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Addiction – 25 years later

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In the twenty-five years since the inception of the *Harvard Review of Psychiatry*, enormous strides have been made in understanding the etiology and neurobiological underpinnings of addiction and in demonstrating evidence-based pharmacologic and behavioral treatments. Yet we have made minimal progress in closing the gap between the overall prevalence of substance use disorders (SUDs) and the proportion of individuals with these disorders who ever receive any treatment in the course of their lifetimes.¹ When the first issue of the *HRP* was published, the U.S. was just emerging from a cocaine epidemic, and now as the 25th anniversary volume of the *HRP* goes to press, the U.S. is in the midst of a ravaging opioid epidemic. During this interval, the neurobiology underlying these disorders has become increasingly clarified, behavioral interventions such as cognitive behavioral therapy (CBT), relapse prevention (RP), motivational interviewing (MI), brief interventions (BIs), twelve-step facilitation (TSF), contingency management (CM), and others have demonstrated effectiveness, and new medication-assisted treatments for alcohol, opioid, and nicotine use disorders have received approval from the Food and Drug Administration (FDA). However, the treatment system in the U.S. has struggled to disseminate these life-saving treatments to the approximately 20% of the U.S. population who would benefit from them. The gap between available evidence-based treatments and the delivery of these treatments to the majority of patients in need of them is the focus of the 2016 landmark report – Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health.¹

In its first publishing year, the *HRP* published five articles on addiction that were emblematic of the state of the field at that time^{2–6} including evidence for adaptations to chronic drug administration in the brain's ventral tegmental area and nucleus accumbens;² clinical and preclinical studies of buprenorphine treatment of opioid and cocaine dependence;³ the role of psychotherapy in the treatment of substance use disorders;⁴ emerging evidence of gender differences in alcohol-related disorders;⁵ and the importance of treating co-occurring psychiatric disorders.⁶ There has been a rapid acceleration of new knowledge in each of these areas over the last two decades.

Basic and translational research have subsequently expanded our understanding of the reward circuitry underlying addiction, including brain circuits that mediate substance-

induced reward pathways, stress-related changes during withdrawal, and craving and compulsion.⁷ These interconnected neural circuits are disrupted through the chronic use of substances, and affect the pathways of reward, learning, and control. A convergence of data over the past two decades also demonstrates that 40 to 60% of risk for addiction is conferred by genetics and the array of gene variants implicated in the development of SUDs grows each year. In addition, in the past decade new research has highlighted epigenetic mechanisms that can switch on genes implicated in development of addiction. Early childhood trauma may be a particularly powerful environmental stressor that produces potentially heritable epigenetic changes that confer greater risk for addiction in later life. To provide even greater understanding of the developmental risks for SUDs, a new ten-year longitudinal study, the Adolescent Brain Cognitive Development (ABCD) study was launched by the National Institutes of Health in 2016 to investigate the effects of substance use at critical stages of adolescent brain development.

Parallel to discoveries in the areas of neuroscience and genetics, treatment research has expanded the evidence base for effective medications and behavioral treatments across different substances of abuse and levels of SUD severity. In 2003, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) published *Helping Patients who Drink too Much: A Clinician's Guide*⁸ with updates in 2005 and 2008 to keep pace with outcomes of alcohol treatment studies including the multi-site, randomized controlled trial of combinations of medications and behavioral treatments for alcohol dependence, COMBINE.⁹ In 1993, disulfiram was the only FDA-approved medication for alcohol dependence. Since then, naltrexone (in both oral and extended-release depot injection forms) as well as acamprosate have been approved by the FDA for treatment of alcohol use disorders (AUDs), and research studies have shown promise for topiramate^{10–12} and gabapentin,¹³ although they are not currently approved by the FDA. The development of the 10-question Alcohol Use Disorders Identification Test (AUDIT) had just been published in 1992¹⁴ and over the past 25 years, countless studies have demonstrated its effectiveness as a screening tool to detect AUDs in patients presenting for treatment in primary care and mental health settings. In addition, 3-question and 1-question AUDIT screeners have been shown to be time-efficient and effective^{15,16} and brief effective screening questions for special populations such as adolescents¹⁷ and pregnant women¹⁸ have been developed. Screening, Brief Intervention, and Referral to Treatment (SBIRT) for alcohol misuse and emerging hazardous drinking is now considered an important component of care delivery in primary care and emergency medicine.¹⁹ In the same time frame as the initial development of the AUDIT, the first edition of Motivational Interviewing (MI)²⁰ was published with updated editions in 2002²¹ and 2013²² reflecting the many clinical trials that have given support for the effectiveness of this approach to brief interventions in assisting people with AUDs to engage in treatment. Indeed, the shift away from an emphasis on confrontation to the collegial, empathy-based MI is one of the major advances in SUD treatment over the past 25 years.

In addition to MI, an approach that is now used for both alcohol and drug use disorders, other behavioral treatments have been demonstrated as effective in the treatment of SUDs including cognitive behavioral treatment (CBT), relapse prevention, motivational enhancement therapy, contingency management, and twelve-step facilitation in group and individual formats as well as more-recently in computerized formats such as CBT4CBT²³

and other web-based formats added to usual care.²⁴ A multi-site study of one of these web-based treatment interventions²⁵ was conducted through the National Institute on Drug Abuse (NIDA) National Clinical Trials Network (CTN), a national collaboration of researchers and clinicians that was initiated in 2000 to conduct multi-site trials in community-based SUD treatment programs and, more recently, in general medical settings. Seventeen years later the NIDA CTN has completed multiple large multi-site randomized clinical trials demonstrating the effectiveness of a range of medications, behavioral treatments²⁶ and their combination. These have included a study demonstrating the effectiveness of buprenorphine/naloxone in adolescents and young adults²⁷ and the largest study yet conducted of prescription opioid addiction treatment, examining optimal combinations of buprenorphine/naloxone and counseling.²⁸

The passage of the Drug Addiction Treatment Act of 2000 (DATA 2000) by Congress, heralded a sea change in the treatment of opioid use disorders (OUDs), in that it allowed trained and waived physicians, for the first time, to prescribe agonist treatment (the partial agonist buprenorphine) for OUDs as part of office-based practice. Prior to 2000, methadone was the only agonist medication available for the treatment of OUD, and it could only be dispensed in Opioid Treatment Programs (OTPs).²⁹ In 2010, depot naltrexone was approved by the FDA for the treatment of OUD, and could also be prescribed in office-based practice. In 2016 a buprenorphine implant,³⁰ was approved by the FDA for treatment of OUD. Thus, the landscape of OUD treatment has changed dramatically since 1993. At that time, physicians either had to refer their patients for agonist (methadone) treatment in an OTP or prescribe oral naltrexone in the office, which had a very low acceptance rate among patients with OUD. Now, physicians have the ability to prescribe buprenorphine in either sublingual or implant form, and can prescribe extended-release injectable naltrexone. Another significant advance in the treatment of OUDs occurred as a result of a multi-site clinical trial that demonstrated the relative safety and effectiveness of buprenorphine compared with methadone in the treatment of pregnant women with OUDs.³¹

A number of advances have also occurred in the treatment of cigarette smoking. Studies have demonstrated the effectiveness of single and combined effective behavioral and medication treatment for tobacco cessation including varenicline, bupropion, nicotine replacement treatments, and brief counseling.³² Despite the fact that the effectiveness of these treatments has been demonstrated in the last twenty-five years, the treated prevalence of nicotine dependence among smokers remains low³³ and one group who are significantly affected are individuals with mental health disorders.³⁴

Over the last twenty-five years, epidemiologic, treatment outcome studies, and biological research has demonstrated that sex and gender affect the risk, onset, progression, and treatment outcomes of substance use disorders.³⁵ In the U.S., there has been a narrowing of the gap between males and females in the prevalence of alcohol and drug use disorders across the age spectrum, and the prevalence of use is approximately the same for alcohol and other drugs in younger birth cohorts. In addition, the more rapid acceleration of adverse consequence of SUDs in women compared with men, as well as the greater prevalence of psychiatric co-morbidity and trauma histories in women are now known risk factors for SUD treatment outcomes.³⁵ While women with SUDs may be more likely to have co-occurring

depression, anxiety, eating, and post-traumatic stress disorders, studies during the last two decades have shown the importance of providing integrated treatment of psychiatric and substance use disorders.³⁵ Indeed, the commonplace use of the term “addiction psychiatry,” once seen as an oxymoron, is emblematic of the dramatic shift in the past 25 years, in which the central role of psychiatry in the treatment of patients with SUDs has become well-recognized.

Emerging epidemics of drugs of abuse provide ongoing challenges. Recent epidemiologic studies indicate that while alcohol use is declining among youth, there is a concomitant rise in cannabis use among youth, as perceptions of dangerousness of cannabis declines with state legislative action to legalize marijuana.³⁶ Opioid use disorders including prescription opioids, heroin, and fentanyl, with the ongoing rise in opioid overdose deaths, continue to challenge the health system and U.S. society at every level. The critical and sustained need for public health and health care system interventions to prevent and treat SUDs in the U.S. has been brought into high relief by the recent opioid crisis, and the need to expand capacity of an addiction treatment-trained healthcare work force is now recognized.

Over the last fifteen years, as the field has struggled to train adequate physician prescribers to meet the rising demand for OUD treatment, the Substance Abuse and Mental Health Services Administration (SAMHSA) passed new regulations in 2016 to raise patient limit for whom qualified providers can prescribe buprenorphine.³⁷ In general, however, medical specialties have been slow to implement training of physicians to screen for and treat SUDs. Psychiatry was the first medical specialty to initiate addiction psychiatry specialty training in the mid-1990s by establishing the first American Board of Medical Specialties (ABMS) approved addiction psychiatry fellowship programs. Only in 2015 did other primary care specialties gain approval by ABMS for addiction medicine fellowships to train a range of physicians to treat this patient population. Other health care professions such as nursing are now also emphasizing the need for additional training and education in SUD treatment.

As HRP marks its 25th year, legislation passed by Congress in 2016 could have the potential to increase treatment among individuals with SUDs. The Comprehensive Addiction and Recovery Act (CARA), signed into law in July, 2016, was the first major federal legislation in 40 years and authorized \$181 million each year in new funding to fight the opioid epidemic. However, Congress will need to appropriate the funds annually to provide the coordinated response through prevention, treatment, recovery, law enforcement, criminal justice reform, and overdose reversal. In December, 2016, Congress also passed the 21st century CURES act providing for \$1 billion in grants to help states provide treatment for OUDs. The Affordable Care Act (ACA), through mandatory coverage and parity enforcement, has expanded access to treatment services to many patients with OUD and other SUDs. Beyond these legislative initiatives, the U.S. Surgeon General’s report on addiction in America highlighted even more broadly the need for increased attention by the U.S. health system to the treatment of SUDs. The last twenty-five years has seen a remarkable explosion of knowledge in neuroscience and genetics, and research has resulted in an expanded compendium of evidence-based treatments that can be used to provide early intervention, treatment, and recovery for patients and their families. It remains to be seen, however, whether social and political forces can join together to provide sustained and

meaningful change to the U.S. health system so that the majority of individuals with SUDs can gain access to and benefit from the ever-expanding array of effective treatments now available for these health conditions that are responsible for such great morbidity and mortality.

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