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Opioid Use Disorder: A Desperate Need for Novel Treatments

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Religion is the opium of the people.

—Karl Marx, *A Contribution to the Critique of Hegel's
Philosophy of Right*, 1844

While many interpret this quote as a criticism of organized religion, it also speaks volumes to opium's place in 19th century society. Opium is one of the oldest known drugs in the world. Records from prehistoric times indicate that it may have had ritualistic significance. Greek Gods have been depicted holding or wearing poppies. In addition, opium has played a major historical role in international trade, leading to the Opium Wars between England and China—the first of which had just concluded at the time of the publication of Marx's quote.

Nearly 175 years later, opioids still maintain a conflicted presence in society. Though a problem worldwide, this issue has become increasingly urgent in the United States, with a startling juxtaposition of use and abuse. In 2014, more than 240 million prescriptions for opioids were written; on an average day, more than 4000 people initiate opiate abuse. Prescription abuse costs society \$55 billion each year, with \$20 billion in emergency department and inpatient care alone. Most significant, though, is the human cost: more people died from drug overdoses in 2014 than any previous year, and the majority—more than 28,000—involved an opioid (1). A 2001 study by Hser *et al.* demonstrated the profound impact of this disease: they longitudinally followed 581 people (mean age, 25.4 years) with opiate use disorder (OUD) and found that at the end of 33 years, nearly 50% had died, 4% were incarcerated, 7% continued to use daily, and only 22% were abstinent. Common causes of death were overdose, liver disease, cancer, cardiovascular disease, homicide, suicide, and accidents (2). Engaging in high-risk behaviors, including intravenous use, mixing opioids with other drugs, and having been resuscitated with naloxone at least once previously, carried an even more dire prognosis.

Whether in ancient Greece, 19th century Germany, or today, the effect of opioids on the brain remains the same. Like all addictive drugs, opioids activate the brain's reward system (Figure 1), which includes the ventral tegmental area, nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala, and hippocampus (though we would emphasize that this is one of multiple circuits involved in opiate addiction). A core component of this system is the signaling of dopaminergic neurons originating in the ventral tegmental area onto synapses in the NAc. This dopaminergic firing is a powerful signal of salience—there is increased

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dopamine release with unexpected rewards and decreased dopaminergic firing when an expected reward does not occur. This dopaminergic signal plays a crucial role in learning, motivation, and facilitating reward-seeking behavior, with the amygdala and hippocampus playing key roles in memory and emotional learning (3). The PFC is integral to planning complex actions, decision making, and moderating pleasure-seeking behavior, thus opposing the dopaminergic drive of the ventral tegmental area and NAc.

The reward system is activated by and reinforces primitive behaviors that are critical to survival and reproduction, such as eating food, drinking water, sex, and raising offspring. Drugs of abuse activate dopamine release in greater magnitude than natural behaviors and thus can potentially “hijack” the endogenous system. Over time, substance use may shift balance from cortical control toward more primitive, reward-seeking behaviors, leading to escalating substance use and a decreasing ability to self-regulate.

Before discussing neurobiologically informed treatments of OUD, we emphasize that psychosocial approaches are critical (though, of course, one might broadly conceptualize these interventions as helping engage the PFC to suppress negative affect and to enhance behavioral control of impulses). There are a wide range of evidence-based psychotherapies (largely reflecting a cognitive-behavioral orientation) that are effective for treating substance use disorders. Given the lethality of OUD, another critical intervention is to provide psychoeducation to patients about harm reduction strategies, the principles of which include start low and go slow (particularly following a period of sobriety where tolerance would be diminished); know the supply (overdoses are often caused by inadvertently using unexpected substances); never mix with other substances (especially benzodiazepines or alcohol); never use alone; always have a naloxone rescue kit available; and never share needles or inject directly into the skin.

Another major psychosocial treatment used for addiction is Alcoholics Anonymous (AA) for alcohol use disorder or Narcotics Anonymous for OUD (for the sake of this commentary, we refer to these collectively as AA). AA has been rigorously researched and reviewed, with mixed findings. Many people report personal benefit, as evidenced by the *Big Book of AA* having sold tens of millions of copies and the fact that more than 5 million people attend meetings annually. Additional benefits of the AA approach are that it does not cost the health care system any money, meetings are virtually always available to patients, and it is anonymous.

When conceptualizing treatment for OUD from a neurobio-logical perspective, the most basic approach—and the one that has yielded the greatest success to date—is to begin at the level of the opioid receptor. The two primary pharmacotherapies for OUD are buprenorphine and methadone. Both are synthetic opioids (buprenorphine a partial agonist at the μ receptor and methadone a full agonist) with long half-lives that thereby prevent reward from additional opiate use and minimize craving that can be caused by withdrawal (as seen with heroin, which has a very short half-life). A meta-analysis found that when buprenorphine was used at medium and high doses it was superior to placebo in terms of treatment retention and in its ability to suppress heroin use (4). Methadone has been extensively studied, and higher doses are generally accepted to have superior efficacy to lower doses (5).

Methadone has also been proven to be effective in reducing the harms associated with OUD, including overdose death, human immunodeficiency virus, hepatitis B and C, and criminal activity. Medications for OUD should routinely be used in conjunction with a psychosocial treatment. While evidence shows that medications for OUD are more effective with concomitant psychosocial treatments, the lack of psychosocial treatment should not preclude the use of medications.

A range of other novel treatments are being considered based on a circuit level approach to addiction. Repetitive transcranial magnetic stimulation is being investigated as one potential way to modify the reward network, with early studies across a range of addictive substances focusing on stimulation of the dorsolateral PFC as a means of improving inhibitory control (6). Deep brain stimulation has also been studied in animal models and with several experimental case reports in humans looking at stimulation of the NAc (7). Another novel approach being explored for altering reward circuits is to target specific subunits of G protein-coupled receptors to allosterically modify their function and thereby selectively modulate corticostriatal pathways (8).

A separate line of inquiry has been to explore the use of immunotherapies to treat substance use disorders. One avant garde approach has been to try to prevent drugs of abuse from ever reaching the central nervous system, such as through the development of antidrug vaccines. Such interventions would entail having antibodies attach to the drug peripherally and form a complex that is too large to cross the blood-brain barrier, thus blocking the drug's ability to activate central nervous system reward circuits (9). Another approach relates to findings that drugs of abuse can cause oxidative stress and activate complex inflammatory pathways, thereby leading to structural brain damage and worsening of addiction. Accordingly, studies are exploring immunotherapies that are designed to regulate inflammatory responses and heal substance-induced neuronal damage (9).

In this issue of *Biological Psychiatry*, Egervari *et al.* (10) approach the problem of OUD from a different angle. Their work is predicated on the idea that addiction may be perpetuated by long-term plasticity in key regions of the reward pathway, including the striatum. Using an elegant translational approach, they show that chronic opiate use in humans leads to epigenetic changes that affect the transcription of a glutamatergic gene involved in synaptic plasticity, thereby potentiating addictive behavior. They then return to an animal model and show that a molecule (the bromodomain inhibitor JQ1) known to reverse this epigenetic process also potently reverses addictive behavior in rodents. This work is particularly inspiring for how far it moves beyond traditional treatment approaches for OUDs and strikes at the heart of why addictive behaviors may develop in the first place (i.e., because of induced plasticity in key regions of reward circuitry). The potential of such an approach both for opiate and other addictive disorders is inspiring, and it is especially notable that JQ1 is already being used in Phase I clinical trials for cancer treatments in humans and appears to be relatively well tolerated.

In conclusion, OUD is a common, rapidly growing, and often deadly illness that costs the U.S. health care system billions of dollars each year. While traditional treatments have had relatively limited efficacy, this is now one of the most exciting areas in translational

neuroscience. A range of exciting new approaches are being explored, with the potential to directly affect the core neurocircuitry underlying this disease. Given the severity and deadly nature of OUD, these novel treatment approaches are desperately needed.

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Figure 1.

The basic elements of the reward system. The dopaminergic signal from the ventral tegmental area to the nucleus accumbens plays a crucial role in learning, motivation, and facilitating reward-seeking behavior. The prefrontal cortex is integral to planning complex actions, decision making, and moderating pleasure-seeking behavior—thus acting in opposition to the dopaminergic drive of the ventral tegmental area and nucleus accumbens. The amygdala and hippocampus are involved with the formation of memories and emotional responses.