DISEASES AND DISORDERS

Advances in understanding addiction treatment and recovery

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This *Special Collection on Addiction* focuses on scientific advances in the treatment and recovery mechanisms of addiction related to four widely misused substances: alcohol, nicotine, cocaine, and opioids. Although the opioid crisis has taken center stage across public policy and scientific forums, all of these substances continue to have a profound global impact on health and well-being and on social and economic resources. This collection includes comprehensive review articles on these substances authored by leading researchers in the field of addiction, along with research studies that present recent discoveries with clear translational impact on developing new treatment targets and effective intervention strategies.

Substance use disorder (SUD)—commonly referred to as addiction—is a medical illness with altered behavioral, cognitive, physical, neurobiological, and affective functions associated with compulsive and repeated use of addictive substance(s), whether legal or illegal. Regardless of the differences among the addictive substances, SUDs share common neurobehavioral characteristics, including the progression of the three addiction stages (intoxication → withdrawal → craving) and dysregulation of the neurobiological systems associated with reward, stress, emotion, and executive functions (*1*). SUDs cause millions of years of life lost because of premature death and is also among the leading causes of life with disability worldwide, including both developing and developed countries (*2*–*4*). Tobacco and alcohol, in particular, are among the four leading risk factors for deaths globally (*5*, *6*). In the United States, it is estimated that each year, over 88,000 people die from alcohol related causes, and more than 480,000 deaths are linked to cigarette smoking (*7*, *8*). Other drug-overdose deaths have increased by more than threefold in the United States since 1999, resulting in more than 70,000 deaths in 2017 (*9*). Based on the 2018 study by the Substance Abuse and Mental Health Services Administration (SAMHSA) (*10*), in the United States alone, there are more than 16 million heavy alcohol drinkers, 27 million daily smokers, and more than 50 million illicit drug users, including more than 10 million people who misuse opioids. However, only about 10% of those who needed treatment for SUDs received treatments in 2018 (*10*). Although there are effective medications—except for cocaine addiction—and other treatment options, the effectiveness of SUD treatment remains inadequate, as extensively reviewed by the leading experts in this collection (Kampman, 2019; Kreek, Reed, and Butelman, 2019; Prochaska and Benowitz, 2019; Witkiewitz, Litten, and Leggio, 2019). According to the 2016 United States Surgeon General's Report (*11*), more than 60% of those who received addiction treatments in the United States relapsed within a year, which highlights the challenges in sustaining recovery (i.e., maintaining long-term drug abstinence and well-being). Despite decades of scientific research and the high economic cost (estimated at $740 billion a year in the United States alone), treatment outcomes and recovery from SUDs continue to be very limited.

Scientific studies on addiction have led to the development of a number of medications for pharmacological interventions, along with other nonpharmacotherapies including behavioral, cognitive, and social interventions (see the comprehensive reviews in this collection). These intervention methods have been applied in treating SUDs such as alcohol, nicotine, and opioid use disorders. Unfortunately, there are no targeted and effective medications for treating cocaine addiction at the present time, due to its complex effect on the central nervous system (CNS—the brain and spinal cord) and difficulty in identifying medication targets (see the review by Kampman in this collection). Even for SUDs with validated treatments, their effectiveness is complicated by many factors related to the nature of the illness, particularly for people with severe SUDs. For instance, regardless of etiology, SUDs affect not only the brain but also other systems and vital organs including the liver, lungs, and the cardiovascular and digestive systems. Misused substances can induce epigenetic changes with widespread downstream biological consequences and alter the functioning of the immune and endocrine systems. Moreover, each substance may affect these systems differently and interactively in polysubstance use.

Research findings over the past two decades have substantially enhanced our knowledge on the neurobiological mechanisms and complexity of the illness caused by SUDs (*1*). As presented in the extensive reviews in this collection, we now understand that, unlike many other diseases, pharmacotherapy or behavioral/cognitive therapy alone is unlikely to be sufficient to either restore the damaged system(s) or to prevent relapse and sustain recovery from addiction. Pharmacotherapy alone may only help to reduce the severity of the disorder(s). Current evidence indicates that, to achieve effective treatments and long-term recovery from SUDs, a combination of

therapeutic intervention strategies is likely required that include pharmacological treatments and evidence-based behavioral/cognitive therapies (newer therapies using brain stimulation and other nontraditional approaches are also in development).

Despite our extensive understanding of the effects of addiction on behavior and the underlying neurobiology, knowledge remains limited on how the affected biological systems interact with external environmental factors and across the molecular, cellular, and system levels during the development of and recovery from SUDs. The challenge in identifying successful long-term treatments for SUDs is complex because of various factors. Individual differences in responding to treatments are among the known factors common to all SUDs. These differences are reflected in various ways, including genetic determinants (e.g., sex and other forms of genetic heterogeneity), differences in metabolic responses to medications, comorbidity with SUDs (e.g., addicted to alcohol and nicotine or cocaine and other drugs) and with other illness(s) (e.g., depression, HIV infection, and trauma), and the severity and behavioral manifestations of SUDs. Other issues are the motivation and degree of commitment to treatment(s), social environment and support, and the availability and/or ability to afford the cost of treatments.

Currently, we lack sufficient knowledge of the following relationships that challenge the development of successful treatment strategies: (i) mechanisms underlying the interactions among the affected neural circuits, molecular mechanisms, synaptic plasticity, and their relation to the functioning of the rest of the CNS and behavioral changes; (ii) causal relationships between neurobiological changes in the brain and their effects on the peripheral systems and vice versa (e.g., the interaction between the hormone ghrelin release in the gastrointestinal system and its effect on the CNS in alcohol craving and between the peripheral and central inflammatory systems in depression and addiction) (*12*–*15*); and (iii) the extent to which social connections and environmental factors alter neurobiological mechanisms in brain circuitries in patients with SUDs. These challenges are fundamental knowledge gaps that require continued funding for relevant interdisciplinary research that can foster innovative approaches and discoveries by the engaged scientific communities.

Recent advances in basic and translational research are beginning to transform scientific knowledge and lead to potentially new therapeutic targets for SUD treatment. In this collection, we present several recent research publications in *Science Advances* that aim to uncover the neurobehavioral and molecular mechanisms that have direct translational potential for new treatment strategies. The study by Werner *et al.* (2019) identified a previously unknown molecular mechanism underlying a chromatin remodeler, INO80, its expression in the brain's nucleus accumbens (NAc), and its interaction with E3 ubiquitin ligase Trim3 protein in mediating cocaine craving in rats after prolonged abstinence from the drug. This finding is likely to advance the development of much needed pharmacological targets for the treatment of cocaine use disorder. The study by Adeluyi *et al.* (2019) provided convincing evidence that nicotine and nicotine withdrawal induce changes in the morphology of microglia (a non-neuronal cell type) and their functional activation in the NAc. These changes significantly alter proinflammatory signaling and increase epigenetic expression of NADPH oxidase 2 (Nox2) mRNA, leading to neuronal oxidative stress and anxiety-like behavior in male mice. In a separate study with chronic nontreatment-seeking adult smokers, Flannery *et al.* (2019) found that acute nicotine abstinence significantly increased the activity of the habenula, a subcortical interface between the brain's basal ganglia and limbic system, which was associated with altered hedonic processing and increased tobacco craving. Using functional magnetic resonance imaging, they showed that the administration of nicotine or varenicline, a nicotine receptor partial agonist, significantly reduced habenula activity, demonstrating the underlying neurobiological efficacy of nicotine replacement therapy in alleviating nicotine craving. As smoking is the leading cause of preventable death but only about 5% of those seeking smoking cessation are successful in quitting, understanding the neurobiological mechanisms of nicotine addiction and craving remains a significant part of the scientific objective. As we know, nonpharmacological therapies are a crucial part of the successful treatment of SUDs. The study by Garland *et al.* (2019) provided neurophysiological evidence demonstrating the efficacy of an integrative behavioral and cognitive treatment for opioid use, the Mindfulness-Oriented Recovery Enhancement (MORE) therapy. They showed that, with an 8-week regimen of training with MORE, chronic opioid users can remediate brain activity associated with hedonic dysregulation and opioid-cue reactivity, increase responsiveness to natural rewards, and reduce opioid craving. Another exciting study by Chang *et al.* (2019) provided direct evidence that relatively noninvasive peripheral stimulation with acupuncture at a specific point (Shenmen HT7) induces activation of brain pathways associated with ethanol withdrawal in rats. Acupuncture at HT7, homologous to the human acupoint, significantly attenuated ethanol withdrawal tremor and reduced alcohol self-administration by activating the endorphinergic input to the NAc, up-regulating the β-endorphin levels in the NAc, and reducing neuronal activity in the arcuate nucleus of the hypothalamus. These scientific discoveries and other continuing efforts will, no doubt, open up new research targets and lead to the development of more effective evidence-based therapeutic strategies for SUD treatment and recovery.

Successful SUD treatment and recovery not only are dependent on the steadfast self-determination to change one's behavior patterns in individuals with SUDs (i.e., in seeking treatment and quitting substance use) but also require a concerted effort and support from specialized medical professionals, social communities, industries, and governmental actions, in addition to scientific discoveries. It is vital to advocate for more medical professionals with specialized training in SUD treatment and to equip them with the most current scientific knowledge and clinical skills to tailor treatments based on individual differences and to apply evidence-based therapeutic tools. Continuing effort in social support and awareness that SUDs are medical illnesses is also critical in helping remove stigmas on patients seeking SUD treatments. Governmental policies and regulations are known to be a critical component in substance use prevention, treatment, and recovery (for details, see the comprehensive reviews in this collection). New and/or updated policies and regulations on substance use, substance dispensing products, and the availability of treatments will inevitably be necessary in light of new scientific discoveries and knowledge. The National Institutes of Health (NIH) and the Center for Disease Control and Prevention in the United States have rich scientific resources and most up-to-date information on SUDs and treatment-related information (see https://alcoholtreatment.niaaa.nih.gov; www.drugabuse.gov/related-topics/treatment; www.cdc.gov). NIH also has significant effort under way in highlighting and supporting translational research to accelerate and advance preclinical trials and animal models to human studies. We hope that this *Special Collection on Addiction* will facilitate the effort in advancing the treatment and recovery process of SUDs.

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