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# Addiction III: From mouse to man☆

## 1. Introduction

This mini-issue of the Brain Research Bulletin emerged from the 7th annual Addiction Symposium held at the Penn State University College of Medicine in Hershey, Pennsylvania on December 6th, 2021. The goal of this Symposium, which is organized by our Penn State Addiction Center for Translation (PS ACT), is to bring together students, faculty, basic scientists, clinicians, physicians, state representatives, senators, and leaders of area treatment centers to: (1) Discuss novel preclinical and clinical data as they contribute to a better understanding of the disease; (2) Learn about current challenges facing our emergency rooms, clinics, community, commonwealth, and the nation in the treatment of individuals suffering from a substance use disorder (SUD) and addiction; and (3) Consider how to use this information to advance knowledge and treatment via our Research, Education, Clinical, and Outreach missions of the PS ACT, the Penn State College of Medicine, and Penn State University.

## 2. Addiction: the problem

Like so many other health-related chronic diseases, the long-running problem of SUD and addiction has just gotten bigger. For example, in the United States, drug overdose deaths rose 30 % from 2019 to 2020 with a record loss of 93,655 people in 2020. That number increased by another 15 %, with 107,027 individuals lost to drug overdose in 2021. Opioids accounted for 75 % of those deaths (Centers for Disease Control and Prevention, 2022). The CDC estimated that 140,000 people died each year from excessive alcohol use from 2015 to 2019 (Centers for Disease Control and Prevention, 2022), with a COVID-related 25 % increase reported in 2020 and an additional 22 % increase reported in 2021 (Yeo et al., 2022). More insidious, but even greater in number, cigarette smoking is estimated to contribute to 480,000 deaths annually in the United States (Centers for Disease Control and Prevention. Tobacco-Related Mortality, 2020). Taken together, 727,027 individuals died in 2021 from drug overdose, excessive intake of alcohol, and smoking, or 1992 people/day. This number approaches peak daily death rates from the second and third waves of the COVID-19 (SARS-CoV-2) pandemic in the United States (Murphy et al., 2022). These numbers are fully unacceptable, reveal the marked negative impact of stress and other factors on SUD, and the need for improved treatments and treatment strategies.

## 3. Addiction: the need for further scientific discovery

While there are effective treatments for opioid use disorder (OUD), alcohol use disorder (AUD), and nicotine use disorder (NUD), the number of treatments is too few, they are too rarely prescribed (e.g., less than 20 % of individuals with an OUD access medication for OUD (Substance Abuse and Mental Health Services Administration, 2019)), and only a third of those who do seek treatment are retained in treatment after 6 months (Socias et al., 2018). Further, there currently are no approved treatments to prevent the progression from substance use to addiction (McLellan et al., 2022). This is in contrast to other chronic conditions like diabetes that have standard treatments for those with "prediabetes" who are at high risk for disease progression. Our next advances in the prevention and treatment of the chronic relapsing disease of SUD and addiction, then, depend upon further research into addiction risk, prevention, and treatment. Three questions addressed in this mini-issue include: What increases one's vulnerability to substances of abuse? How does the use of these substances affect vulnerability to disease? Finally, what novel treatments and/or treatment regimens are on the horizon and how might these inform our understanding of the devastating disease of SUD and addiction?

## 4. Risk factors for SUD and addiction

Preclinical and clinical data reveal all manner of risk factors for the development of SUD and addiction, including genetic make-up and sex. In their review in this mini-issue, Goldberg and Gould (2022) describe data suggesting that heritability estimates for nicotine use and abuse are reportedly as high as 80 %. Yet, what genes impact use and, given that nicotine use most often begins in adolescence, what genes might drive initiation of nicotine use in adolescence and then carryover from use to abuse and addiction in adulthood? Goldberg and Gould synthesize a mass of preclinical and clinical data to address these and other important questions. A second risk factor is sex. Goldberg and Gould also discuss data suggesting that heritability for smoking initiation is greater in females; while heritability for smoking persistence is greater in males (Li et al., 2003). These human data overlap with the animal data. Thus, like data reported for fentanyl self-administration in rats (Towers et al., 2022), Crowley et al (Crowley et al., 2019). also reported greater intake of ethanol in female vs. male mice. Further, in this issue, Crowley and her team (Suresh Nair et al., 2022) implicate a mediating role for the bed nucleus of the stria terminalis in binge intake of alcohol in female, but not in male, mice.

☆ Addiction: A preclinical and clinical analysis.

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Not surprisingly, hormones contribute greatly to such male/female differences, with estrogen shown to be critical for the development of a greater addiction phenotype to cocaine (Ramoa et al., 2013) and greater extinction responding and cue-induced reinstatement of fentanyl (Towers et al., 2022) in female rats. Another hormone, ghrelin, also may play a role. Ghrelin is produced by endocrine cells in the fundus of the stomach, it mediates an increase in food intake (Kojima et al., 1999; Hosoda et al., 2002; Date et al., 2000) and it may impact responding for drug. For example, Roux-en-Y gastric bypass (RYBG), a surgery for the treatment of obesity and metabolic disorders, leads to an increase in SUD in humans (King et al., 2017) and in rodents (Thanos et al., 2012; Biegler et al., 2016) and preclinical data implicate a mediating role for ghrelin (Hajnal et al., 2012; Orellana et al., 2021). An alternative weight loss surgery, sleeve gastrectomy, removes ghrelin producing cells in the fundus (see (Orellana et al., 2019) for a review), reduces ethanol intake in rodents (Orellana et al., 2018), reduces drinking in already high-risk human drinkers, but may contribute to an increase in high-risk drinking among humans who were not high-risk drinkers prior to surgery (Wong et al., 2022). In an effort to better understand the impact of these surgeries on vulnerability to the development of SUD (in this case AUD) and the mediating role of ghrelin, Orellana et al. (2022). in this issue use animal models to examine the effect of RYGB or sleeve gastrectomy on plasma levels of the active form of ghrelin, acyl ghrelin, and the inactive form, des-acyl ghrelin, and consequently, on post-surgical intake of a range of doses of ethanol.

Along with individual factors like genetics, sex, and hormones, addiction is a dynamic chronic relapsing disorder and one that can be influenced by associated drug cues and additives. For example, menthol enhances nicotinic acetylcholine upregulation and nicotine bioavailability to increase the addictiveness of cigarettes (Wickham, 2020; Brody et al., 2013). Menthol also serves as a potent cue for smoking that leads to reinstatement of nicotine seeking in animal models (Harrison et al., 2017). Indeed, Lin et al. (2022). show in this issue that relative to human smokers placed on very low nicotine cigarettes (VLNC) without menthol, those placed on VLNC with menthol are 2.8 times more likely to supplement the VLNC with their usual cigarettes. They also are less likely to achieve reductions in cotinine, a nicotine metabolite. This is critical new information because the FDA recently approved a plan to greatly reduce the nicotine content in cigarettes in the United States (Radcliffe, 2022) and have proposed a ban on menthol cigarettes (United State Food and Drug Administration, 2022). Recent evidence suggests that drug-related cues are especially problematic because they elicit not only craving, but also withdrawal (Regier et al., 2021) and can, thereby, further the neurobiological effects of additives like menthol. For people who smoke, nicotine withdrawal and cue-induced craving peak in the morning hours after overnight abstinence and individuals who smoke within five minutes after waking are the least likely to successfully quit smoking (Baker et al., 2007). As such, additives, like menthol, are likely to support cue-induced craving and withdrawal and thereby contribute to the severity of NUD.

Reward relativity impacts responding for drug, and to cues for drug. In this issue, Morris et al. (2022). conducted a scoping review of the literature and found evidence that later OUD was predicted by an initial euphoric response to drug. With such a strong initial euphoric response to drug, natural rewards likely pale in comparison. Natural rewards also pale when predicting future access to drug. Specifically, rats avoid intake of a saccharin cue when paired with either experimenter (Grigson, 1997) or self-administered (Grigson and Twining, 2002; Imperio and Grigson, 2015) drug. The Grigson lab has interpreted avoidance of the drug-paired saccharin cue as reflective of withdrawal because steroid levels are high (Gomez et al., 2000), dopamine levels are low (Grigson and Hajnal, 2007; Wheeler et al., 2008, 2011), and body weight is lost following a naloxone challenge (Nyland et al., 2016). Moreover, when paired with self-administered drug, large individual differences are evidenced whereby greater avoidance of the drug-paired cue predicts a shorter latency to take drug, greater drug self-administration, greater escalation of drug-taking over trials, a strong willingness to work for drug, and greater cue- and drug-induced seeking (Grigson and Twining, 2002; Imperio and Grigson, 2015; Colechio et al., 2014). In our previous mini-issue on addiction, McFalls et al (McFalls et al., 2016). showed that greater avoiders of the saccharin reward cue (i.e., large suppressor/high drug-takers) evidenced greater mRNA expression of corticotropin releasing hormone (CRH), its receptors, and binding protein in the hippocampus (HC), ventral tegmental area (VTA), and medial prefrontal cortex (mPFC). Here, McFalls et al. (2022a). provide evidence that these brain changes are consequent to, not only avoidance of the drug-paired saccharin cue, but also to a history of high drug-seeking and taking because greater avoidance of a saccharin cue paired with experimenter delivered heroin led to increased mRNA expression only in the HC and only of CRHR2 and CRHbp. In McFalls et al. (2022b). in this issue, analysis of the role of the mPFC for large suppressor/high drug-takers is expanded via RNA-sequencing and implicates a role for a number of genes involved in schizophrenia, dopamine signaling, signal transduction, development, and synaptic plasticity. Finally, in a study on recently withdrawn individuals in residential treatment for OUD, Petrie et al. (2022). in this issue used functional near infrared spectroscopy and showed that greater anhedonia, and reduced PFC activity to positive social stimuli, were associated with greater opioid craving. Greater devaluation of natural rewards, then, in both lower animals and in humans, is associated with greater drug craving, greater withdrawal, and ultimately greater drug seeking and taking. Greater drug seeking and taking in the most vulnerable is associated with greater changes in gene expression and neural activation in the reward pathway including the HC, VTA, and PFC.

## 5. Impact of the use of abused substances on health and disease

The COVID-19 pandemic has shined a light on the pain points in the US and around the world, with greater deaths among those with the poorest health and the least access to health care (Dukhovnov and Barbieri, 2022). Preexisting conditions that contribute to a poor outcome from the COVID-19 infection include diabetes, obesity, heart failure, and dementia, for example (Treskova-Schwarzbach et al., 2021; Mena et al., 2021). Another pre-existing condition is SUD. Thus, not only did the COVID-19 pandemic lead to an increase in deaths due to drug overdose, but having a SUD, in turn, also increased the likelihood of death following contraction of the SARS-CoV-2 virus (Banks et al., 2022; Wang et al., 2021a). In this issue, Xu and Randall (2022) confirmed these findings in a retrospective health outcomes study on COVID positive patients in Pennsylvania and extended it by showing even greater overall risk of requiring ventilation, developing pneumonia, and mortality within 30 days of contracting the virus for patients whom were dependent upon both alcohol and nicotine. Remarkably, 85 % of adults with an AUD also use tobacco products (Chatterjee and Bartlett, 2010), making them particularly vulnerable to disease. Excessive alcohol use, alone, is linked to an increase in inflammation, cardiovascular disease, insulin resistance and type two diabetes (Fan et al., 2008). But, these are only endpoints. Identifying the true mediators, i.e., how alcohol, for example, impacts end organ damage, requires careful work. Here, Keller et al. (2022). evidence such work. Specifically, using an in vitro preparation, they showed that greater than 30 min of exposure to ethanol led to a reduction in firing of dorsal motor vagus (DMV) preganglionic parasympathetic motor neurons projecting to the pancreas and to an increase in presynaptic transmission of the major inhibitory neurotransmitter GABA. This is one organ and one mechanism, but the data bring us an important step closer to understanding how alcohol may contribute to insulin resistance, type two diabetes, and ultimately to increased vulnerability to additional challenges such as COVID-19. Finally, it should be noted that, while SUD and many other comorbid conditions contribute to a poor outcome from SARS-CoV-2, some factors confer protection. For example, Nyland et al. (2021). found in a

retrospective study that mortality from COVID-19 was reduced by 42 % in those treated with a glucagon-like peptide-1 receptor (GLP-1R) agonist for their type two diabetes. Importantly, Tuan et al. (2022). report in this issue that, while having a mental health condition, including attention deficit hyperactivity disorder (ADHD), is associated with a higher mortality rate due to COVID-19 infection (Wang et al., 2021b), those treated with a stimulant for their ADHD are at reduced risk for using the emergency department and, importantly, for mortality due to the COVID-19 infection. This finding was thought due to the effect of the drug on the dopaminergic system, on the cardiovascular system, and possibly on the ability to execute behaviors that increase the probability of improved healthcare for this patient population.

## 6. Novel treatments/interventions

Given the devastating impact of SUD on individuals, their families, and on our communities at large, it is critical that alternative treatments, behavioral and otherwise, continue to be explored. In our 2016 mini-issue in BRB, Woodworth and McLellan (Woodworth and McLellan, 2016) made the point that recovery is possible, even highly probable, if treatment for this disease is ongoing as is the case for other chronic diseases such as diabetes, for example. Indeed, this was the great hope with the passage of the Affordable Care Act over a decade ago – and progress has been made with insurance companies providing coverage for more to receive treatment, barriers to care lifted such as the waiver requirement for the prescription of medication for the treatment of OUD (MOUD), and increased availability of intranasal naloxone to rescue victims from opioid overdose. Changes such as these were, in fact, beginning to lead to a leveling off in overdose deaths as of 2019, but as discussed, deaths due to the use of nicotine, alcohol, stimulants, and opioids skyrocketed again with the onset of the COVID-19 pandemic (National Institute on Drug Abuse, 2022). The work, then, must push on. In a recent pilot study described in this issue, Yingst et al. (2022). confirmed the safety and tolerability of a new nicotine replacement therapy (NRT), the oral dissolving film. Thereafter, she and her team tested whether smoking cessation could be facilitated by random, rather than steady state, delivery of nicotine via this novel NRT. This trial follows from prior research showing that random, unpredictable delivery of cocaine leads to greater peak “bad effects” in humans (Donny et al., 2006) and to avoidance of a drug-paired location and reduced willingness to work for cocaine in rats (Twining et al., 2009).

Regarding the treatment of OUD, there are as described only three approved treatments including methadone, buprenorphine (Suboxone), and extended release naltrexone. It is without doubt that these medications allow individuals with OUD to return to a happier and healthier lifestyle and certainly save lives (Larochelle et al., 2018). There are, however, limitations as described with less than 20 % of individuals with an OUD receiving access to medication (Substance Abuse and Mental Health Services Administration, 2019), and only a third of those remaining in treatment after 6 months (Socias et al., 2018). This would be akin to the unthinkable - insulin being prescribed for only 20 % rather than 100 % of patients with type one diabetes. New candidates, then, are essential for the treatment of OUD. To this end, the GLP-1R agonist found protective against COVID-related deaths in patients with type two diabetes (Nyland et al., 2021) is a new non-opioid medication currently under study for the treatment of SUD, including OUD. Indeed, treatment with short acting GLP-1R agonists, either systemically or into the brain, has been shown to reduce responding for nicotine, cocaine, oxycodone and fentanyl (Egecioglu et al., 2013; Hernandez et al., 2018; Reddy et al., 2016; Schmidt et al., 2016; Sorensen et al., 2015; Turton et al., 1996; Zhang et al., 2020, 2021). Here in this issue, Urbanik et al. (2022). show that acute treatment with the longer acting GLP-1R agonist, liraglutide, reduces both cue-induced fentanyl seeking and drug-induced reinstatement of fentanyl seeking in rats. Evans et al. (2022). expand upon this finding by showing that chronic treatment with increasing doses of liraglutide across the abstinence period and prior to test also is effective in reducing both cue-induced heroin seeking and drug-induced reinstatement of heroin seeking in rats. Given that GLP-1R agonists are known to induce satiety (Prasad-Reddy and Isaacs, 2015; Alhadeff et al., 2012; Merchenthaler et al., 1999), this finding, along with others (Douton et al., 2022a, 2022b, 2021), was taken as support for the hypothesis that SUD and addiction involves not only the liking and wanting of drug (Morales and Berridge, 2020), but also the physiological need for drug. The need state is thought to be experienced, at least in part, as withdrawal. Interestingly, a recent study showed that withdrawal, more so than craving, mediated the effect of drug use severity on activation of the nucleus accumbens to a drug-paired cue (Shi et al., 2021). Finally, Fang et al. (2022). in this issue showed that acute treatment with a GLP-1R agonist also is effective in increasing NREM sleep, which may further contribute to the protective effects of the drug on risk of relapse. The GLP-1R agonist, liraglutide, currently is being tested for safety and efficacy in reducing risk of relapse in patients in treatment for opioid use disorder (Bunce, 2021).

In sum, this mini-issue in the Brain Research Bulletin is the third in a series and reflects some of the work coming out of our 7th annual Addiction Symposium organized by the PS ACT at the Penn State College of Medicine, Penn State University. Collectively, the work includes preclinical data, human data, and an increasingly available and informative source, retrospective analyses of large data sets to address factors influencing the initiation, development, and treatment of substance use disorder and addiction spanning NUD, AUD, OUD, and polysubstance use. The data reveal a range of risk factors including genetics, age (e.g., adolescence), sex (i.e., being female), hormones (i.e., estradiol and possibly ghrelin), drug-related cues and additives like menthol, a first-time euphoric response to drug, greater devaluation of a natural reward cue and/or anhedonia, and greater craving and withdrawal. Neural mechanisms play an important role in understanding vulnerabilities to substance use disorder and addiction. The somatostatin neurons in the bed nucleus of the stria terminalis were implicated in greater ethanol intake in female mice, the HC and the CRH stress pathway were implicated in greater avoidance of a saccharin cue paired with experimenter delivered heroin (the HC, VTA, and mPFC are implicated when the same saccharin cue predicts the opportunity to self-administer the opioid), and a reduction in PFC activity was identified in humans with an OUD who failed to respond to positive social stimuli and exhibited greater craving for drug. Several papers also addressed the impact of SUD on health and disease. The use of nicotine or alcohol was associated with an increase in COVID-related mortality and this effect was greatest in those individuals whom were dependent upon both substances, as most often is the case for individuals with an AUD. A mechanism for alcohol-induced end-organ damage was provided in an in vitro study showing a GABA mediated ethanol-induced reduction in firing of DMV preganglionic parasympathetic motor neurons projecting to the pancreas. Finally, while mental health disorders and SUD lead to poorer COVID outcomes, treatment of ADHD with a stimulant was found to be protective in this patient population. In the last section, novel treatment regimens were considered. The effect of random nicotine delivery via a novel oral dissolving film on smoking cessation held some promise in a pilot study; and acute and chronic treatment with the glucagon-like peptide-1 agonist, liraglutide, already approved for the treatment of type two diabetes and obesity in humans, significantly reduced both cue-induced heroin and fentanyl seeking and drug-induced reinstatement of heroin and fentanyl seeking in rats. These findings are consistent with the conclusion that SUD and addiction involve a hijacking of not only reward substrates, but of substrates involved in homeostatic need as well and they offer promise for the ongoing human clinical trials to test the same.

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[1] Special Issue Overview.