of even effective addiction pharmacotherapy. Increasing problems caused by heroin addiction have added urgency to the search for policies and programs that improve the access to and quality of opiate addiction treatment. Recent initiatives aiming to reintegrate methadone maintenance and other addiction pharmacotherapies into medical practice may promote both expanded treatment capacity and increased physician expertise in addiction medicine. These initiatives include changes in federal oversight of the opiate addiction treatment system, the approval of physician office–based methadone maintenance programs for stabilized patients, and federal legislation that could enable physicians to treat opiate addiction with new medications in regular medical practice.

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There are an estimated 980,000 long-term heroin users in the United States.[1] Medical and social problems attributed to heroin addiction are increasing, as measured by emergency room and criminal justice surveillance statistics, as well as by overdose deaths.[1–4] Despite large governmental expenditures for interdiction programs that aim to reduce the supply of illicit drugs, the purity of heroin is increasing and the price decreasing.[5] The costs of heroin addiction to the health care system and to society in 1996 were conservatively estimated at $5.0 billion and $21.9 billion, respectively.[6] In addition, the recent epidemic of sustained-release oxycodone abuse adds to the burden of opiate addiction in the United States.[7,8]

Opioid maintenance treatment of opiate addiction, including methadone maintenance, has been found to be effective in curtailing drug use, reducing crime, enhancing social productivity, and preventing both overdose deaths and the spread of infectious diseases, including HIV.[9] These potential benefits, however, have been limited by poor access to treatment; only 15% of opiate-dependent individuals in need of treatment can be accommodated within existing programs, and waiting lists in many areas extend to months.[9,10] Strict policies regulating opiate treatment programs have isolated methadone therapy from the medical mainstream, contributing to an addiction treatment system with few resources and tenuous political support. In addition, this isolation has slowed the development of physician expertise in addiction medicine, since physicians have had little incentive to learn about addiction treatments—even pharmacotherapies—that they cannot provide.

Recent policy initiatives have emerged that aim to improve both the access to and quality of opiate addiction treatment by reintegrating opiate addiction treatment into mainstream medicine. A new accreditation system of federal oversight of opiate treatment programs has been put in place that may reduce the regulatory burden within the addiction treatment system and recast it to more closely resemble other medical care systems. In addition, new programs have been approved that enable stabilized methadone patients to be treated in physician offices, and federal legislation has been signed that would allow physicians to treat opiate addiction with new medications outside the current treatment program structure. These innovations have the potential to expand access to needed therapies, increase physician expertise in addiction treatment, and decrease the stigma associated with effective addiction treatments.

HISTORY OF PHYSICIANS IN OPIATE ADDICTION TREATMENT

Physicians were permitted to maintain patients on opiates in their medical practices as recently as the early 20th century, until the rising temperance movement led to the criminalization of opiate addiction.[11] The Harrison Act of 1914 was interpreted as prohibiting physicians from maintaining patients on opiates for "non-medical" uses, including opiate addiction. Through the mid-1900s, treatment for opiate addiction was restricted solely to detoxification, with extremely high relapse rates documented.[11]

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In the 1960s, many large U.S. cities experienced a major heroin epidemic, and the associated increase in crime became a powerful political issue.[12] Coincident with this crisis, medical researchers discovered that methadone could effectively stabilize patients addicted to heroin, reducing drug craving, heroin use, and criminal behavior. It was primarily methadone's effect on crime that led the Nixon administration to rapidly expand methadone treatment nationally, from 400 patients in 1968 to 73,000 in 1973.[12] So rapid was this expansion that program quality was inconsistent, and documented cases of methadone diversion from treatment programs and individual physicians to street use led to federal legislation in 1974 strictly regulating the use of methadone for addiction treatment.[13] While the impact of methadone diversion on public health and law enforcement is difficult to specify,[14,15] the reduction of diversion was and remains a cornerstone of the rationale for strict regulation.[13]

Federal regulations have required that all methadone for the treatment of addiction be provided through programs licensed and monitored by the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and state methadone authorities. In general practice, physicians may prescribe methadone for the treatment of pain, but not for the treatment of addiction. Methadone for addiction treatment became and remains the only medication with such tight restrictions on physician discretion.

EFFECTIVENESS OF METHADONE MAINTENANCE

Since the 1960s, both placebo-controlled and dose-ranging clinical trials of methadone combined with counseling have demonstrated its effectiveness in reducing drug use and crime.[16–19] Extensive observational data have provided strong support for the benefits of methadone treatment in reducing mortality, overdose deaths, drug use, criminal behavior, and the spread of infectious diseases, including HIV.[9] Higher doses of methadone and a longer duration of treatment have consistently improved outcomes, and methadone retains patients longer than any other treatment modality.[20–23] Randomized trial data support the superiority of maintenance treatment with methadone compared to slow detoxification.[24] Over 80% of patients who leave methadone treatment return to compulsive daily heroin use within 1 year.[20,25]

These clinical studies support the re-conceptualization of opiate addiction as a neurobiologic disease treatable with medications and counseling.[26] Extensive laboratory research has documented the disruption of neurobiology that occurs after repeated administration of short-acting opiates such as heroin. These neurochemical alterations persist even years after cessation of use, and are normalized during maintenance therapy with methadone.[27]

Methadone has been criticized primarily on philosophical grounds as substituting one addiction for another. This critique fails to distinguish physiologic dependence, characterized by physical withdrawal if a medication is stopped, from addiction, which implies an all-consuming relationship with a substance. When judged on the basis of complete abstinence from all drug use, methadone is clearly not a cure. However, by any measure of effectiveness applied to other medical interventions, methadone works well in reducing the medical and social harms caused by drug use.[28]

IMPETUS FOR POLICY CHANGE

Despite the effectiveness of opioid maintenance therapy, its separation from mainstream medicine and its restrictive regulatory structure have limited access to treatment and compromised the quality of care. These problems have created an impetus toward system change, supporting the reintegration of opiate addiction treatment into mainstream medical systems and a reduction of the regulatory burden.

The isolation of opiate addiction treatment from mainstream medicine has increased the vulnerability of new programs to local political opposition, hindering the expansion of treatment capacity. Eight states currently have no methadone maintenance programs. In those that do, waiting lists often force programs to make treatment decisions in a setting of scarce resources. Patients who decrease but do not eliminate all drug use are at risk of being discharged from treatment as nonresponders, even if they, and society, benefit greatly from continued treatment.

Separation from the medical mainstream is also associated with few ancillary services and poor funding in comparison with other medical therapies. Limited medical oversight of current treatment programs may contribute to the frequent use of less-than-optimal methadone dosages.[29,30]

Methadone treatment has been the most highly regulated form of medical therapy, with substantial federal, state, and local constraints on clinical practice.[31] Regulation of clinical issues, such as frequency of take-home dosages, urine drug testing, and in some instances even limitations on dose have decreased the flexibility of programs to craft individual treatment plans. During initial treatment, patients must pick up their methadone daily, making treatment inconvenient and adding significant barriers to treatment entry.

Current regulations, focused on making methadone maintenance safe and curtailing diversion, are poorly designed to address the needs of patients who are successful in eliminating illicit drug use through treatment with methadone and counseling. Until recent changes, FDA rules required even highly successful patients to undergo treatment for 3 years before being permitted to take home enough methadone to last 6 days. Frequent clinic visits hinder such patients' full reintegration into society by restricting their ability to travel and imposing continued contact with less-stable patients. Such restrictions may

also deter out-of-treatment patients, who see an unending, inconvenient, and stigmatized regimen.

INTERNATIONAL MODELS

Unlike the Unites States, many other countries do not rely solely on a specialized structure for opiate addiction treatment. Methadone maintenance treatment has been provided through generalist physicians in office-based practice in many European countries,[32–37] Australia,[38,39] Canada,[40] and Thailand,[41] often as an effort to expand opiate addiction treatment capacity in response to the HIV epidemic. The experience of other countries can inform policy changes in the United States, especially regarding the role of physicians in opiate addiction treatment.

International models vary widely. Some countries or regions rely almost exclusively on generalist physicians and community pharmacies, and others utilize mixed models where new or more complicated patients are treated in specialized clinics and moved to general practice once stabilized. A "shared care" approach has also been developed, in which patients concurrently receive prescriptions for methadone from general practitioners and psychosocial addiction services from drug treatment centers.[42–44]

These less restrictive international models have resulted in substantial increases in treatment capacity and physician involvement in addiction treatment. For instance, treatment capacity in Australia grew from 2,000 to 15,000 between 1985 and 1995, with much of the expansion due to generalist physician involvement.[45,46] In Edinburgh, Scotland nearly 60% of all general practitioners provide some methadone maintenance services, and 60% to 80% of injection drug users are enrolled in methadone maintenance treatment, compared with 15% in the United States.[47]

However, the general lack of expertise in addiction issues among generalists has raised safety concerns. Deaths have been reported among methadone patients newly entering treatment and given high doses without careful dose titration,[48] and concerns regarding methadone diversion in the office-based practices of loosely monitored physicians argue for enhanced education of generalist practitioners.[49,50] These safety concerns are being addressed in Ontario, Canada, where medical record audits for patients prescribed methadone by general practitioners are used for both clinical oversight and ongoing physician education (D. Gourlay, MD, written communication, November 2001). The use of daily methadone dispensing through community pharmacies in Scotland helps assure patient and public safety while expanding access.[47]

These international experiences suggest that increased physician involvement in less restrictive opiate addiction treatment structures can support expanded treatment capacity while addressing important safety concerns. International models have been cited in calls to reduce the regulatory burden of the U.S. system and to allow more physician involvement.[9,13] While policy change in the United States has thus far been incremental, recent initiatives include changes in federal oversight of opiate treatment programs, the approval of programs allowing physicians to treat stabilized methadone maintenance patients, and legislation that could facilitate physician treatment of opiate addiction with new medications.

CHANGES IN FEDERAL OVERSIGHT: FROM REGULATION TO ACCREDITATION

In January 2001, the Department of Health and Human Services published its final regulation that transfers the federal authority over opiate treatment programs from the FDA to the Center for Substance Abuse Treatment (CSAT) within the Substance Abuse and Mental Health Administration. The new structure replaces the regulatory system with an accreditation model that parallels federal oversight of other medical care facilities, such as hospitals.[51] The move to accreditation emphasizes the status of opioid maintenance as an effective medical therapy and provides a more flexible mechanism for improving the quality of opiate addiction treatment.

The change to an accreditation model is accompanied by enhanced clinical flexibility. For instance, the federal regulatory limitations of take-home methadone doses are relaxed, and up to 1 month of take-home doses are permitted after 2 years in successful treatment. Also rescinded was the prohibition of take-home doses of levomethadyl acetate, a longer-acting opiate agonist with efficacy comparable to that of methadone,[52,53] although recent cardiac safety concerns may continue to limit the use of this medication. Increased clinical flexibility will require evaluation of opiate treatment programs on the basis of clinical outcomes rather than process compliance.

An accreditation system has the potential to foster more-rapid implementation of new research results in routine clinical practice. Instead of requiring cumbersome regulatory or legislative action prior to implementation of new clinical strategies, accreditation standards can be routinely updated. Improved medical oversight of treatment may also be encouraged through such standards. While accreditation has potential benefits, it could prove costly if accreditation standards are overly burdensome.

EXPANDING THE PHYSICIAN ROLE: MEDICAL MAINTENANCE

A second policy innovation directly incorporates physicians into opiate addiction treatment through a model known as "medical maintenance." Medical maintenance reintegrates methadone treatment into medical practice by transferring successful, long-term methadone maintenance patients to a medical setting and allowing them fewer treatment visits and more take-home medication than in traditional methadone programs. The early experimental medical maintenance programs, which began in the mid-1980s, were authorized through the Investigational

New Drug (IND) process of the FDA, but were not available to patients outside these research settings.

Medical maintenance programs are designed for clinically stabilized patients, defined as those who have demonstrated their ability to handle take-home doses of methadone responsibly and have abstained from illicit drugs and criminal activity. These patients need fewer of the intensive services provided in traditional methadone treatment programs, and would benefit from improved access to primary care medical services because of their high rates of viral hepatitis, HIV, and tobacco use. For patients, the added responsibility of medical maintenance acknowledges the strides they have made in recovery, and further limits their contact with less stable patients.

Twelve- to fifteen-year outcomes have been reported recently for 2 experimental medical maintenance programs.[54,55] Both document very high treatment retention rates, few problems with ongoing drug use, no methadone diversion, and protection from HIV exposure. These programs selected patients who had been in treatment for at least 5 years, were employed, and had refrained from drug use or criminal activity for at least 3 years. Patients were transferred to the medical offices of private physicians, where they were allowed monthly methadone pick-up but received no other required addiction services. These results demonstrate the feasibility of long-term medical maintenance for a select group of stabilized patients.

A separate randomized study in Chicago in the early 1980s experimented with a medical maintenance model for patients who had spent less time in treatment.[56] While clinical stability was defined as in previous medical maintenance programs, this study admitted patients who had been in methadone treatment for 1 year and had been stable for just 6 months. Results showed no difference in addiction severity or retention between patients in usual care and those transferred from traditional methadone maintenance to a less intensive drug treatment clinic. Patient acceptance was excellent, costs were reportedly reduced, and there was no evidence of methadone diversion.

From a policy perspective, moving stabilized patients out of regular methadone programs can improve access to treatment by freeing up spaces for new patients without necessitating approval of new programs. Medical maintenance may also increase the acceptability of initial methadone treatment for out-of-treatment patients by providing a concrete goal associated with excellent progress in recovery. As a result, experts convened by the Institute of Medicine (1995)[13] and the National Institutes of Health (1997)[9] have advocated medical maintenance as one vehicle to enhance access to methadone treatment.

RECENT POLICY PROGRESS FOR MEDICAL MAINTENANCE

Despite the success of experimental programs, the authorization of medical maintenance under the IND process was intended for the pursuit of new research. Those wishing to apply the medical maintenance research results to regular methadone programs have faced regulatory obstacles to widespread implementation. As a response, a new generation of medical maintenance programs has been developed that seeks regulatory approval through exemptions from current regulations that are available to any program rather than through specialized research waivers. These programs are models that can be widely replicated and are intended to improve access to methadone treatment.

In 1997, the Connecticut State legislature passed a bill authorizing a feasibility study of medical maintenance. The resulting pilot project randomized patients with 1 year of clinical stability and no evidence of illicit drug use to receive methadone either from their treatment program or from a physician's office. Patients visited the physicians monthly, and registered nurses dispensed the methadone from physician offices on a weekly basis. To allow stabilized patients with less than 3 years in treatment to receive a 6-day supply of take-home methadone, the FDA approved a program-wide exemption, the first such exemption for office-based methadone maintenance. Results of this 6-month program documented high patient satisfaction and no differences in addiction outcomes between usual methadone treatment and the office-based treatment model.[57]

A more recent initiative in Seattle, Washington, the Methadone Maintenance in Primary Care Program, aims to integrate methadone maintenance and primary medical care for stabilized methadone patients. Extending the precedent of the Connecticut program, multiple program-wide exemptions from FDA regulations were sought and approved in December 1999, including a provision to allow patients stabilized for 1 year to receive up to a 1-month supply of methadone.

The Seattle program is structured and licensed as a satellite of a local methadone program, Evergreen Treatment Services, and physicians are registered on Evergreen's FDA license. Eligible patients visit their physicians monthly for primary medical care and methadone treatment, and may continue counseling at the traditional methadone program if they desire. Methadone orders are filled at the Harborview Medical Center pharmacy, which is registered as a DEA Narcotic Treatment Program. Dispensing visits include an observed dose and clinical assessment by trained pharmacists. Safety protocols have been developed that include routine urine drug testing and unannounced medication call-backs to verify appropriate use, and patients requiring more intensive treatment may immediately return to Evergreen should the need arise. The initial 30-patient pilot program evaluation results are expected later this year.

These recent programs demonstrate that physician office–based models closely tied to traditional methadone programs are now feasible, and that the necessary program exemptions from existing regulations can be obtained. In March 2000, a letter to the field from the leadership of FDA

and CSAT indicated that requests for program-wide exemptions for medical maintenance will be considered, with the Connecticut and Seattle programs cited as appropriate models.[58] This federal leadership, and the precedents set by these programs may assist others in their efforts to use medical maintenance to expand and improve methadone treatment.

LIMITATIONS OF MEDICAL MAINTENANCE

Although these initiatives are a step forward, the development and implementation of medical maintenance faces many obstacles and requires a strong collaborative effort involving multiple participants. Support from state methadone authorities has been crucial to the approval of program exemptions for medical maintenance, and the willingness of other states to follow these precedents is not yet known. Opiate treatment programs may resist medical maintenance because of the financial implications of losing stable patients who require few services and who subsidize the treatment of less stable patients with multiple needs. Physicians may balk at the complexities of integrating methadone treatment into medical practice, including the need for extra training and coordination with clinical support.

Unless the patient selection criteria for medical maintenance are significantly widened, these programs have only limited potential for expanding access to methadone treatment. A minority of patients in current methadone treatment meets the requirement of long-term abstinence from illicit or nonprescribed drugs, and patients who are new to methadone treatment are not eligible for current medical maintenance models. Medical maintenance may improve the U.S. treatment system primarily by making traditional programs more attractive to patients who reject the inflexible structure of current methadone programs, but who would consider long-term methadone treatment if medical maintenance were part of the continuum of care.

PHARMACY INVOLVEMENT

The involvement of community pharmacists in methadone dispensing has been an important component of the expansion of methadone treatment in other countries and has a number of advantages. Pharmacies may be able to provide more flexible dispensing hours than physician offices, and are better suited to institute the rigorous record-keeping systems required for methadone accountability. Pharmacists in the Seattle medical maintenance program are involved in the clinical assessment and monitoring of patients, and were trained alongside the physicians. Specific protocols were developed to allow pharmacists to tailor dispensing schedules within the parameters delineated by physicians. Pharmacy dispensing may also play a role in bringing methadone treatment to rural areas, where large treatment programs are not feasible.

In an effort to apply the lessons learned internationally and to improve access to opiate addiction treatment in the United States, pharmacy models are being considered that would incorporate treatment of patients new to methadone maintenance. While regulatory policies have thus far deterred development of this model, a feasibility study of physician- and community pharmacy–based methadone treatment is underway in San Francisco, with a primary goal of initiating new patients directly into physician office settings.[59] In New York, a trial to increase medical involvement in methadone maintenance treatment is ongoing. In this program, primary care physicians are given control of the methadone prescription for patients who continue to receive services from traditional methadone programs. A pharmacy dispensing model is now being developed.[60]

OFFICE-BASED BUPRENORPHINE

A third major policy initiative in the United States may soon enable physicians to directly admit and treat new patients in office-based practice using a new medication. Buprenorphine is a partial opiate agonist that is currently awaiting final FDA approval. Like methadone, buprenorphine reduces drug craving and blocks the effects of heroin, but as a partial agonist it has less potential for overdose and a less severe withdrawal syndrome. To reduce the risk of abuse, buprenorphine has been formulated with naloxone, an opiate antagonist used to reverse opiate overdose. When given sublingually, the naloxone is not absorbed, but if the combination is injected, all opiate effects are blocked.

Studies of buprenorphine efficacy have shown it to be comparable to or slightly less effective than methadone,[53,61,62] although its safety features may make it a more attractive medication for physician office–based opiate addiction treatment.[63] Trials of buprenorphine in the United States have included protocols allowing multiple take-home doses early in treatment so as to model its use in physician office practice rather than through opiate treatment programs.

Buprenorphine has been used extensively in France, where general practitioners have prescribed buprenorphine to approximately 55,000 patients since 1996. Observational studies of treatment retention and other addiction outcomes in office-based practice have been positive[64] and comparable to treatment in specialized drug treatment clinics.[65] Under a minimally monitored prescription policy, misuse of buprenorphine (without naloxone) has been documented,[66] though overdose deaths are rare.[67]

Federal legislation (The Drug Addiction Treatment Act of 2000) was recently signed into law that would allow buprenorphine to be prescribed outside traditional opiate treatment programs. The legislation limits buprenorphine practice to licensed physicians who demonstrate clinical expertise through completion of 8 hours of specific training, certification in addiction medicine or addiction

psychiatry, or participation in a clinical trial of buprenorphine. Physicians must register with the federal Substance Abuse and Mental Health Services Administration, and limit any single office-based practice to 30 patients.

Widespread implementation of office-based buprenorphine treatment will depend on patient and physician acceptability as well as provision of adequate financing for the associated medical, pharmacy, and psychosocial addiction treatment services. The use of buprenorphine for the initial treatment of opiate addiction will require considerable effort to integrate medication prescription with patient monitoring and counseling, services beyond those offered in most generalist practices. Calls for more restrictive regulation of office-based buprenorphine, based on the perception of inappropriate physician prescribing or widespread buprenorphine abuse, could also threaten this treatment modality just as regulatory constraints have limited access to methadone.

PHYSICIAN TRAINING

The separation of opiate addiction treatment from the medical care system has resulted in a lack of education and experience among physicians in methadone treatment and addiction medicine more generally. While physicians regularly treat the medical complications of addiction, physicians lack skills in the screening, assessment, treatment, and referral of patients with substance abuse problems.[68–70] Current curricula within medical school, residency, and continuing education programs for generalist physicians devote little time to addiction medicine topics.

Physicians practicing medical maintenance or using buprenorphine will need both basic training and clinical support as patient care issues arise; a mentoring model may be most appropriate as physicians begin these new areas of practice. The American Society of Addiction Medicine and the American Methadone Treatment Association have provided general courses on opiate addiction and methadone treatment. Specific courses have also been developed for generalist physicians entering medical maintenance practice and for those considering buprenorphine. These courses include a review of the epidemiology, neurobiology, natural history, and treatment of opiate dependence, including relapse prevention. In addition, case studies and discussions with patients are featured.[72] Participation in appropriate training and medical maintenance or office-based buprenorphine practice may give physicians tools they can apply to their other patients with addiction problems.

CONCLUSION

Restrictive regulations and political opposition have curtailed the physician's role in opiate addiction treatment, creating an isolated and inflexible treatment system and limiting access to effective therapy. Recent policy developments support an emerging consensus that the reintegration of opiate addiction treatment into mainstream medicine can improve access to needed services and increase physician understanding of and experience in treating substance abuse problems. Although this reintegration is challenging, it begins to address the isolation and stigma that have prevented opiate addiction treatment from reaching its full potential.

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REFERENCES

1. Office of National Drug Control Policy. National drug control strategy. Washington, DC: Office of National Drug Control Policy; 2000.
2. Solet D, Hagan H, Nakaguwara J, Plough A, Ball JK. Unintentional opiate overdose deaths—King County, Washington, 1990–1999. Morb Mortal Wkly Rep. 2000;49:636–8.
3. Oxman GL, Kowalski S, Drapela L, et al. Heroin overdose deaths—Multinomah County, Oregon, 1993–1999. Morbid Mortal Wkly Rep. 2000;49:633–6.
4. Drug Abuse Warning Network Annual Medical Examiner Data 1999. Substance Abuse and Mental Health Services Administration, Office of Applied Studies Web site. Available at: http://www.samhsa.gov/oas/DAWN/99me_annual.pdf. Accessed March 15, 2002.
5. Bach PB, Lantos J. Methadone dosing, heroin affordability, and the severity of addiction. Am J Public Health. 1999;89:662–5.
6. Mark TL, Woody GE, Juday T, Kleber HD. The economic costs of heroin addiction in the United States. Drug Alcohol Depend. 2001; 61:195–206.
7. Meadows M. Prescription drug use and abuse. FDA Consum. 2001;35:18–24. Available at: http://www.fda.gov/fdac/features/2001/501_drug.html. Accessed March 15, 2002.
8. Community Epidemiologic Work Group. Epidemiologic Trends in Drug Abuse: Advance Report. Rockville, Md: National Institute on Drug Abuse; 2001.
9. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. JAMA. 1998;280:1936–43.
10. Rounsaville BJ, Kosten TR. Treatment for opioid dependence: quality and access. JAMA. 2000;283:1337–9.
11. Musto DF. The American Disease: Origins of Narcotic Control. Expanded ed. New York: Oxford University Press; 1987.
12. Massing M. The Fix. New York: Simon and Schuster; 1998.
13. Rettig RA, Yarmolinsky A, eds. Federal Regulation of Methadone Treatment. Washington, D.C: National Academy Press; 1995.
14. Spunt B, Hunt D, Lipton D, Goldsmith D. Methadone diversion: a new look. J Drug Issues. 1986;18:569–83.
15. Barrett DH, Luk AJ, Parrish RG, Jones TS. An investigation of medical examiner cases in which methadone was detected, Harris County, Texas, 1987–1992. J Forensic Sci. 1996;41:442–8.
16. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. JAMA. 1965;193:80–4.
17. Gunne LM, Gronbladh L. The Swedish methadone maintenance program: a controlled study. Drug Alcohol Depend. 1981;7: 249–56.
18. Newman RG, Whitehill WB. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. Lancet. 1979;2:485–8.
19. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. Lancet. 1999;353:221–6.

20. Ball J. The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes. New York: Springer-Verlag; 1991.
21. Caplehorn JR, Bell J. Methadone dosage and retention of patients in maintenance treatment. Med J Aust. 1991;154:195–9.
22. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose-response effects of methadone in the treatment of opioid dependence. Ann Intern Med. 1993;119:23–7.
23. Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. JAMA. 1999;281:1000–5.
24. Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. JAMA. 2000; 283:1303–10.
25. Hubbard RL, Marsden ME, Rachel JV. Drug Abuse Treatment: A National Study of Effectiveness. Chapel Hill: University of North Carolina Press; 1989.
26. Dole VP. Implications of methadone maintenance for theories of narcotic addiction. JAMA. 1988;260:3025–9.
27. Stimmel B, Kreek MJ. Neurobiology of addictive behaviors and its relationship to methadone maintenance. Mt Sinai J Med. 2000;67: 375–80.
28. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000;284:1689–95.
29. D'Aunno T, Vaughn TE. Variations in methadone treatment practices. Results from a national study. JAMA. 1992;267: 253–8.
30. Cooper JR. Ineffective use of psychoactive drugs. Methadone treatment is no exception. JAMA. 1992;267:281–2.
31. Parrino MW. State Methadone Treatment Guidelines. Treatment improvement protocol (TIP) series no 1. Rockville, Md: Center for Substance Abuse Treatment; 1993.
32. Wilson P, Watson R, Ralston GE. Methadone maintenance in general practice: patients, workload, and outcomes. BMJ. 1994; 309:641–4.
33. Peters AD, Reid MM. Methadone treatment in the Scottish context: outcomes of a community-based service for drug users in Lothian. Drug Alcohol Depend. 1998;50:47–55.
34. Hutchinson SJ, Taylor A, Gruer L, et al. One-year follow-up of opiate injectors treated with oral methadone in a GP-centred programme. Addiction. 2000;95:1055–68.
35. Brewer C. Recent developments in maintenance prescribing and monitoring in the United Kingdom. Bull NY Acad Med. 1995;72: 359–70.
36. Gruer L, Wilson P, Scott R, et al. General practitioner–centred scheme for treatment of opiate-dependent drug injectors in Glasgow. BMJ. 1997;314:1730–5.
37. Klingemann HK. Drug treatment in Switzerland: harm reduction, decentralization and community response. Addiction. 1996;91: 723–36.
38. Caplehorn J, Batey R. Methadone maintenance in Australia. J Drug Issues. 1992;22:661–79.
39. Byrne A, Wodak A. A census of patients receiving methadone treatment in a general practice. Addict Res. 1996;3:341–9.
40. College of Physicians and Surgeons of Ontario. Methadone Maintenance Guidelines. Toronto: The College of Physicians of Ontario; 1996.
41. World Health Organization Programme on Substance Abuse Substitution Project. Report of WHO Consultation, Geneva, 15–9 May 1995. Geneva: World Health Organization; 1996.
42. Morrison C. Obstetric liason in drug dependency. Addict Res. 1995;3:93–101.
43. Greenwood J. Persuading general practitioners to prescribe—good husbandry or a recipe for chaos? Br J Addict. 1992;87:567–75.
44. Greenwood J. Creating a new drug service in Edinburgh. BMJ. 1990;300:587–9.
45. Hall D. The Demand for Methadone Maintenance Treatment in Australia. National Drug and Alcohol Research Center, Technical Report No. 28. Sydney, Australia: National Drug and Alcohol Research Center; 1995.
46. Ward J, Mattick RP, Hall D. Methadone Maintenance Treatment and Other Opioid Replacement Therapies. Amsterdam: Harwood Academic Publishers; 1998.
47. Weinrich M, Stuart M. Provision of methadone treatment in primary care medical practices: review of the Scottish experience and implications for US policy. JAMA. 2000;283:1343–8.
48. Drummer OH, Opeskin K, Syrjanen M, Cordner SM. Methadone toxicity causing death in ten subjects starting on a methadone maintenance program. Am J Forensic Med Pathol. 1992;13: 346–50.
49. Strang J, Sheridan J. Methadone prescribing to opiate addicts by private doctors: comparison with NHS practice in southeast England. Addiction. 2001;96:567–76.
50. Fountain J, Strang J, Gossop M, Farrell M, Griffiths P. Diversion of prescribed drugs by drug users in treatment: analysis of the UK market and new data from London. Addiction. 2000;95:393–406.
51. Substance Abuse and Mental Health Services Administration. Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction; Final Rule. Fed Regist. 2001;66:4075–102.
52. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med. 2000; 343:1290–7.
53. Glanz M, Klawansky S, McAullife W, Chalmers T. Methadone vs. L-alpha-acetylmethadol (LAAM) in the treatment of opiate addiction. A meta-analysis of the randomized, controlled trials. Am J Addict. 1997;6:339–49.
54. Salsitz EA, Joseph H, Frank B, et al. Methadone medical maintenance (MMM): treating chronic opioid dependence in private medical practice—a summary report (1983–1998). Mt Sinai J Med. 2000;67:388–97.
55. Schwartz RP, Brooner RK, Montoya ID, Currens M, Hayes M. A 12-year follow-up of a methadone medical maintenance program. Am J Addict. 1999;8:293–9.
56. Senay EC, Barthwell A, Marks R, Bokos PJ. Medical maintenance: an interim report. J Addict Dis. 1994;13:65–9.
57. Fiellin DA, O'Connor PG, Chawarski M, Pakes JP, Pantalon MV, Schottenfeld RS. Methadone maintenance in primary care: a randomized controlled trial. JAMA. 2001;286:1724–31.
58. Lepay D, Clark HW. Federal Advisory on Methadone Medical Maintenance Exemptions. Rockville, Md: U.S. Department of Health and Human Services; 2000.
59. San Francisco Department of Public Health. A Program for Physician Prescription of Methadone in San Francisco. San Francisco, Calif: San Francisco Department of Public Health; 1999. Available at: http://www.dph.sf.ca.us/Reports/methrep.pdf. Accessed March 15, 2002.
60. Drucker E, Hartel D, Tuchman E, Bonuck K, Vavaglakis P, McCarthy W. Office Based Methadone Prescribing In Primary Care: Results of a Randomized Clinical Trial of Safety and Efficacy. San Juan, Puerto Rico: College on Problems of Drug Dependence; 2000.
61. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. Addiction. 1998;93:475–86.
62. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry. 1997;54:713–20.
63. O'Connor PG, Oliveto AH, Shi JM, et al. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. Am J Med. 1998;105:100–5.
64. Fhima A, Henrion R, Lowenstein W, Charpak Y. Two-year follow-up

of an opioid-user cohort treated with high-dose buprenorphine (Subutex). Ann Med Interne (Paris). 2001;152(Suppl 3):IS26–36.
65. Vignau J, Brunelle E. Differences between general practitioner– and addiction centre–prescribed buprenorphine substitution therapy in France. Preliminary results. Eur Addict Res. 1998; 4(Suppl 1):24–8.
66. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. Addiction. 2001; 96:267–72.
67. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. JAMA. 2001;285:45.
68. Saitz R, Mulvey KP, Plough A, Samet JH. Physician unawareness of serious substance abuse. Am J Drug Alcohol Abuse. 1997;23: 343–54.
69. Hasin DS, Grant BF, Dufour MG, Endicott J. Alcohol problems increase while physician attention declines. 1967 to 1984. Arch Intern Med. 1990;150:397–400.
70. Stimmel B. Appropriate training in alcohol and substance abuse for primary care physicians: defining the problem. In: Sirica C, ed. Training about Alcohol and Substance Abuse for All Primary Care Physicians. A Conference Sponsored by the Josiah Macy, Jr. Foundation, chaired by David C. Lewis, Phoenix, Arizona, October 2–5, 1994. New York: Josiah Macy, Jr. Foundation; 1995:249–74.
71. Fiellin DA, Storti SA, Schottenfeld RS, Biscoe JD, Pantalon MV, O'Connor PG. Methadone medical maintenance: a training and resource guide for office-based physicians. Vol. 2001: New England Addiction Technology Transfer Center; 2000. Available at http://www.caas.brown.edu/ATTC-NE/pubs/OBOT/. Accessed 11/24/01.