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Epidrugs vs. The Opioid Epidemic

By: Katie Murakami



“One of the Biggest Mistakes in Modern Medicine.”

As described by former FDA commissioner Dr. David A. Kessler, OxyContin is infamously regarded as the catalyst of the opioid epidemic in the United States.¹ The opioid epidemic is still prevalent today, with approximately 80,000 Americans dying from opioid overdoses in 2023.² Treatments for opioid use are also seldom obtained, with only 1 in 4 adults with an opioid use disorder receiving medication.³

Uppers, Downers, and a Resulting Dependency

When the body experiences pain, the central nervous system produces chemicals called endorphins. These chemical regulators play an essential role in relieving pain and stress. When endorphins are released,

they bind to a special signal receiver in the brain called an opioid receptor. These receptors are associated with regulating a variety of vital functions such as pain, mood, digestion, and respiratory function.

Opioids are a class of drugs that mimic the activity of endorphins. Most clinical opioids target the μ receptor, which enables pain relief. Similar to alcohol, opioids are “downers” or central nervous system depressants. Opposite to “uppers”, like cocaine, nicotine, and methamphetamine, opioids slow down brain and body activity upon binding to an opioid receptor. This depressant effect happens in a number of ways. For example, the μ receptors, located in neurons, are responsible for regulating respiratory rhythm. When the receptor is activated by opioids, this rhythm is disrupted and causes slower and weakened breathing. In severe cases, this can lead to complete respiratory depression.⁴ This particular side effect of opioid use is the leading cause of opioid overdose deaths, as severely reduced respiratory rates are often fatal.

In addition to these physiological effects, another familiar effect of opioids is the neurochemical response: opioids cause brain cells to release a chemical regulator called dopamine. Dopamine release produces feelings of euphoria or happiness. When excessive dopamine is repeatedly released, it disrupts the regulation of the brain’s reward system and can lead to the development of an opioid addiction.

Treatments for Opioid Addiction

There are limited treatment options for opioid addiction. Beyond traditional cognitive psychotherapy, which involves a therapist working with the individual in addressing thoughts, behaviors, and emotions related to addiction, some individuals respond well to medications such as Naltrexone, Buprenorphine, and Methadone.^{5,6} Naltrexone is an opioid antagonist, completely blocking binding to the μ receptors to inhibit the continued production of dopamine and minimizing the effects of opioid receptor activation. However, this medication often causes intense withdrawal symptoms if it is taken while trace amounts

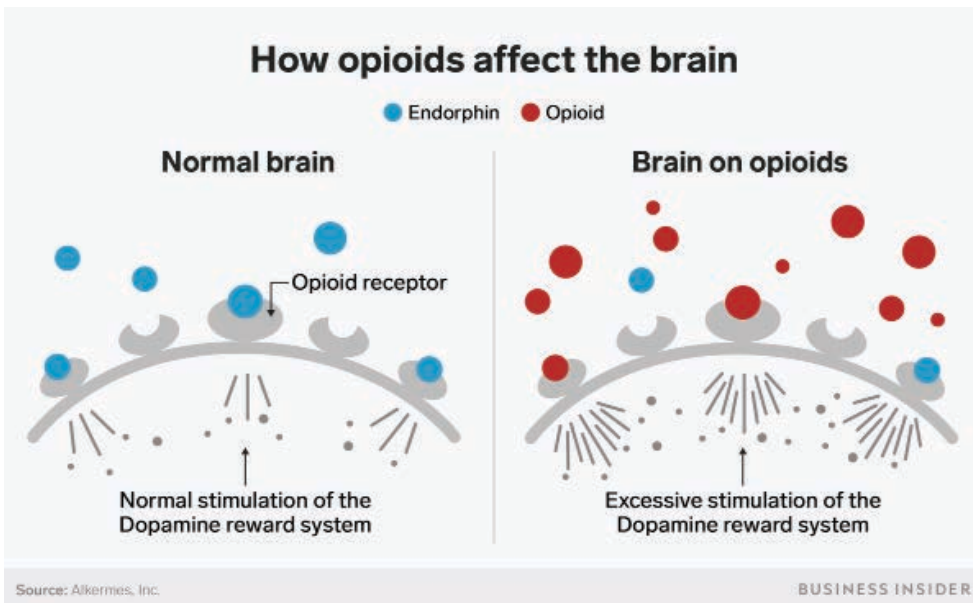


Figure #1: How Opioids Affect the Brain. (Left) Endorphins, a pain-relieving chemical naturally found in the human body, typically stimulate the release of dopamine through its attachment to opioid receptors. (Right) Opioids attach to these same receptors, but cause intense dopamine release, creating excessive activation of the reward system

of opioids are still present within the body. Thus, patients must have undergone a complete drug detox prior to taking the drug. Conversely, Buprenorphine and Methadone are μ -receptor agonists, meaning they bind to opioid receptors to constantly but minimally stimulate them. This prevents extreme withdrawal symptoms and curbs intense cravings. While Buprenorphine requires the patient undergo a partial detox, Methadone is a full agonist, so it can be taken while the patient is still depen-

dent on opioids. While generally effective, these drugs pose risks of withdrawal and relapse and yield substantial side effects. In addition, many of these treatments require long-term adherence.

Given these limitations, researchers are investigating novel and alternative addiction treatment therapies. One novel therapeutic is neuromodulation, which is the use of non-invasive brain stimulation techniques to “rewire” the parts of the brain

associated with addiction. Additionally, immunotherapy is a treatment option that involves anti-opioid vaccines to neutralize opioid molecules before reaching the brain.

Lastly, and most notably, are Epidrugs: a novel gene-based therapy that may fully treat addiction while minimizing known risks and side effects.

“Epidrugs have the potential to directly target an individual’s specific opioid response and dependency, creating opportunities for more personalized treatment options compared to existing drugs.



Figure #2: Medications for Opioid Use Disorder

The chemical mechanisms of Methadone, Buprenorphine, and Naltrexone vary, offering different effects in terms of opioid addiction treatments.

How do Epidrugs Work?

In addition to brain cells, our bodies contain other specialized cell types, such as liver, heart, and lung cells. Each cell contains genetic information called DNA which encodes our genes. Nearly every cell contains identical copies of our string-like DNA, which gets condensed and wrapped around spool-like proteins called histones. What distinguishes one cell type from another is how specific genes are turned on or off through gene regulation. One way this process is mediated is through proteins called transcription factors, which regulate gene expression in each cell by binding to DNA. Epigenetics is a specific form of gene regulation that alters how DNA and associated proteins interact. For example, chromatin, or condensed DNA, can be compressed or relaxed to allow transcription factors to better bind to DNA. Notably, epigenetic regulation can be impacted by environmental factors such as diet, psychological state, and most notably, drug use.

Some of these associated proteins that interact with DNA are writers, readers, and erasers. Epigenetic writers refer to a group of proteins that add chemical “tags” to DNA or histones. These tags condense chromatin, therefore inhibiting gene transcription, or loosen it, which promotes gene transcription. Readers then interpret and regulate these chemical tags, often controlling gene expression by blocking writers and erasers from accessing specific sites on the DNA. Finally, erasers can remove the epigenetic tags placed by writers.^{7,8} Many epigenetic regulators fall into one of these three categories, and their activity is strongly influenced by environmental factors.

An individual’s environment can profoundly influence the epigenetic state of their cells. Chronic opioid exposure, for example, changes the epigenetic landscape of neurons, causing permanent changes within the nervous system. Upon initial exposure to opioids, the resulting dopamine surge activates neurons. This activation stimulates production of epigenetic modifications that can change neuron physiology and activity. With repeated drug use, the affected neurons develop “molecular mem-

ory,” in which the constant opioid exposure hardwires the brain to remain sensitive to further drug intake. As a result, neurons become increasingly responsive to opioid use due to altered epigenetic patterns. For instance, opioids can prompt writer proteins to add activating tags to reward-system genes, reinforcing addictive mental states. Over time, these epigenetic changes can become permanent, contributing to drug cravings, relapse, and the persistence of a drug-dependent reward system.⁹

Epidrugs are medicines that regulate these epigenetic proteins. In the context of addiction, a study found that Epidrug suberoylanilide hydroxamic acid (SAHA), an inhibitor of an eraser protein called histone deacetylase (HDAC), led to heightened and longer-lasting addiction effects. When mice were administered morphine alongside SAHA, they exhibited sustained and heightened pain sensitivity, opioid tolerance, and opioid dependence for at least four weeks. The amplified addiction-like behavior demonstrated a clear

link between epigenetic modification and opioid addiction.¹⁰ This finding also suggests that the inverse may hold true—with targeted inhibitors or activators, specific epigenetic pathways could potentially be manipulated to reduce opioid dependence. Notably, HDAC function is also being investigated in other neurological disorders, such as Alzheimer’s, for its role in neuronal function.

Limitations of Epidrugs

There are thousands of genes in the human body that can undergo epigenetic modification. Thus, with many potential targets, there is much promise for epidrugs. However, epidrug solutions come with some challenges. Unintended changes to a cell’s epigenetic state can have harmful consequences, underscoring the need for precision in targeting epigenetic proteins.

Additionally, epigenetic changes can be irreversible, presenting safety concerns and making clinical testing especially

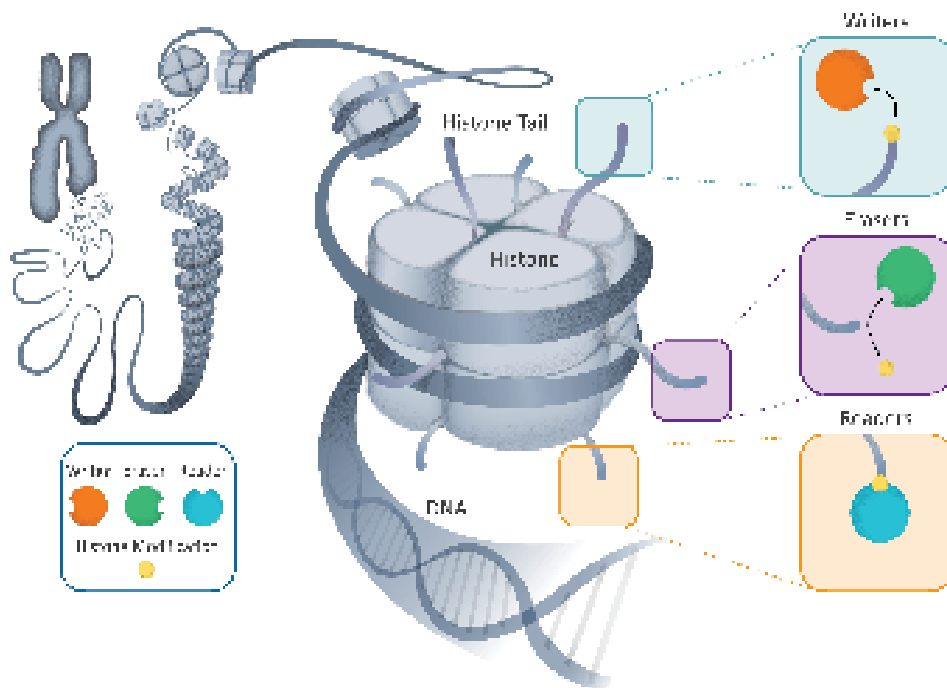


Figure #3: Writers, Erasers, and Readers

The writer attaches a histone modification to the histone tail, leading to the manipulation of the histone and chromatin orientation. The eraser removes this histone modification, while the reader interprets the histone modification.

risky. Complicating matters further, the rate and extent of opioid-induced epigenetic changes vary widely from person to person. Therefore, any effective epidrug therapy would require a highly personalized treatment plan rather than a one-size-fits-all approach.

Epidrugs demonstrate the versatility of cutting-edge therapeutics and their potential applications across many disorders. While Epidrugs are a promising addiction treatment, there are still challenges that must be addressed for them to be realized as an effective treatment against Opioid Use Disorder.

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