Personalizing the Treatment of Substance Use Disorders

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The opioid crisis in the United States has brought drug addiction to the forefront of the public mind and to the attention of health care personnel, organizations, and agencies. The epidemic of overdoses, beginning with those caused by prescription opioid analgesics and then broadening to include heroin and fentanyl and its analogs, has prompted major initiatives in local communities, states, and at the federal level to treat addiction and pain more effectively. The crisis has highlighted an insulated addiction treatment system that for decades was segregated from the rest of health care because of stigma associated with addiction and, by extension, the medications used to treat it. Stigmatizing attitudes have been slow to erode, but the moralizing and punitive viewpoints of the past are gradually giving way to a medical and even a cultural consensus that addiction is a chronic disorder of the brain, one that is strongly influenced by social factors, and one that is also treatable.

Parallel research in animal models and brain-imaging studies in individuals with substance use disorders has given us an increasingly precise picture of their neurobiology, including molecular and synaptic changes and the neuronal circuits involved, along with the consequences of their disruption. Most people are exposed to addictive substances at some point in their lives, including alcohol and nicotine, and many use these substances recreationally without developing addiction. Similarly, many patients who use opioids to treat their pain don't develop addiction. But in a subset of individuals who are vulnerable because of genetics, age, and other variables, repeated exposure to addictive drugs diminishes the capacity of basal ganglia circuits to respond to natural reward and to motivate the behaviors needed for survival and well-being, while enhancing the sensitivity of stress and emotional circuits, including those from the extended amygdala, triggering anxiety and dysphoria when not taking the drug and weakening prefrontal executive-control circuitry necessary for self-regulation (1).

These changes, along with learning mechanisms that tie expectation of reward to drug cues, intensify each other in a kind of perfect storm: Inability to feel reward from non-drug activities, including social interactions, takes away the enjoyment of life and increases social isolation. Intense symptoms of withdrawal drive a search for temporary relief, and constant reminders of the drug in the environment contribute to persistent craving and preoccupation with obtaining the drug. Weakened capacity to resist the urge to take the drug or follow through on resolutions to quit leads, very often, to relapse and the accompanying regret or shame at having failed. Further increasing relapse risk are the frequently associated symptoms of depression, anxiety, and impaired sleep.

Until recently, the development of treatments for addiction was aimed at bringing about cessation of drug consumption (abstinence), which was the outcome required for U.S. Food and Drug Administration (FDA) approval of medications for substance use disorders. However, our current understanding of the mechanistic processes underlying addiction identifies a much broader set of clinically beneficial outcomes. For example, reduction of use in a person who uses heroin could decrease his or her risk of overdose, and improvements in sleep, depression, or executive function could also reduce relapse risk. In addition, technological advances and our growing understanding of the underlying neurobiology have given us the opportunity to target discrete neurobiological processes and personalize interventions to the unique deficits in a given individual and across the course of an individual's disorder. A dimensional, personalized, and dynamic approach to treating substance use disorders could draw from medication use, neuromodulation techniques, behavioral approaches, and their combinations as the individual moves toward recovery.

ALTERNATIVE ENDPOINTS

To achieve a dimensional approach to treatment requires thinking anew about how we develop new treatments and what we expect in a treatment.

The existing pharmacopoeia for substance use disorders is severely limited. The FDA has approved medications only for alcohol, nicotine, and opioid use disorders (Table 1), and currently there are no approved medications for cannabis, cocaine, methamphetamine, or inhalant use disorders. The absence of medications to treat most substance use disorders and the limited number of existing medications for alcohol, nicotine, and opioid use disorders make development of new

TABLE 1. Drugs approved by the FDA for treatment of substance use disorders[a]

Substance and Medication	FDA Approval	Mechanism of Action
Opioids		
Methadone	Treatment of opioid dependence	μ-Opioid receptor agonist
Buprenorphine	Treatment of opioid dependence	μ-Opioid receptor partial agonist
Extended-release naltrexone	Treatment of opioid dependence	μ-Opioid receptor antagonist
Lofexidine	Treatment of opioid withdrawal	α_{2A}-Adrenergic receptor agonist
Naloxone	Reversal of opioid overdose	μ-Opioid receptor antagonist
Alcohol		
Acamprosate	Treatment of alcohol dependence	NMDA antagonist, GABA-A allosteric modulator
Naltrexone	Treatment of alcohol dependence	μ-Opioid receptor antagonist
Disulfiram	Treatment of alcohol dependence	Acetaldehyde dehydrogenase inhibitor
Gabapentin	Used off-label to treat alcohol dependence	Unknown; increases GABA concentration
Topiramate	Used off-label to treat alcohol dependence	Voltage-gated sodium channel blocker, GABA-A allosteric modulator, AMPA/kainate receptor antagonist, carbonic anhydrase inhibitor
Nicotine		
Nicotine replacement therapy	Nicotine cessation	Nicotinic acetylcholine receptor agonist
Varenicline	Nicotine cessation	α4β2 Nicotinic acetylcholine receptor antagonist
Bupropion	Nicotine cessation	Dopamine and norepinephrine transporter blocker

[a] AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; FDA=U.S. Food and Drug Administration; GABA=γ-aminobutyric acid; NMDA=*N*-methyl-D-aspartate.

therapeutics a high priority. Yet drug development for substance use disorders faces great hurdles.

To obtain FDA approval for most substance use disorders, medications until recently had to demonstrate that they produce abstinence in a significant subset of patients, as measured by negative urine tests. However, the abstinence endpoint is a high bar to achieve, equivalent to requiring remission of pain from an analgesic or remission of depression from an antidepressant. Yet, the FDA granted approval of analgesics and antidepressants on the basis of reduction of symptom severity, not remission (2). The high bar for addiction medications has discouraged investment by the pharmaceutical industry, and significant public sector help was required to bring many of the currently available medications for substance use disorders to market, including buprenorphine, extended-release naltrexone, lofexidine, and naloxone nasal spray.

Treatment programs for substance use disorders inherited a dichotomous working definition of recovery from the 12-step world of past generations, where being completely "drug free" was not merely the gold standard but the only standard, short of which an addicted individual was regarded as having failed or would not be considered to be "recovering." Yet evidence indicates that abstinence is not the only clinically relevant outcome for every individual and that alternative endpoints can contribute to recovery even when abstinence is not completely achieved.

Reduced alcohol use (measured as percentage of heavy drinking days) is now being used as an endpoint in clinical trials for treatments for alcohol use disorder. The FDA has also recently expressed its openness to considering endpoints other than abstinence as targets in medication development for other substance use disorders (3, 4). Given the illegality of many addictive drugs, it has been argued that *any* reduction in use should be considered a benefit to the individual's health and safety (5). Every time a person addicted to heroin must obtain the drug, he or she faces the risks associated with the drug trade as well as with exposure to fentanyl or a contaminant that could lead to overdose or poisoning.

Recently, researchers found in a pooled sample of study participants with cocaine use disorder that those who had high-frequency use at the start of the study and had reduced to low-frequency use by the end of the study showed outcomes at 1-year follow-up similar to those of participants who had quit altogether (6).

TREATING THE DIMENSIONS OF SUBSTANCE USE DISORDER

Endpoints other than abstinence may lead not only to treatments that are helpful in reducing drug use but also to the use of compounds that target specific neurobiological processes and symptoms relevant to addiction and the risk for relapse.

In April 2018, the FDA, in partnership with the Addiction Policy Forum and the National Institute on Drug Abuse (NIDA), convened a meeting to solicit input from patients with opioid use disorder as part of its Patient-Focused Drug Development initiative (7). Among other things, participants emphasized their desire for a more holistic and individualized approach to treatment, as well as their wish for medications that would address specific symptoms of withdrawal, such as cravings, depression, cognitive impairments, pain, and sleep problems. The same year, the FDA

approved lofexidine for treating physical symptoms of opioid withdrawal during detoxification—the first approved drug for treating symptoms associated with opioid use disorder with a restricted purpose and not expected to lead, by itself, to continued abstinence. After detoxification, the individual would ideally be treated with naltrexone or buprenorphine as a longer-term treatment to help prevent relapse and achieve recovery. Other potential targets for medications are those that, while not addressing addiction directly, target major risk factors for relapse.

One such factor is insomnia, for it is frequently interrelated with substance use disorders, with each exacerbating the risk of the other. Findings of shared targets and circuits between disrupted sleep and addiction offer unique opportunities for treatment development. For example, while studying the role of orexin in narcolepsy, researchers serendipitously discovered an unusually high number of orexin-producing neurons in the postmortem brain of a heroin-addicted individual (8). They subsequently established in preclinical models and postmortem brain studies that long-term use of heroin was associated with an increase in orexin-producing neurons. Since orexin is already targeted by suvorexant, an FDA-approved drug for insomnia, NIDA is funding research to test its efficacy, along with that of other novel orexin receptor antagonists, as therapeutic agents in opioid use disorder.

Similarly, dysphoria and depression, which are frequently associated with protracted withdrawal, are another relevant area where our growing understanding of underlying neurocircuitry could guide selection of promising new targets. For example, the habenular complex is intricately involved in dysphoria and negative emotional states and is associated with depression (9) and addiction (10). Both alpha-5 nicotinic acetylcholine receptors and mu-opioid receptors are highly expressed in the habenula, where they modulate its activity, contributing to the adverse symptoms of withdrawal that follow nicotine and heroin discontinuation, respectively, and to the relief that follows during intoxication. Targeting the habenula has already been shown to be beneficial in animal models of addiction treatment (11), and it has been a target for deep brain stimulation for the treatment of depression (12).

Because of the high comorbidity of substance use disorder with depression, psychiatrists have used antidepressants off-label to treat their addicted patients, even though randomized clinical trials of antidepressants have failed to achieve the desired outcome of abstinence. Recognizing that improving depression could still be beneficial for patients with substance use disorders, studies should revisit the possible efficacy of antidepressants as an element of addiction treatment, using endpoints other than abstinence. Bupropion, which blocks the dopamine and norepinephrine transporters and is an approved antidepressant medication, is also approved for the treatment of nicotine addiction. Given the involvement of the mu-opioid receptor system in mood, it would be expected that targeting depression might have particular value in treating opioid use disorder; an interesting feature of the opioid partial agonist buprenorphine is that it has antidepressant properties (13), and opioid-addicted patients who have depression respond particularly well to this medication (14).

Another important therapeutic target is that of addressing social isolation, and while this might be optimally achieved with behavioral interventions, including group treatment, medications could still hold promise. Addicted individuals report reduced pleasure from social contact, as well as fear of the stigma attached to their drug use, and thus they tend to isolate themselves. Isolation in turn drives drug taking (15). Here again, we could take advantage of our increased understanding of the neurobiology of social attachment to bolster social connections. For example, oxytocin, a neurochemical involved in social bonding that also modulates key processes associated with addiction, including reward and stress responses, is being evaluated as a possible addiction treatment and may enhance the efficacy of psychosocial addiction treatments (16, 17).

A dimensional approach to the treatment of substance use disorder is also relevant to neuromodulation. Early research has shown that transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) may be useful in reducing drug cravings, and TMS is already an approved therapy for treatment-resistant depression. Research is needed to study how TMS, tDCS, or peripheral nerve stimulation could be used to improve symptoms associated with addiction, from acute symptoms of withdrawal to the more protracted symptoms of dysphoria and sleep problems. As we understand better how to use neuromodulation technologies to modify brain circuits, it may create opportunities to strengthen specific circuits that can buffer or compensate for others that have been impaired by drug use or constitute a predisposing vulnerability.

Behavioral therapies are also suited to dimensional approaches to substance use disorder treatment. Considerable research already shows the benefits of cognitive-behavioral treatments in improving self-regulation and of contingency management in strengthening the degraded motivation to engage in non-drug-related activities, so clearly these modalities are effective for addressing specific dimensions of the addiction process. Similarly, behavioral treatments to improve executive function could help build resilience against relapse, as shown by methylphenidate's reported ability to reduce impulsivity in individuals with cocaine use disorder (18).

MAKING ADDICTION TREATMENT MORE DYNAMIC AND PERSONALIZED

Trajectories of use vary among people who use drugs, ranging from persistent use or declining use to cessation and relapse or sustained cessation. Studies of people who inject opioids, for example, have identified factors that, to some extent, are predictive of these trajectories (19). Being in a stable relationship, for instance, has been associated with early cessation (highlighting the importance of social support).

Addiction is an evolving disorder that changes through time and across the lifespan of the individual and one that has an unpredictable element that springs from the unique experiences an individual is exposed to. Some widely used behavioral treatments already accommodate and address this changeability of substance use disorder. Cognitive-behavioral therapy teaches the individual to identify external triggers and respond more appropriately to internal states (e.g., mood, craving) that place them at risk for relapse. New technologies are developing algorithms to identify indicators of relapse risk and incorporating them into wearable devices and smartphones with the goal of delivering an intervention in a timely, targeted manner. In the future, as big-data analytics and machine-learning algorithms yield more insight into behavioral and biological markers of relapse risk, tools or devices to avert relapse farther in advance may be developed.

TOWARD THE FUTURE

Neuroscience has revealed that addiction involves a set of interconnected processes that can be targeted strategically, rather than being a disorder defined principally by a single behavior (uncontrollable excessive drug use). Addiction medicine is also increasingly recognizing that factors traditionally associated with recovery are components of treatment. For example, for any meaningful recovery to occur, the individual must be able to integrate him- or herself into a socially meaningful environment. People with substance use disorders who are professionally active or engage in meaningful activity and have a caring family face less of a challenge than those who have no social supports and whose isolation places them at high risk for relapse. The integration of peer mentors, recovery coaching, and supportive housing into addiction treatment is an example of this shift, but more research is needed to determine the most effective ways to sustain social inclusion and to achieve recovery (20).

Addiction is a complex disorder that involves brain circuits necessary for survival and one that is strongly influenced by genes, development, and social factors. We now understand the underlying mechanisms well enough that we can turn this complexity into an opportunity to include these dimensions as targets for substance use disorder treatment, as well as to personalize interventions to accommodate the unique neurobiological characteristics and social contexts of individual patients.

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The author thanks Eric M. Wargo and Emily B. Einstein for their valuable help in the preparation of this article.

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Accepted December 16, 2019.

Am J Psychiatry 2020; 177:113–116; doi: 10.1176/appi.ajp.2019.19121284

REFERENCES

1. Koob GF, Volkow ND: Neurocircuitry of addiction. Neuropsychopharmacology 2010; 35:217–238 (erratum in Neuropsychopharmacology 2010 Mar; 35:1051)
2. Volkow ND, Woodcock J, Compton WM, et al: Medication development in opioid addiction: meaningful clinical end points. Sci Transl Med 2018; 10:eaan2595
3. Kiluk BD, Carroll KM, Duhig A, et al: Measures of outcome for stimulant trials: ACTTION recommendations and research agenda. Drug Alcohol Depend 2016; 158:1–7
4. US Food and Drug Administration Draft Guidance (FDA): Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment: Guidance for Industry. Silver Spring, Md, FDA, August 2018. https://www.fda.gov/media/114948/download
5. McCann DJ, Ramey T, Skolnick P: Outcome measures in medication trials for substance use disorders. Curr Treat Options Psychiatry 2015; 2:113–121
6. Roos CR, Nich C, Mun CJ, et al: Clinical validation of reduction in cocaine frequency level as an endpoint in clinical trials for cocaine use disorder. Drug Alcohol Depend 2019; 205:107648
7. Center for Drug Evaluation and Research, US Food and Drug Administration: The Voice of the Patient: A Series of Reports From the US Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative: Opioid Use Disorder. Rockville, Md, Center for Drug Evaluation and Research, 2018. https://www.fda.gov/media/124391/download
8. Thannickal TC, John J, Shan L, et al: Opiates increase the number of hypocretin-producing cells in human and mouse brain and reverse cataplexy in a mouse model of narcolepsy. Sci Transl Med 2018; 10:eaao4953
9. Lawson RP, Nord CL, Seymour B, et al: Disrupted habenula function in major depression. Mol Psychiatry 2017; 22:202–208
10. Velasquez KM, Molfese DL, Salas R: The role of the habenula in drug addiction. Front Hum Neurosci 2014; 8:174
11. Friedman A, Lax E, Dikshtein Y, et al: Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behavior. Neuropharmacology 2010; 59:452–459
12. Morishita T, Fayad SM, Higuchi MA, et al: Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. Neurotherapeutics 2014; 11:475–484
13. Serafini G, Adavastro G, Canepa G, et al: The efficacy of buprenorphine in major depression, treatment-resistant depression, and suicidal behavior: a systematic review. Int J Mol Sci 2018; 19:2410
14. Dreifuss JA, Griffin ML, Frost K, et al: Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: results from a multisite study. Drug Alcohol Depend 2013; 131:112–118
15. Venniro M, Zhang M, Caprioli D, et al: Volitional social interaction prevents drug addiction in rat models. Nat Neurosci 2018; 21:1520–1529
16. Stauffer CS, Moschetto JM, McKernan SM, et al: Oxytocin-enhanced motivational interviewing group therapy for methamphetamine use disorder in men who have sex with men: study protocol for a randomized controlled trial. Trials 2019; 20:145
17. Lee MR, Weerts EM: Oxytocin for the treatment of drug and alcohol use disorders. Behav Pharmacol 2016; 27:640–648
18. Goldstein RZ, Woicik PA, Maloney T, et al: Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. Proc Natl Acad Sci USA 2010; 107:16667–16672
19. Dong H, Hayashi K, Singer J, et al: Trajectories of injection drug use among people who use drugs in Vancouver, Canada, 1996–2017: growth mixture modeling using data from prospective cohort studies. Addiction 2019; 114:2173–2186
20. Substance Abuse and Mental Health Services Administration (SAMHSA): Social Inclusion (web page). Rockville, Md, SAMHSA, 2019. https://www.samhsa.gov/homelessness-programs-resources/hpr-resources/social-inclusion