Perspective

Opioid Addiction, Opioid Addiction Treatment, and HIV Infection

Available data indicate that opioid substitution treatment can successfully reduce rates of HIV transmission and that patients receiving such treatment can adhere to therapies for HIV, hepatitis C, and tuberculosis infection. Integration of opioid substitution treatment into the HIV clinic setting can make such treatment easier and improve retention in treatment. This article summarizes a presentation by R. Douglas Bruce, MD, MA, MS, at the IAS–USA continuing education program held in Chicago, Illinois, in May 2018.

Keywords: Opioids, addiction, HIV, methadone, buprenorphine, naloxone

Opioid overdose is a leading cause of accidental death in the United States. Figure 1 shows the increase in deaths involving opioids in this country between 2000 and 2016. Prescribers tend to be the target of blame for the current epidemic of opioid addiction. Although prescribers did have a role to play in the current state of affairs, there are a number of factors that contribute to this problem. Heroin was invented in Europe in the late 1800s, and veterans returning from Germany after World War I brought it to the United States. The situation was so dire that for 1 year, a heroin maintenance program was run in New York City, until it was struck down by the US government for being in violation of the Harrison Narcotic Act. With that Act, the treatment of opioid addiction was removed from the hands of primary care physicians. The problems of opioid use and the connections between opioid use and HIV infection are not limited to the United States; they are truly global issues.

Opioid Addiction

Addiction can be defined as a state in which an individual engages in compulsive behavior. The behavior is reinforcing (that is, pleasurable or rewarding), and there is a loss of control in limiting the intake of the substance. Drug use is a personal experience, with individuals taking drugs to *feel good*, to have novel feelings, sensations, and experiences, as well as to share them. Or they may take drugs to *feel better*, to lessen anxiety, worries, fears, depression, and hopelessness. Most individuals with addiction are taking drugs to *feel better*; some have been victims of sexual assault, physical violence, or emotional violence. In Africa, female drug users often even feel threatened and intimidated within health care settings.[1] Such individuals are taking drugs, instead of continuing to relive a negative experience, because they want to *feel better*.

As to why some people who use drugs become addicted and some do not, the prevailing model is that addiction represents a continuum between biology and genetics, and the environment. Although someone may have a genetic predisposition to having addiction, this does not necessarily mean that they will become addicted. Often an environmental trigger (eg, domestic violence) or environmental exposure (eg, growing up with people who use drugs) precipitate a movement into drugs. Among people who use drugs, those with a genetic predisposition have a greater probability of becoming addicted. Drug dealers are functionally aware of this continuum when they provide free drugs to new users, knowing the drugs are going to make some proportion of the users feel so much better that they will want more.

Drugs hijack brain circuits designed for survival and strongly influence motivational priorities. Dopamine bursts in the nucleus accumbens are induced by eating a meal, having sex, and using heroin—with heroin use providing the greatest dopamine reward. Many heroin users state that using heroin is "better than sex," giving an idea of the degree to which the substance can make individuals feel better, and an idea of the degree to which the individual's motivational priorities may be directed to continue using the substance. Figure 2A presents a model of a day in the life of the heroin user. The tic marks indicate injection time points, which correspond to the individual's attempt to "feel better." A minority of the day is spent in the "normal" versus "high" state.[2] A problem arises for someone who uses heroin: the body adapts to the presence of these substances (ie, up-regulating receptors) and, over time, the same amount of substance does not produce the same "high." The individual is now tolerant; the same amount of substance that previously led to euphoria now simply helps avoid withdrawal. Avoiding withdrawal becomes a primary motivating factor in the life of the individual who uses drugs. That strong motivation can prompt engagement in many risky behaviors, including risky sexual and drug-using behaviors and the use of large quantities of drugs meant to regain euphoria but often resulting in overdose.

Opioid Substitution Treatment

In the 21st century in the United States, outbreaks of HIV infection among people who use drugs continue (eg, the Indiana outbreak), even though treatment for opioid use disorders can prevent HIV transmission. A study by Metzger and colleagues reported in 1993 showed that HIV antibody conversion occurred within 18 months in 22% of 103 out-of-treatment people injecting heroin, compared with 3.5% of 152 who received methadone.[3]

Medication-assisted treatment can reduce injection-related HIV risk

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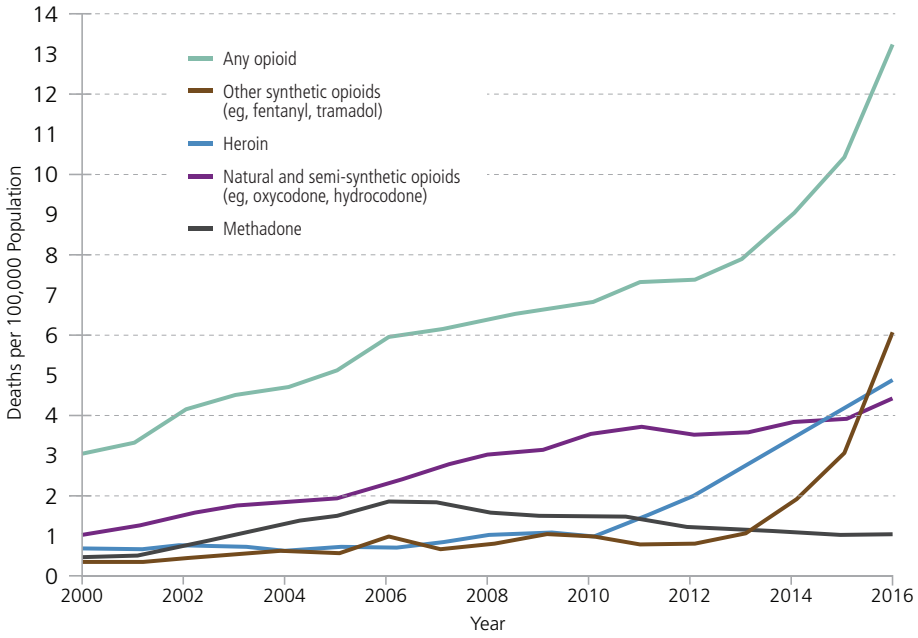

Figure 1. Overdose deaths involving opioids, by type of opioid, in the United States from 2000 to 2016. Adapted from the CDC WONDER database.[10]

behavior, decrease psychosocial and medical morbidity, increase access to and retention in antiretroviral therapy (ART), and improve overall health status. It is also associated with decreased criminal activity.

Figure 3 shows cross-sectional magnetic resonance imaging pictures of the brain in the top row and corresponding positron-emission tomography (PET) scans showing μ-opioid receptor availability at increasing doses of buprenorphine. Without any buprenorphine ingested, a high degree of receptor availability is evident on the first row of the PET scan. The nucleus accumbens, a key area of neurobiologic reward in the brain, is visible as a red area in the far-right PET image. Subsequent rows demonstrate a reduction in receptor availability as buprenorphine occupies those receptors and competes with the radiolabeled substance As can be seen, administration of even 2 mg results in high receptor occupancy, with upwards of 95% of μ-opioid receptors being occupied at a dose of 16 mg. In this setting where the "parking lot is full," if an individual takes heroin, it has "no place to park."

Figure 2B presents a model of a day in the life of an individual addicted to heroin who is receiving methadone for treatment. With once-daily dosing of methadone, the individual formerly using heroin now avoids the opioid withdrawal and spends the day in the "straight" zone. Use of heroin after methadone results in a blunted response—the parking lot is mostly full—that does not reach a "high," and thus may result in reduced craving for repeated heroin use.

Medications available for the treatment of opioid use disorder include methadone, buprenorphine, and naltrexone. Methadone is available only through opioid treatment programs, and cannot be used in an office-based setting in the United States. Methadone, although suffering under substantial bad press,[4] must be remembered as first and foremost a life-saving medication.[5] It is efficacious in treating opioid addiction and has the best retention rates among medication-assisted treatment for opioid use disorders.[6] Additionally, of the 3 available medications, methadone has the greatest analesgic potential. Buprenorphine has a strong advantage for scale-up because it can be used in an office-based setting. Although it is as efficacious as methadone for those retained in treatment, treatment retention rates are lower than with methadone.[6] This finding appears to reflect the pharmacology of the medication, characterized by fewer withdrawal sym-ptoms when it is discontinued. One possible implication is that buprenorphine may not be as effective as methadone for prevention of HIV infection, because staying on the medication is crucial in this regard.[6] Finally, there is a new depot naltrexone formulation. The oral tablet is not effective because patients simply discontinue its use; however, the new depot formulation offers improved adherence possibilities. In a recently reported

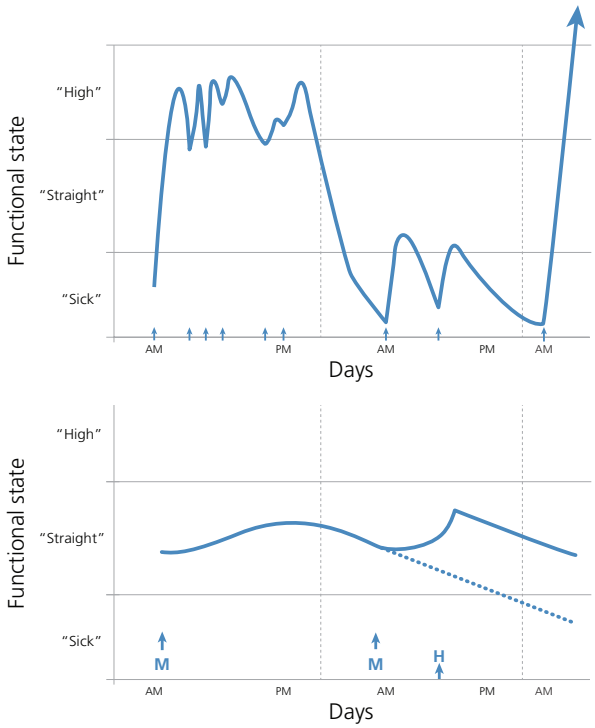

Figure 2. Top—Model of functional state of typical "mainline" heroin user. Arrows show times of injection. Bottom—Functional state of heroin user with methadone treatment. M arrows show time of methadone dosing; H arrows, effect of heroin injection under methadone treatment; dotted line, course if methadone is omitted. Adapted from Dole et al.[2]

study in patients with HIV infection who were incarcerated, Springer and colleagues found that the patients randomly assigned to depot naltrexone or a placebo saw a stability or improvement in HIV viral suppression. There was no significant difference at 6 months, however, when compared with placebo.[7] Although it can be used in the office-based setting, depot naltrexone was studied among individuals with HIV infection who started treatment while in prison and were continued post-release. Although some patients clearly benefited, viral suppression between the active arm and the placebo arm were not statistically significant. Although the treatment is effective for some individuals who use the medication, it has a lower retention rate than either buprenorphine or methadone. If available, methadone and buprenorphine are preferred for most patients.

Integrating Substitution Treatment in the Clinic

Representative data on retention in methadone treatment indicate that if people simply discontinue treatment, up to 82% of people who inject drugs will return to injection within 8 to 10 months. There is thus considerable need to keep patients engaged in treatment. Best practices call for "low threshold"[5] treatment that is easily accessible, and "high volume" treatment that has sufficient ability to address the demand in the community, also known as the "community viral load." The goal is an intervention that is large enough to impact individuals who are not even directly encountering the program. This means that unnecessary barriers must be removed so that a patient who presents in need can be addressed immediately. A failure to address patients pushes them back out into an environment fraught with risk. Treatments must be appropriately dosed to be efficacious. Culturally appropriate counseling for heroin addiction is crucial, and can take a variety of forms, from Narcotics Anonymous to cognitive behavioral therapy. In this regard, the most important element of treatment is engagement with patients; medical therapy

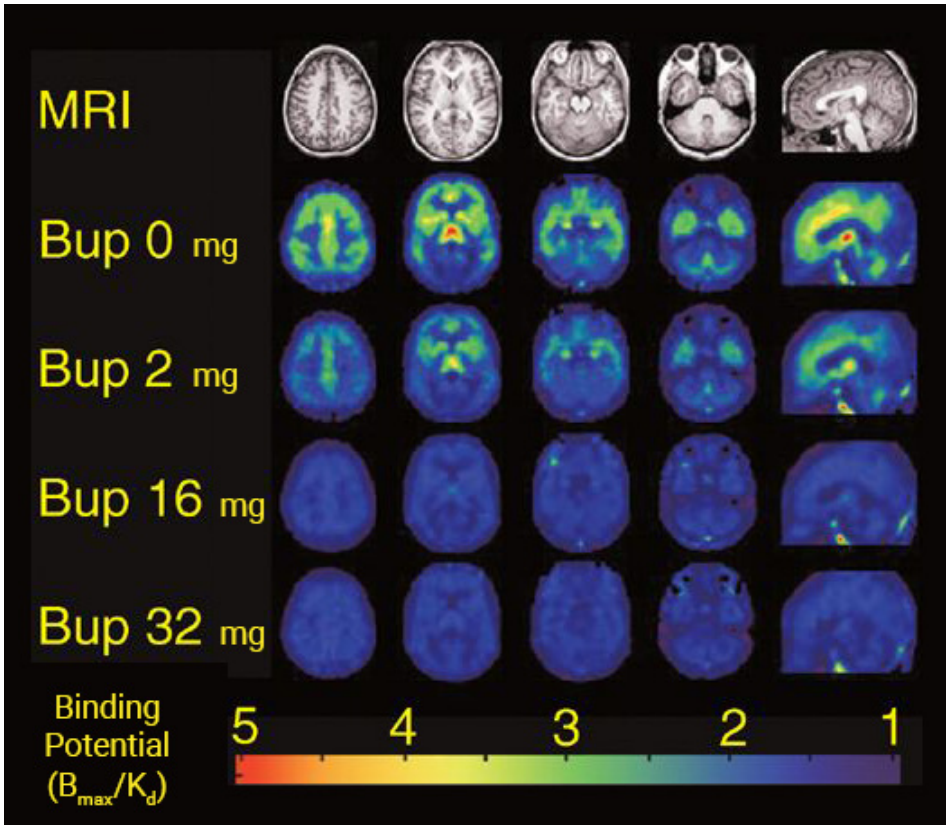

Figure 3. Occupancy of μ-opioid receptors by buprenorphine (Bup) dose. Blue indicates receptor occupancy. MRI indicates magnetic resonance imaging; B_{max}, the maximum number of binding sites; K_d, the ligand concentration that binds to half the receptor sites at equiplibruim. Reprinted with permission from Springer Nature: *Neuropsychopharmacology*. "Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers." Greenwald MK, Johanson CE, Moody DE, et al. © Nature Publishing Group 2003.[11]

is much less likely to be successful in the absence of counseling and therapy. In addition, treatment of the medical consequences of addiction, such as HIV, hepatitis B, hepatitis C, and tuberculosis (TB) infection, remains crucial.

Discrimination persists against individuals who have substance use disorders in terms of providing treatment for HIV, hepatitis C, and TB infection, in the United States and globally. Adherence to treatment regimens for these diseases remains possible, even in the setting of ongoing substance use.

Indeed, in the past, people who inject drugs were denied HIV therapy until they ceased drug use. Although drug use is multifactorial, there was a bias against drug users and a failure to recognize addiction as a medical illness. In contrast, people living with HIV infection with other medical illness were not denied treatment. Indeed, in some settings (eg, HIV/hepatitis C and HIV/TB coinfections), having another medical illness with HIV infection makes ART access a priority. Woods and colleagues in British Columbia showed that in a cohort of 1191 ART-naive patients monitored from the time of ART initiation, antiretroviral drug resistance was found in 25% of the cohort during the first 30 months (protease inhibitor and nonnucleoside reverse transcriptase inhibitor resistance). There was no difference in incidence of resistance between people who inject drugs and those who do not inject. Integration of treatment is now being performed all over the world. In India, there is directly observed therapy with direct-acting antivirals for hepatitis C and buprenorphine. In Tanzania, there are programs for adherence support for HIV and TB medications in the context

Organization/Guidelines	Website Address
American Pain Society	http://americanpainsociety.org/education/overview
American Academy of Pain Medicine Research Library	http://www.painmed.org/library/main.aspx
Providers Clinical Support System	https://pcssnow.org/resources/clinical-tools/
Substance Abuse and Mental Health Services Administration	https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training
2017 HIV Medicine Association of Infectious Diseases Society of America Clinical Practice Guideline for the Management of Chronic Pain in Patients Living With Human Immunodeficiency Virus	https://academic.oup.com/cid/article/65/10/e1/4157299

Table. Useful Websites for Pain Management and Opioid Issues

of methadone treatment. In New Haven, Connecticut, HIV and hepatitis C treatments have been integrated into methadone clinics.

In terms of screening for substance use disorders in the HIV clinic setting, 2 standardized questions that have been validated in the primary care environment prove very useful: (1) How many times in the past year have you had 5 or more standard drinks in a day? (2) How many times in the past year have you used an illegal drug or a prescription medication for nonmedical reasons?[8] People who use opioids or other substances can take medications for other illnesses and should be eligible for care for HIV, hepatitis B, hepatitis C, and TB infection. Clinicians should be willing to prescribe naloxone, the drug used to reverse opioid overdose, and should consider obtaining the necessary waiver to prescribe buprenorphine. Clinicians who prescribe opioids must be prepared to prescribe naloxone. Clinicians should also review guidelines on the treatment of chronic pain and reevaluate how they prescribe opioids; useful websites are shown in the Table. The HIV Medicine Association of Infectious Diseases Society of America has recently released a clinical practice guideline on the management of chronic pain in patients with HIV infection.[9]

Buprenorphine treatment for opioid addiction is one of the easier treatments provided by clinicians: easier than HIV care, given factors such as the absence of mutations conferring drug resistance and the relatively high motivation of patients to take the medication. Clinics can maintain patients in HIV care who are also receiving methadone or a buprenorphine-naloxone film, because patients return to the clinic for treatment, permitting more extensive contacts for ensuring other types of care. One clinic employs a waiver-based system that enables patients to pick up buprenorphine-naloxone directly from the on-site pharmacy, with the waiver being available at many points of care within the clinic (eg, outreach workers, at the laboratory, etc). This approach obviates the additional step of forcing the patient to make an additional appointment with a therapist, appointments that frequently are missed, to obtain a voucher before obtaining the medication.

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References

1. Balaji D, Mlunde LB, Tran OC, et al. First report of gender based violence as a deterrent to methadone access among females who use heroin in Dar es Salaam, Tanzania. *AIDS Behav.* 2017;21(7):2093-2100.
2. Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. *Arch Intern Med.* 1966;118(4):304-309.
3. Metzger DS, Woody GE, McLellan AT, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. *J Acquir Immune Defic Syndr.* 1993;6(9):1049-1056.
4. Bruce RD. The marketing of methadone: how an effective medication became unpopular. *Int J Drug Policy.* 2013;24(6):e89-e90.
5. Bruce RD. Methadone as HIV prevention: high volume methadone sites to decrease HIV incidence rates in resource limited settings. *Int J Drug Policy.* 2010;21(2):122-124.
6. Woody GE, Bruce D, Korthuis PT, et al. HIV risk reduction with buprenorphine-naloxone or methadone: findings from a randomized trial. *J Acquir Immune Defic Syndr.* 2014;66(3):288-293.
7. Springer SA, Di PA, Azar MM, et al. Extended-release naltrexone improves viral suppression among incarcerated persons living with HIV with opioid use disorders transitioning to the community: results of a double-blind, placebo-controlled randomized trial. *J Acquir Immune Defic Syndr.* 2018;78(1):43-53.
8. Bowman S, Eiserman J, Beletsky L, Stancliff S, Bruce RD. Reducing the health consequences of opioid addiction in primary care. *Am J Med.* 2013;126(7):565-571.
9. Bruce RD, Merlin J, Lum PJ, et al. 2017 HIV Medicine Association of Infectious Diseases Society of America Clinical Practice Guideline for the Management of Chronic Pain in Patients Living With Human Immunodeficiency Virus. *Clin Infect Dis.* 2017;65(10):1601-1606.
10. Centers for Disease and Control and Prevention (CDC). CDC WONDER. https://wonder.cdc.gov/Welcome.html. Accessed on June 20, 2018.
11. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology.* 2003;28(11):2000-2009.

Top Antivir Med. 2018;26(3):89-92.