By Bohdan Nosyk, M. Douglas Anglin, Suzanne Brissette, Thomas Kerr, David C. Marsh, Bruce R. Schackman, Evan Wood, and Julio S.G. Montaner

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ANALYSIS & COMMENTARY

A Call For Evidence-Based Medical Treatment Of Opioid Dependence In The United States And Canada

ABSTRACT Despite decades of experience treating heroin or prescription opioid dependence with methadone or buprenorphine—two forms of opioid substitution therapy—gaps remain between current practices and evidence-based standards in both Canada and the United States. This is largely because of regulatory constraints and pervasive suboptimal clinical practices. Fewer than 10 percent of all people dependent on opioids in the United States are receiving substitution treatment, although the proportion may increase with expanded health insurance coverage as a result of the Affordable Care Act. In light of the accumulated evidence, we recommend eliminating restrictions on office-based methadone prescribing in the United States; reducing financial barriers to treatment, such as varying levels of copayment in Canada and the United States; reducing reliance on less effective and potentially unsafe opioid detoxification; and evaluating and creating mechanisms to integrate emerging treatments. Taking these steps can greatly reduce the harms of opioid dependence by maximizing the individual and public health benefits of treatment.

Forty-five years after the introduction of opioid substitution treatment, practitioners have at their disposal more tools than ever to treat opioid dependence. This treatment replaces illicit or off-label opioid use with opioids that are longer acting but induce less euphoria, such as methadone or buprenorphine, which must be delivered under medical supervision. The treatment eliminates withdrawal symptoms and cravings, and it blocks the euphoric effects of other opioids. Yet these tools are not being used to their greatest potential in the United States or Canada.

As of 2009 there were approximately 2.3 million people in the United States with opioid dependence[1]—that is, a dependence on heroin or prescription opioids such as oxycodone. In Canada there were an estimated 75,000–125,000 injection drug users (the vast majority of whom injected opioids)[2] and some 200,000 people with prescription opioid dependence as of 2012.[3] Increases in the prevalence and related hazards of opioid use, particularly from the misuse of prescription opioids, have been reported in both countries.[4,5]

Opioid overdose is now the second leading cause of accidental death in the United States—surpassed only by motor vehicle accidents—and has been labeled a national epidemic.[6] In Ontario deaths related to prescription opioids doubled from 13.7 deaths per million people in 1991 to 27.2 deaths per million people in 2004, with oxycodone a major contributor to the increase.[7]

Substitution treatment with methadone or buprenorphine has been shown to be effective in numerous randomized trials, meta-analyses,

Bohdan Nosyk (bnosyk@cfenet.ubc.ca) is an associate professor of health economics in the Faculty of Health Sciences at Simon Fraser University, in Burnaby, British Columbia, and a research scientist at the British Columbia Centre for Excellence in HIV/AIDS, in Vancouver.

M. Douglas Anglin is associate director of the University of California, Los Angeles, Integrated Substance Abuse Programs.

Suzanne Brissette is an addictions physician at the Hôpital Saint-Luc, in Montreal, Quebec.

Thomas Kerr is a codirector of the Addiction and Urban Health Research Institute at the British Columbia Centre for Excellence in HIV/AIDS and a professor of medicine at the University of British Columbia, in Vancouver.

David C. Marsh is associate dean of community engagement at the Northern Ontario School of Medicine, in Sudbury.

Bruce R. Schackman is an associate professor of public health at Weill Cornell Medical College, in New York City.

Evan Wood is a codirector of the Addiction and Urban Health Research Institute at the British Columbia Centre for Excellence in HIV/AIDS and a professor of medicine at the University of British Columbia.

Julio S.G. Montaner is clinical director of the British Columbia Centre for Excellence in HIV/AIDS and a professor of medicine at the University of British Columbia.

and large-scale longitudinal studies on several continents.[8–11] Methadone costs less and is more effective in retaining clients in treatment, while buprenorphine has been reported to have a lower risk of abuse, including being diverted for nonprescription use. Details on these medications, their modes of delivery, and their effectiveness are in Exhibit 1.

Prolonged retention in treatment typically results in reductions in illicit drug use, behaviors that increase the risk of contracting HIV, and criminal activity.[8] Discontinuing treatment typically results in relapse and elevated risk of mortality, with the risk of death after discontinuing treatment estimated to be 2.4 times greater than during treatment.[12] Fewer programmatic restrictions and higher methadone dosing practices are known predictors of positive treatment outcomes,[13] and retention generally improves during subsequent treatment attempts.[11] Treatment may be more effective for prescription opioid abuse than for heroin abuse.[14]

Opioid substitution treatment can offer synergies with infectious disease treatment and prevention. Substance abuse treatment reduces drug injecting and needle sharing, and it facilitates access to HIV testing as well as access and adherence to antiretroviral therapy for HIV.[15] Recent innovations in HIV prevention through antiretroviral treatment[16] and emerging treatment options for hepatitis C[17] can further increase the health benefits of opioid substitution treatment.

The treatment has also been deemed highly cost-effective, if not cost saving.[18–21] Often the costs of treatment are more than offset by reductions in acquisitive crime (theft or burglary)[20] and in the use of health resources related to

EXHIBIT 1

Characteristics Of Opioid Substitution Treatment Medications And Their Delivery In Canada And The United States

Characteristic	Methadone	Buprenorphine (B) or buprenorphine and naloxone (BN)
Description	Opioid agonist;[a] controls opioid craving, eliminating withdrawal symptoms on long-term basis and blocking effects of self-administered opioids	B: Partial opioid agonist;[b] similar characteristics as methadone, but with ceiling effect, which lowers abuse and overdose potential BN: Partial opioid agonist[b] paired with opioid antagonist,[c] which if injected or snorted induces withdrawal symptoms, further discouraging abuse
Administration	Oral; liquid form	Oral tablet or film; administered under tongue
Prescription source, US	Federally regulated drug treatment centers that must adhere to detailed regulations, including on-site counseling and urine toxicology testing	Federally regulated drug treatment centers, physicians' offices
Prescription source, Canada	Drug treatment centers, physicians' offices	Drug treatment centers, physicians' offices; available in some jurisdictions under special authority (as second-line therapy)
Dispensing, US	On site at federally regulated drug treatment centers; take-home doses available only for patients who demonstrate stability in adherence and test negative in urine drug screens	Community-based pharmacies or on site at federally regulated drug treatment centers
Dispensing, Canada	Community-based pharmacies, with ingestion directly observed by pharmacists; take-home doses available only for patients who demonstrate stability in adherence and test negative in urine drug screens	Community-based pharmacies
Effectiveness	Superior to non–medication based treatment; more effective than buprenorphine in maintenance treatment of heroin dependence	Superior to non–medication based treatment
Potential risks and side effects	Constipation, excess sweating, drowsiness, decreased libido; irregular heartbeat at higher doses Susceptible to abuse and overdose, particularly during first two weeks Risk of overdose among opioid-naïve individuals[d] if medication is diverted from intended use	Headache as well as constipation, excess sweating, drowsiness, decreased libido; possible liver problems and stomach pain Sublingual buprenorphine can be dissolved, then injected, resulting in possible overdose risk BN formulated to prevent abuse; naloxone has no effect when taken under the tongue but has unpleasant antagonist properties when injected or snorted

SOURCES (1) Amato L, et al. An overview of systematic reviews of the effectiveness of opiate maintenance therapies (Note 8 in text). (2) Fiellin DA, O'Connor PG. New federal initiatives to enhance the medical treatment of opioid dependence. Ann Intern Med. 2002;137(8):688–92. (3) Mattick RP, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Note 10 in text). [a]Full opioid agonists bind to opioid receptors and activate them, thereby decreasing or eliminating the effect of any subsequent heroin use. [b]Partial opioid agonists bind to opioid receptors and activate them, but not to the same degree that full agonists do. As higher doses and the medication ceiling effects are reached, partial agonists can act like antagonists—occupying receptors but not activating them (or only partially activating them), while at the same time displacing or blocking full agonists from receptors. [c]Opioid antagonists block opioid receptors and thus counteract the effects of opioids. [d]Individuals who have not previously taken any form of opioid.

The diversion of prescription opioids remains an issue in the areas of criminal justice and public health.

transmissions of HIV or hepatitis C.[21] The treatment also results in improvements in health-related quality of life.[22] Substitution treatment may be even more advantageous if potential increases in workplace productivity are realized,[19] resulting in additional economic benefits outside of the health care sector.

The next sections of this article discuss the following four key areas of concern: restrictions on office-based opioid substitution treatment, financial barriers to treatment, the use of opioid detoxification, and the consideration of new and emerging treatment approaches. We then summarize recommendations for policy changes that would address these concerns.

Expanding Treatment To Office-Based Settings

Methadone maintenance treatment is the most common opioid substitution treatment worldwide.[9,23] However, access to methadone is more restricted in the United States than elsewhere in the developed world.[23] Methadone may be prescribed and dispensed only on an outpatient basis through opiate treatment programs that are certified and regulated by the federal Drug Enforcement Agency and Substance Abuse and Mental Health Services Administration (SAMHSA). The use of methadone to treat opioid addiction is subject to a tripartite system of regulation involving SAMHSA, the Drug Enforcement Agency, and individual states. In some locations, dispensing may also be subject to county or municipal regulations.

The number of methadone-prescribing facilities in the United States has remained relatively constant since 2002, constituting about 8 percent of all substance abuse treatment facilities; coverage varies by region.[24] It has been estimated that less than 10 percent of Americans addicted to heroin and prescription opioids are receiving opioid substitution treatment.[25]

Treatment in doctors' private offices could expand access to methadone in a less stigmatizing environment than clinics, where patients arrive en masse for their doses. Office-based treatment would further enable care of comorbidities such as HIV, hepatitis C, and psychiatric illnesses.[26] In Canada great increases in access to methadone treatment were observed following the implementation of office-based treatment in 1996. For instance, the number of clients receiving methadone in British Columbia rose from 2,800 in 1996 to 13,000 in 2012 (Ailve McNestry, deputy registrar, College of Physicians and Surgeons of British Columbia, personal communication, April 14, 2012). In Ontario the increase was from 700 to nearly 30,000.[27] However, the availability of office-based treatment remains limited in many provinces and rural settings, and long waiting lists for treatment slots are common.[27]

The argument for restricting access to methadone because it might be abused or diverted to an illegal use becomes moot if the drug is provided only under direct observation in a pharmacy or clinic. Because methadone can be lethal to people who have no experience with opioids, including children, it is important to control the availability of the drug. However, methadone typically provides no high, or feeling of euphoria, to people with opioid dependence. Methadone is therefore less subject to abuse and less desirable than heroin, oxycontin, and other prescription opioids.

Although mortality related to methadone overdose has been cited as a key barrier to office-based treatment, evidence indicates that increases in overdose during the past decade stem largely from methadone prescriptions for pain.[28] Reports from opioid diversion surveillance systems confirm that methadone tablets (prescribed for pain) are more likely to be diverted than oral-form solutions of methadone (prescribed for opioid dependence) or buprenorphine.[29] Similar trends in methadone-related overdose deaths in the United Kingdom were reversed following the introduction of office-based prescribing of methadone in conjunction with its supervised dispensing.[30]

The diversion of prescription opioids remains an issue in the areas of criminal justice and public health. Nonetheless, undue restrictions on prescribing medications for treatment of opioid dependence are counterproductive. Indeed, it is plausible that illicit demand for these medications has been driven by existing barriers to treatment, although this hypothesis has not been tested formally.

The policy of restricting access to methadone to drug treatment centers in the United States, in contrast to standard practice elsewhere in the

developed world,[23] needs to be reversed. The American Society of Addiction Medicine recommended that change in 2004,[31] but it has not yet taken place.

Policies aimed at expanding access to substitution therapy would also require the widespread participation of physicians and pharmacies. Barriers to such participation include general practitioners' limited training in addiction medicine and physicians' ambivalence about providing the therapy, driven by the complexity complexity of cases and the stigma attached to drug addiction.

The experience in British Columbia and Ontario, where weekend training and certification programs for general practitioners were instituted and actively promoted, provides hope that office-based methadone maintenance treatment could succeed in the United States. That said, challenges in recruiting physicians to prescribe buprenorphine have been observed throughout Canada and the United States. This problem may be solved in part by mandated addiction education in medical schools, along with increased financial incentives in the form of specific physician billing codes for providing opioid substitution treatment.[27] Office-based methadone treatment in the United States could help meet the increased demand for opioid substitution treatment that health reform is expected to produce.

In Canada the availability of buprenorphine and the buprenorphine-naloxone combination and their inclusion in drug formularies can provide alternative treatment options for those unable to be maintained on methadone. Several Canadian provinces have allowed coverage of buprenorphine under the special authority of provincial colleges of physicians and surgeons—generally only if methadone is contraindicated or not medically tolerated—and have incorporated its use into certification courses for general practitioners.[32] Nonetheless, a recent report by the Canadian Executive Council on Addictions suggested that buprenorphine prescribing remains uncommon,[27] although there is little evidence on the extent of its use and associated outcomes.

2,528

Facilities

A total of 2,528 facilities in the United States reported offering opioid substitution treatment.

Financial Barriers To Treatment

In describing drug dependence as a chronic medical condition, Thomas McLellan and coauthors[33] argued that treatment for drug dependence should be covered by public and private insurers. This goal has not been reached in the United States or Canada, despite the demonstrated economic value of that treatment.[18–21]

According to 2010 data from SAMHSA,[34] 2,528 facilities in the United States reported offering opioid substitution treatment. Nearly a quarter of them (24.1 percent) reported accepting only self-payment or private or military insurance. Only 40 percent reported that at least partial payment assistance was available through state and private insurance. Although these data provide useful information on the funding and use of the treatment, it is unclear how many patients drop out of a program or never seek treatment because of the associated out-of-pocket costs. Financial barriers may therefore limit access and continuity of treatment for disadvantaged people, whose cases are often the most complex to treat.

The increasing privatization of methadone clinics provides further impetus for offering methadone in office-based settings in the United States. Nearly 31 percent of outpatient methadone centers were private for-profit facilities in 2011, while another 57 percent were private and nonprofit.[35] Compared to public and nonprofit clinics, for-profit clinics have smaller staffs[36] and are less likely to provide access to treatment and provide treatment of shorter duration for clients with no insurance who are unable to pay.[37]

Although Canada boasts universal health care coverage for in- and outpatient care, drug treatment is not covered nationally. Instead, it is covered to varying degrees by provincial insurance plans. All citizens are eligible for coverage, but such plans often fully cover medications for poor and elderly people only, charging copayments for people earning an income. This fact may prevent people with opioid dependence from reentering the workforce. Relaxing constraints on the availability of take-home doses of methadone and on the length of eligibility for such doses could reduce costs to clients who pay for their own pharmacy services. That change would also provide better access to clients in rural areas, many of whom must now travel a considerable distance to retrieve their medication, and would allow greater freedom to participate in family life and employment for patients who have demonstrated stability in their adherence to treatment and test negative in urine drug screens.

In the United States health reform provides an opportunity to address shortfalls in the provision of opioid substitution treatment. The Affordable Care Act has the potential to eliminate gaps in the coverage of this treatment, particularly among people successfully maintained in treatment.[38] Importantly, the law mandates the inclusion of substance abuse and mental health services in the essential benefits that the new state insurance exchanges must offer.

In states that elect to expand Medicaid eligibil-

A systematic review of methadone detoxification revealed a high risk of relapse into illicit opioid use following detoxification.

ity, people whose annual income is below 133 percent of the federal poverty level will be eligible for Medicaid beginning in 2014,[38] greatly expanding the opportunity for substance abuse treatment. Pharmacological treatments are likely to be included in this expanded coverage, because treatment directed by a physician is a general requirement for most Medicaid outpatient services. However, in states that opt out of the Medicaid expansion, people with incomes below 133 percent of poverty will have no new access to treatment, nor will they benefit from the requirements to include opioid substitution treatment services at parity with other essential benefits offered to newly eligible beneficiaries.[38] We agree with McLellan and coauthors[33] that public and private insurers in both Canada and the United States should provide full coverage, to help both nations realize the health and economic benefits of the treatment.

Opioid Detoxification

The continued use of methadone and buprenorphine to detoxify patients from opioids is the most damaging aspect of current treatment of opioid dependence. Here we refer to either the detoxification that is a preplanned treatment regimen, which often lasts twelve weeks and has the explicit or implicit intention of tapering the dose to zero and achieving subsequent abstinence, or the detoxification that follows a period of maintenance treatment.

This is in contrast to short-term detoxification (lasting up to one week), in which sustained abstinence is not an explicit goal. In that scenario, a doctor delivers the treatment following a patient's overdose or gives it to relieve severe withdrawal symptoms, with the option of entering long-term maintenance treatment afterward. Detoxification can serve a useful function desired by clients in this context.

A systematic review of methadone detoxification revealed a high risk of relapse into illicit opioid use following detoxification[39] and suggested that detoxification generally should not be considered adequate treatment for opioid dependence—which is a chronic, recurrent condition. Detoxification also confers an elevated risk of mortality within the month following any relapse.[40] In light of these risks and the well-established effectiveness of long-term maintenance treatment, the continuing frequent use around the world of opioid detoxification and dose tapering among maintained clients is a concern.[41–43]

In the United States detoxification with methadone or another medication was available in 60 percent of facilities offering treatment,[35] which may be partly because of limited-term coverage policies.[44] However, we are unaware of any studies estimating the effect of health insurance coverage policies on the duration of opioid substitution treatment.

In British Columbia, where a maintenance-oriented approach to opioid treatment is advocated, dose tapering was observed in nearly half of all completed methadone episodes between 1996 and 2007.[41] Results from a subsequent study suggest that roughly 95 percent of patients attempting to taper their methadone doses to zero do not succeed in achieving prolonged abstinence, but their chance of success was increased by gradual dose reductions interspersed with periods of dose stabilization.[45] These results are contrary to the vague guidelines for dose tapering and the rapid detoxification techniques now widespread in Canada and the United States.

A study in six community-based programs in the United States that included 152 people ages fifteen to twenty-one—primarily noninjectors who had a relatively short history of opioid use—found that maintenance-oriented treatment was more effective than detoxification in retaining patients and reducing illicit opioid use.[46] This study confirmed the negative outcomes of detoxification treatment and, indeed, raised questions regarding its continued evaluation in controlled-trial settings.[47]

It has been suggested that because of buprenorphine's faster relief of withdrawal symptoms, it may be more effective than methadone for patients wishing to taper off of treatment. Two meta-analyses have demonstrated a slight advantage for buprenorphine over methadone,[48,49] but some uncertainty surrounds these results. The primary outcome was treatment completion, measured most often at twelve weeks; sustained

abstinence was not assessed and was probably not achieved in the majority of cases.[8] Therefore, there is not enough evidence to support methods of opioid detoxification in which the objective of treatment is sustained abstinence.

In light of these facts, the current emphasis on opioid detoxification needs to be addressed. However, clients' desire to achieve a drug-free state is unlikely to change. Practitioners should obtain patients' informed consent before beginning dose tapering and follow clinical guidelines regarding the timing and rate of dose reductions.

New Tools To Tackle Opioid Dependence

Several advances in treatments for opioid dependence have been introduced in the past decade. Slow-release buprenorphine implants[50] are a promising approach aimed at improving treatment adherence, a noted challenge of routine treatment.[11] Similarly, Vivitrol (injectable naltrexone)[51] is a long-acting opioid antagonist—meaning, as explained in Exhibit 1, that it blocks opioid receptors and thus counteracts the effects of opioids—that comes in the form of an extended release depot (administered via injection, with a slow-release formulation). Vivitrol has received Food and Drug Administration approval for treatment of opioid dependence, and a slow-release buprenorphine implant has been reviewed by a Food and Drug Administration advisory committee. The agency subsequently rejected the buprenorphine implant application and requested more information.

Alternative agonists—which bind to opioid receptors and activate them (Exhibit 1)—such as morphine,[52] dihydrocodeine,[53] hydromorphone,[54] and injectable diacetylmorphine[55] either are available in other countries as second-line treatment or are being evaluated for use. Evidence of the effectiveness and cost-effectiveness of injectable diacetylmorphine or heroin maintenance as a second-line treatment for heroin dependence is particularly strong, yet this approach has received little consideration because of the drugs' controlled status.[56]

Although it is unclear whether or not these treatment options will supplant methadone or buprenorphine combined with naloxone as preferred first-line options, it can be beneficial to have various treatment options available. If deemed safe, effective, and cost-effective, these options need to be integrated into certification programs and clinical guidelines and made available alongside existing treatments, according to clients' need.

Recommended Policy Changes

To summarize, we make the following recommendations. Methadone maintenance treatment must be adopted in office-based settings in the United States, with direct administration and dispensing in pharmacies. This will require changes in federal and, in some cases, state law. Policies mandating addiction education in medical schools are also needed. Buprenorphine should be listed on the drug formularies of all Canadian provinces and made available in currently approved treatment contexts.

In addition, in both Canada and the United States, public and private insurers should provide universal coverage for opioid substitution treatment, to realize its full health and economic benefits. Furthermore, the reliance on opioid detoxification treatment needs to be reduced, particularly in the United States, in light of strong scientific evidence that it is ineffective and possibly harmful.

Finally, institutions involved in the delivery of opioid substitution treatment need to assess new and emerging medication options to optimize treatment. Medical associations and medical schools should work together to promote the wide-scale implementation of appropriate physician training to treat opioid and other drug dependence.

Conclusion

Although our review has focused on four specific areas, we do not intend this as an exhaustive list of the challenges and shortcomings of providing opioid substitution treatment in North America. The social and structural reasons behind the low rates of access to this treatment—including stigma and discrimination perpetuated by contradictory social policies that simultaneously treat addiction as a health problem and a crime—must also be addressed. In addition, the lack of appropriate treatment in jails is a problem and represents a missed opportunity for rehabilitation.[57]

The recommendations made here are intended as initial steps toward maximizing the individual and public health benefits of treatment. The abuse of opioids and other drugs is pervasive around the world.[58] Either complete control of or an unmitigated victory over this scourge is a utopian goal. Nonetheless, policy makers can greatly reduce the harms resulting from opioid abuse and dependence by easing restrictions that stand in the way of using existing tools to their maximum effect and by promoting the implementation of emerging evidence-based practices. ■

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