Perspective

Medical Interventions for Addictions in the Primary Care Setting

Primary care physicians treating HIV-infected patients should not be afraid or reluctant to engage in medication-assisted treatment for substance dependence. Effective medications are available for many types of substance addictions, including buprenorphine for opioid dependence, disulfiram for cocaine dependence, bupropion for methamphetamine dependence, and naltrexone for alcohol dependence. Physician use of medications coupled with encouragement to adhere to all aspects of treatment including counseling and other psychosocial interventions can produce substantial rewards in terms of keeping patients involved in their HIV care and improving overall patient health and functioning. This article summarizes a presentation made by R. Douglas Bruce, MD, MA, MSc, at the 12th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in October 2009 in Dallas, Texas. The original presentation is available as a Webcast at www.iasusa.org.

The National Institutes of Health consensus on drug treatment for substance dependence emphasizes that drug addiction is a disorder of the brain and therefore a medical disorder. It calls for broader access to drug treatment and reduced federal and state barriers to treatment, and it stresses the importance of providing substance dependence counseling, psychosocial therapies, and other supportive services.

Just as pharmacologic therapy can improve depression, medications can assist in the successful treatment of opioid, cocaine, methamphetamine, alcohol, and nicotine dependence, and can thereby improve practitioners' abilities to keep these patients connected to their HIV care. Primary care practitioners should not be reluctant to engage in drug treatment for substance dependence in their HIV patients.

The Problem: Addiction

Drug addiction has many and well-known adverse consequences for the individual and for society. Despite these negative consequences, people continue to engage in drug use for a variety of reasons. Some people take illicit drugs to *feel good*—that is, to have novel feelings, sensations, and experiences and to share them—whereas others take them to *feel better*—that is, to lessen the symptoms of anxiety, fears, depression, and hopelessness. Indeed, the prevalence of major depressive disorder is more than 50% among opioid-dependent patients in some data sets.

Addiction is a state in which a person engages in a compulsive behavior that is reinforcing—pleasurable or rewarding—and there is loss of control in limiting the intake of that addictive substance. Understanding why some people become addicted to substances and others do not will help clarify strategies for prevention and treatment. Vulnerability to addiction is on a spectrum between genetics (biology) and environmental factors. Specifically, some individuals are genetically predisposed to specific addictions so even a brief exposure to a substance will produce very reinforcing effects. In contrast, some individuals may not be genetically predisposed to find a particular substance as reinforcing as the addictive group; however, these individuals may reside in environments that promote or make easily available particular substances.

As for the biology underlying addiction, the answers to most questions on this topic revolve around dopamine and dopamine receptors. An early study by Volkow and colleagues (*Am J Psychiatry,* 1999) in nonaddicted subjects indicated that those with

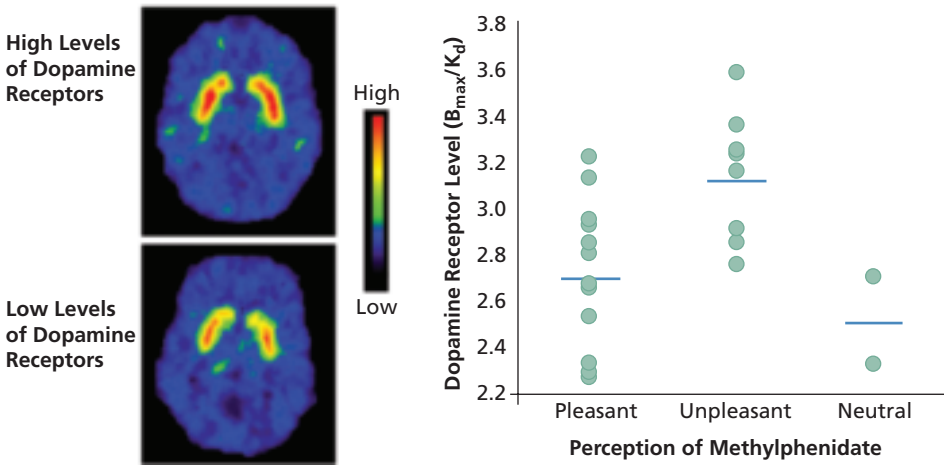

Figure **1**. Perception of methylphenidate use according to dopamine receptor levels in nonaddicted subjects. B_{max} indicates receptor density; K_d, receptor affinity; horizontal lines, means for the different groups. Adapted from Volkow et al, *Am J Psychiatry*, 1999. Photos reprinted with permission from *Am J Psychiatry* (copyright 1999). American Psychiatric Association.

Dr Bruce is assistant professor of medicine at Yale University School of Medicine in New Haven, Connecticut.

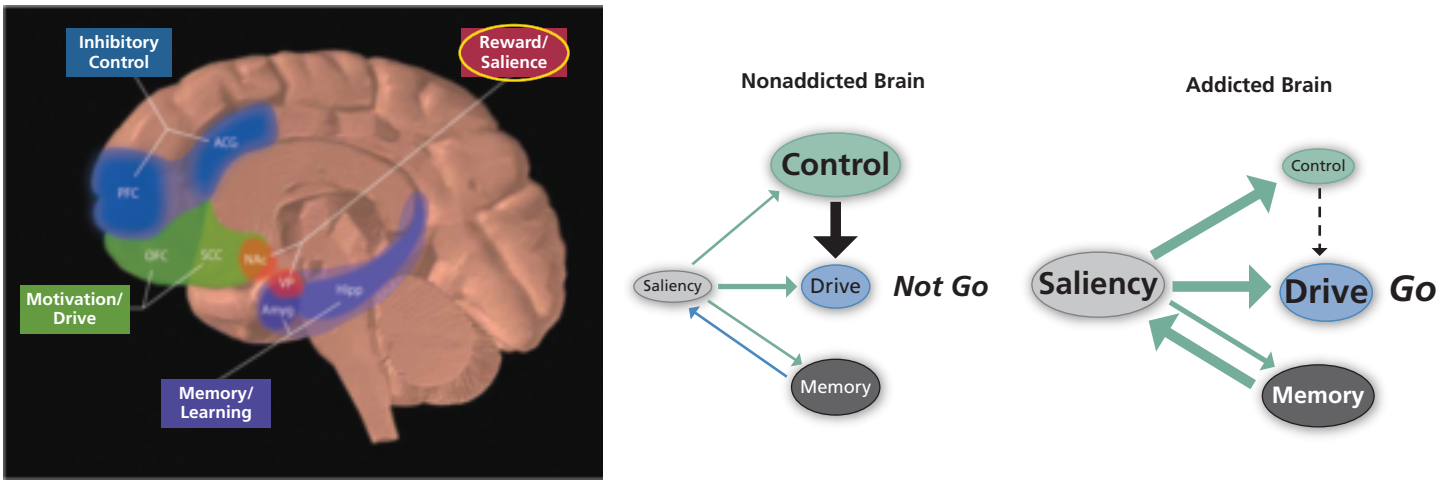

Figure **2**. Brain circuits involved in drug use and addiction (left). ACG indicates anterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SCC, subcallosal cortex; VP, ventral pallidum. Adapted from National Institute on Drug Abuse Web site, 2010. Schematic of changes in brain circuits with addiction (right). Adapted from Volkow et al, *Neuropharmacology*, 2004.

lower concentrations of dopamine receptors in the brain find the stimulant methylphenidate "pleasant," whereas those with higher dopamine receptor levels find it "unpleasant" (Figure 1). Numerous brain circuits, however, are involved in drug use and addiction, representing the mechanisms of reward and salience, as well as those of memory and learning, motivation and drive, and inhibitory control (Figure 2). All of these must be considered in strategies to treat addiction effectively.

Studies of dopamine release in the nucleus accumbens of rats, one of the brain centers involved in reward and salience, showed that the natural rewards of food and sex are associated with peak increases in dopamine level of approximately 150% and 200%, respectively (Bassareo and Di Chiara, *Neuroscience*, 1999; Fiorino et al, *J Neurosci*, 1997). In contrast, peak dopamine increases were 1000% above basal levels with amphetamine, 300% above with cocaine, 200% above with nicotine, and from about 150% to 200% above at different morphine doses (Di Chiara and Imperato, *Proc Natl Acad Sci USA*, 1988). Such results help explain the common finding that substance-dependent patients will engage in sexual risk behaviors for drugs or for money to obtain drugs because the end goal is more rewarding neurobiologically. In other words, if sex were the greater reward, the patient would stop further activity after sex; however, they experience far greater reward with the drugs than they do with the natural behaviors of food and sex.

Complicating this picture is the realization that numerous data indicate that dopamine 2 receptor levels are lower in addicted brains than in nonaddicted brains, and that addiction itself changes brain circuits involved in saliency, drive, control, and memory (Figure 2). This emphasizes the challenge of treating the substance user: if medical practitioners are unable to have patients be sexually abstinent (because sex is less rewarding than heroin use) by counseling the patient on the risks of a sexually transmitted disease, for example, they must look beyond simple advice and consider prescribing medications that may assist the patient in achieving sobriety. Thus, illicit drugs usurp naturally occurring brain circuits and alter associated motivational priorities, and thereby change behavior. This is why substance-dependent patients cannot "just quit" and why comprehensive treatment, including the prescription of medications to assist in achieving sobriety, are essential.

Pharmacology in Primary Care

Treatment for addiction includes pharmacologic treatment, behavioral therapies, medical treatment for complications of addiction (eg, HIV and hepatitis C virus [HCV] infection), and social services. The author came to the field of treating addiction from working in the HIV disease treatment field. In some sense, treating addiction with drug therapy is simpler than managing HIV infection with drug therapy, in that resistance does not develop to treatments for addiction. If a practitioner can manage the pharmacotherapy of HIV infection, that medical practitioner is already well equipped to incorporate medication-assisted treatment strategies to help manage treatment of addiction. The following sections provide an overview of medication treatment strategies for various addictions.

Buprenorphine for Opioid Dependence

Heroin is a short-acting, semisynthetic opioid produced from opium. The rationale for treating heroin dependence with buprenorphine is to satisfy the brain's craving for an opioid in a safe and controlled manner. In contrast to heroin, the use of which is character-

ized by rapidly alternating states of craving and satiety, buprenorphine, for example, permits a steady release of dopamine, bringing some stability to the patient's neurobiology and some organization to what is essentially a chaotic neurocognitive environment. This, in turn, allows practitioners and patients to concentrate on the business of deriving and maximizing benefits of HIV disease treatment, rather than spending time and resources dealing with drug-seeking behaviors, withdrawal, and other narcotics issues. Thus, the aim of providing opioid treatment is to provide cross-tolerance, preventing withdrawal and relieving the craving for opioids. In addition, buprenorphine provides a narcotic blockade that blocks the euphoric effect of exogenous opioids. In the primary care setting, buprenorphine remains the best option for the treatment of opioid dependence, as it has been shown to be superior to naltrexone (Schottenfeld et al, *Lancet*, 2008).

Buprenorphine is a partial opioid receptor agonist. Unlike full agonists (heroin, levo-alpha-acetylmethadol [LAAM], methadone, and morphine), which increase receptor-specific effects to a maximal effect with increasing dose, dose increases of buprenorphine result in a lesser increase in effects and a lesser maximal effect. Buprenorphine affects mu-opioid receptor availability by occupying available receptors in the brain, thereby satisfying the craving for an opioid and preventing any additional "reward" to be experienced from heroin use. Data reported in 2000 indicate that the percentage of patients retained in treatment over 17 weeks was 58% with buprenorphine, compared with 73% with high-dose methadone, 53% with LAAM, and 20% with low-dose methadone, respectively. Mean percentages of patients with opioid-negative urine were 40%, 39%, 49%, and 19%, respectively (Johnson et al, *N Engl J Med*, 2000).

Buprenorphine is a valuable tool, and the author believes every physician treating HIV-infected drug users should obtain a buprenorphine waiver and a special X number from the Drug Enforcement Agency so as to be ready to prescribe it (see buprenorphine.samhsa.gov for details on how to obtain licensure). Buprenorphine treatment is less complicated than the treatment of HIV or HCV infection. It is safer and less liable to abuse than is oxycodone as a treatment for pain or alprazolam as a treatment for anxiety. Also, its use can markedly expand patient involvement in their HIV treatment.

Disulfiram for Cocaine Dependence

Disulfiram, approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence, is also effective in treating cocaine dependence, a fact that does not seem to be widely appreciated. After an effect of decreasing cocaine use was observed in patients with joint alcohol-cocaine dependence, disulfiram was found to reduce cocaine use in cocaine-dependent patients receiving methadone. Six randomized controlled trials have now shown the efficacy of disulfiram in treating cocaine dependence (George et al, *Biol Psychiatry*, 2000; Carroll et al, Arch Gen Psychiatry, 2004; Petrakis et al, *Addiction*, 2000).

Disulfiram acts by inhibiting dopamine beta-hydroxylase activity, thus increasing dopamine levels in the brain (via a mechanism somewhat similar to that of cocaine). Compared with cocaine, which has a rapid onset of action and rapid attenuation of effect, leaving the dependent person constantly chasing the next "high," disulfiram is slow-acting. Again, the goal of treatment is to relieve the craving for dopamine by maintaining stable, elevated levels. Taking cocaine in addition to disulfiram frequently results in a nonrewarding, dysphoric response caused by excessive amounts of dopamine.

Although the dose of disulfiram that has been studied most extensively is 250 mg/d, practitioners in the author's clinic for HIV and HCV coinfected patients typically start treatment at around 125 mg/d because of the lack of data in this patient group and the concern about potential effects of disulfiram on aspartate aminotransferase and alanine aminotransferase levels. One problem with disulfiram treatment, as with other dependency treatments, is adherence. Treatment works well for motivated patients and for patients receiving disulfiram along with methadone maintenance. Disulfiram is underutilized in methadone programs and substance dependence programs. Primary care physicians can help increase the beneficial use of this valuable resource in their cocaine-dependent patients.

Bupropion for Methamphetamine Dependence

Methamphetamine can have profound effects on the central nervous system and can cause permanent brain damage. Methamphetamine users show a loss of dopamine transporters in the brain, and this loss is associated with slowing of motor reactions and memory loss (Volkow et al, *Am J Psychiatry*, 2001). The neurocognitive effects associated with methamphetamine use are exacerbated in HIV-infected patients, and reduced neurocognitive performance in these patients can severely compromise HIV disease care. The use of bupropion 150 mg twice daily produces some reduction in methamphetamine use among *mild* users of methamphetamine, with the mainstay of treatment being counseling. As with disulfiram for cocaine dependence, bupropion is not a panacea for methamphetamine use. Treatment may tip the balance for some patients in favor of greater stability of behaviors and better participation in HIV disease care.

Naltrexone for Alcohol Dependence

Naltrexone, an opioid receptor antagonist, is the most studied and consistently most effective pharmacotherapy for alcohol dependence (Anton et al, *JAMA*, 2006). Opioid receptor antagonists bind to but do not activate the receptor, and they prevent activation by full (eg, heroin, LAAM, methadone, and morphine) and partial (eg, buprenorphine) agonists. Alcohol stimulates receptor-mediated dopamine release through a complex mechanism

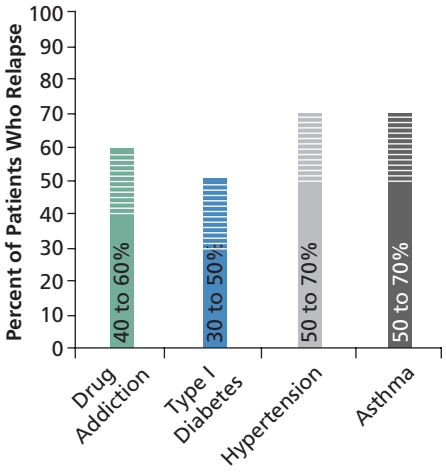

Figure **3**. Relapse rates for drug addiction compared with other common chronic illnesses. Adapted from McLellan et al, *JAMA*, 2000.

involving gamma-aminobutyric acid activation and the opioid receptor. By blocking the mu-opioid receptor, naltrexone acts to decrease the dopamine reward. Patients consume less alcohol while receiving naltrexone, and those who are sober while receiving treatment tend to have relapses of reduced severity. The currently recommended dosage is 100 mg/d, and vigilance for hepatotoxicity must be maintained (as indicated by the drug's black box warning). Expert opinion suggests that even lower doses of naltrexone may be effective in the treatment of alcohol dependence; therefore, medical practitioners should be encouraged that even low doses of the medication may be helpful in assisting patients to have improved health outcomes. Acamprosate and disulfiram are also FDA approved for treatment of alcohol dependence, but each is inferior to naltrexone.

The anticonvulsant drug topiramate, which appears to act at gamma-aminobutyric acid receptors, has been shown to be effective for alcohol dependence in several studies (Kenna et al, *Curr Drug Abuse Rev*, 2009; Johnson et al, *Arch Intern Med*, 2008) but is not FDA approved for the treatment of alcohol dependence. Doses vary by study, but generally treatment is started at low doses (eg, 25 mg/d) with titration to a maximum dose of 300 mg/d over 6 weeks. Topiramate has proved useful in decreasing alcohol consumption and reducing symptoms of withdrawal. Naltrexone, an opioid antagonist, cannot be prescribed to patients taking opioids (eg, methadone or buprenorphine); therefore, topirimate is a possibility for alcohol-dependent patients receiving treatment with opioids.

Nicotine

Cigarette smoking is so prevalent among HIV-infected drug users that it almost seems odd to encounter a patient who does not smoke. Advising patients to stop smoking does help, and encouragement to quit should be offered repeatedly. With regard to pharmacotherapy, nicotine replacement is effective. Bupropion doubles quit rates. Standard dosing of bupropion is 150 mg once daily for 3 days and then 150 mg twice daily for 7 to 12 weeks (Hurt et al, *N Engl J Med*, 1997). Because bupropion is metabolized by cytochrome P450 2D6, pharmacokinetic interactions with nelfinavir, ritonavir, and efavirenz need to be considered.

Varenicline, a partial nicotine receptor agonist, is FDA approved for the treatment of nicotine dependence and, in comparative studies, was better than bupropion (Gonzales et al, *JAMA*, 2006). The author finds it very effective, with patients generally choosing to either quit smoking or discontinue the medication (West et al, *Psychopharmacology* [Berl], 2008). However, there is a concern that varenicline may exacerbate serious neuropsychiatric symptoms (including the extremes of suicidality and homicidality), and its use requires circumspection and caution. Slow upward titration is necessary to minimize side effects.

Harm Reduction and Benefits of Physician Involvement

Those who work in HIV medicine are familiar with the concept of harm reduction as a goal of treatment. Sometimes the "success" of treating substance dependence will have to be, not the cessation of use, but the return of a patient to the next HIV-related appointment. Decreasing the frequency of adverse events related to a behavior is also a success, as is changing substance use behavior. A patient changing from heroin injection to sniffing can avoid endocarditis, for example. Of course, practitioners want harm removal—cessation of substance use—but if they can avoid at least some medical consequences of substance dependence and increase participation in HIV disease care in their patients, they have improved the overall health of their patients.

Harm reduction is crucial because drug addiction is a chronic illness with relapse rates similar to those in diabetes, hypertension, and asthma (Figure 3; McLellan et al, *JAMA*, 2000). In this regard, it should be remembered that primary care practitioners and society as a whole tend to moralize drug addiction, with relapse often seeming tantamount to confirmation of the categorical failure of the substance user. Instead, relapses should be seen and responded to in the same way as relapses in patients with hypertension,

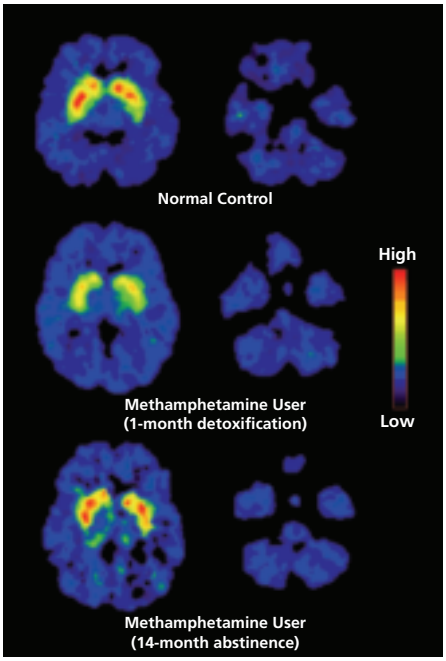

Figure **4**. Dopamine transporter recovery over a period of abstinence from methamphetamine (non–HIV-infected patient), as measured by brain images of the distribution volume of [C-11]*d-threo*-methylphenidate. Adapted with permission from Volkow et al, *J Neurosci*, 2001.

for example. Patients should be reminded of how much better they were feeling when they were taking their medications and of the health benefits that accrued during treatment, and they should be encouraged to resume treatment.

Practitioners never know when their efforts in extending medication-assisted treatment might tip the balance in favor of an improved health outcome such as helping the patients to stop using substances, reducing the adverse consequences of substance use, and improving patient participation and benefit in HIV care (Figure 4). Thus, HIV care practitioners would serve their patients well to prescribe pharmacotherapy for substance dependence. Similarly, advice and encouragement from physicians to stop smoking has proved to help patients quit smoking, and further benefits accrue when practitioners emphasize the importance of counseling for their patients and constantly encourage them to persist in it.

Presented by Dr Bruce in October 2009. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Bruce in January 2010.

Financial Disclosure: Dr Bruce has received grants and research support from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc, Merck & Co, Inc, and Reckitt Benckiser Pharmaceuticals, Inc.

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