

Opioid Use Disorder and Treatment In Nebraska

Nebraska sits at the very bottom of a list that includes all of the states in the United States: Overdose deaths. At 8.2 overdose deaths per 100,000 persons, Nebraska is well below the national average of 21.7 overdose deaths per 100,000 persons and has the least number of overdose deaths of all states. In 2018 there were 60 opioid overdose deaths reported in Nebraska¹ compared to 888 overdose deaths reported in West Virginia in 2018². Although that statistic might be reassuring, that is still 60 too many deaths. Many of those deaths can be avoided when our patients are afforded the life-saving treatments that are currently available.

It is estimated that Nebraska has around 7,000 persons 12 and older with an opioid use disorder (OUD), which is around 0.4% of our population. However, it is also estimated that around 50,000 persons in Nebraska misused prescription pain relievers.³ Adolescents and young adults up to age 25 are the groups that have the highest number of people in these categories per capita.

Of the 4,827 physicians registered in Nebraska in September 2019 there were 170 physicians that were waivered to prescribe buprenorphine for opioid use disorder. There were also 56 advanced practice providers in the state who were able to prescribe buprenorphine for OUD. Few if any of these providers are prescribing at the limit they are allowed by the DEA. As treatment and prevention of OUD is one of the goals to curb the opioid overdose epidemic in our country and a goal of Nebraska, we definitely need more providers willing and able to treat patients with OUD.

Addiction research and state of the art guidelines that have come out of that research have provided evidence based medical management that can help address the opioid epidemic. These tools include three medications that have been approved by the U.S. Food and Drug Administration (FDA) that have been sorely underused in the healthcare sector. Most of the factors that impede their use can and must be addressed if real progress can be made. These elements include misunderstandings and stigma surrounding both substance use disorders and the medications used to treat them. Also, there are counterproductive thoughts by folks that consider addiction a failure of willpower or a moral weakness and that people with substance use disorders just lack strength and discipline. Research and facts tell us the opposite; that substance use disorders are chronic diseases of the brain that require medical treatment and can't be resolved with willpower just as someone with diabetes can control their blood sugars with willpower. These ideologies have resulted in hundreds of thousands of patients being denied access to care that is vital in recovery in the U.S., and especially in recovery from OUD.

The American Society of Addiction Medicine (ASAM) defines addiction as follows: "Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful

consequences.”⁴ The brain circuits continue to be investigated and involve reward, memory and motivation. Dysfunction in these circuits lead to characteristic biological, psychological, social and spiritual manifestations. It is important to understand that the confluence of genetic, environmental, and social factors shape a person’s vulnerability to addiction, and to the ease of recovery from the disease. They also make a person susceptible to the particular types of neurobiological changes in the brain that characterize the progression to addiction.

As noted, addiction is a chronic disease that involves compulsive or uncontrolled use of one or more substances in the face of negative consequences.⁵ The brain disease model of addiction is the bedrock upon which the understanding of OUD as a chronic disease is built. According to this model, substance use disorders (SUD) are diseases of the brain because of the effects that those substances have on brain structure and function.

Opioids target the opioid system that exists within the brain, not only in humans, but in many mammalian species. This system has developed over time to play an important role in the control of pain, stress, reward, eating, sleep, emotions, and cognition.⁶ Endorphins or endogenous opioids are the natural opioids that activate the brain’s opioid receptors to generate their critical effects on brain function and behavior. This is one of the main areas that neuroscience research has defined and outlined in natural brain function and structure. This system features component molecules that include the endogenous opioid neuropeptides beta-endorphin, the enkephalins, and dynorphin. Their brain distribution and the three classes of opioid receptors (mu, kappa, and delta) that mediate the actions of endogenous and exogenous opioids are important to understand in the explanation of the brain disease model of addiction.

It is understood that prolonged opioid use may lead to OUD by overriding the natural effect of the natural endorphins at the opioid receptors (mainly the mu-opioid receptor) which can overtake the opioid system and prevent its ability to self-regulate. The effects of opioids in the brain of a person without OUD are self-limited by numerous checks and balances. Repeated use of exogenous opioids, however, can produce powerful and sustained euphoric effects that dramatically upset this natural regulation of balance that results in tolerance, physical dependence, and addiction. The euphoric effects come not only as a result of stimulation of the opioid receptors, but also through the subsequent release of the neurotransmitter dopamine in the brain’s reward circuit, also known as the meso-cortical-limbic system. That involves the ventral tegmental area, the nucleus accumbens, the amygdala and the prefrontal cortex. With repeated opioid use, the dopamine response becomes more sensitized or magnified after repeated exposures. It is believed that this in part is what contributes to active craving (a cognitive experience focused on the desire to use a substance and is often highly related to expectancies for the desired effect of the substance).⁷

Over time, the use of opioids also blunts the influence of the prefrontal cortex, or area where the striatocortical circuits exist that are tied to executive function. Brain imaging studies from people addicted to drugs show physical changes in these areas of the brain that are critical for judgment, decision-making, learning, memory, and behavior control. This leads to the poor decision making that seems to exist in persons that continue to use substances despite

significant negative consequences. This combination of an increased drive for reward and craving coupled with the loss of inhibitory control can lead to a person with opioid use disorder to act impulsively, and with seeming selfishness, to pursue instant gratification by consuming opioids.

In addition to the changes noted above, alterations in brain function during chronic opioid use lead to negative emotions and the ability to feel pleasure that arise during periods when intoxication with opioids does not exist, such as when a person runs out of opioids or tries to stop using opioids. This involves disruption of circuits in the extended amygdala that regulate emotions and stress. These negative emotions and anhedonia are so uncomfortable, leading to a person being vulnerable to dysphoria or depression, anxiety, and irritability, that patients will seek out opioids to relieve these difficult feelings. It is thought that at this point there is a change from impulsive drug seeking to feel pleasure to a state of compulsive drug seeking to avoid withdrawal and suffering. A particular component of the brain opioid system known as the dynorphin-kappa system has been widely implicated in this persistent and stubborn negative affective state that is thought to drive continued drug use, craving and relapse. To make things even more difficult, it is thought that these changes can persist for 1-2 years, well beyond the time of symptoms of acute withdrawal have abated. This makes long term recovery even more difficult and is one of the reasons why continued treatment of opioid use disorder long past the acute withdrawal phase is thought to be necessary.⁸

Taken together, the diagnosis of opioid use disorder involves craving, loss of control and consequences and can be viewed as follows:

Craving	Loss of Control	Consequences
Craving	Larger quantities used over a longer period of time	Failure to fulfill major role obligations
Tolerance	Unsuccessful attempts to cut back or control use	Social or interpersonal problems related to substance use
Withdrawal	Increased time spent buying or using substance or recovering from effects of using substance	Activities given up due to substance use
		Use in hazardous situations
		Medical and psychological consequences

2-3 symptoms = mild, 4-5 symptoms = moderate, >6 = severe

The significant changes in brain function and structure outlined above highlights the need to bring treatment, including medication-based treatment for opioid use disorder, into the mainstream of medicine. Opioid use disorder is a life-threatening condition. In addition to the overdose deaths due to overstimulation of the mu-opioid receptors in the brainstem, other causes of death associated with OUD include infectious diseases, trauma, and suicide. In fact,

OUD is associated with a 20-fold greater risk of early death.⁹ Within the mainstream of medicine exists medication-based treatment of OUD (also known as medication assisted treatment or MAT) which has a wealth of evidence that has been amassed outlining the effectiveness of these medications. Treatment using agonist medication is estimated to reduce mortality by up to 50 percent among people with OUD. In addition to the lower death rates, treatment with medications for OUD is associated with lower rates of other opioid use, improved social functioning, decreased injection drug use, reduced HIV transmission risk behaviors, reduced risk of hepatitis C virus infection, reduced criminality, and better quality of life compared to patients with OUD not in treatment. Subjectively, patients taking medications for OUD have reduction in opioid withdrawal symptoms and reduction in opioid craving.

Methadone, buprenorphine, and extended-release naltrexone are the three medications currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of OUD. These medications work by targeting the mu-opioid receptor within the endogenous opioid system, although each has a distinctive mechanism of action.

Methadone is a synthetic, long-acting opioid agonist that fully activates the mu-opioid receptors in the brain. As it occupies the receptors it lessens the painful symptoms, including anhedonia and anxiety associated with opioid withdrawal. At therapeutic doses (greater than 60 mg per day) it blocks the euphoric high of short acting licit and illicit opioids. Methadone can be started at any point during opioid treatment because it is a full agonist and will not put a patient in precipitated withdrawal. However, it does require days to weeks to achieve a therapeutic dose to decrease cravings and prevent return to opioid use. By law in the U.S., outpatient methadone treatment can only be administered to people enrolled in state- and federally-certified opioid treatment programs (OTPs), historically called methadone clinics. Most patients are required to visit an OTP in person to receive their daily dose. Opioid overdose death is a risk in the first two weeks of treatment but the risk is significantly reduced beyond that two week period compared to folks with OUD who are not receiving treatment. Overdose risk is higher with patients taking other sedatives such as benzodiazepines, but the FDA has advised that “methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system” because overdose risk is even higher for people who are not on medication for OUD.¹¹ Nebraska has 3 OTP's, 2 in Omaha (BAART Clinic and the Omaha Treatment Center) and one in Lincoln (Lincoln Treatment Center). These clinics do have patients that drive hours to get methadone treatment for OUD, but the requirement for daily dosing and distance does limit who in the state can benefit from this treatment.

Buprenorphine is a high-affinity partial opioid agonist as well as an antagonist of the kappa-opioid receptor and an agonist of the opioid like-1 receptor. Like methadone, buprenorphine can bring relief to a patient in opioid withdrawal and reduce the rewarding effects of short acting opioids. Because it is a partial agonist, buprenorphine has less of an effect on respiratory depression and as such has a lower risk of overdose than methadone or other opioids. Finally, unlike methadone, a therapeutic effect can be achieved in days and it can be prescribed outside of an OTP by a provider who undergoes additional training and becomes waivered from the DEA to prescribe buprenorphine to treat OUD. The most prominent risk of buprenorphine to

patients with OUD is precipitated withdrawal if taken when opioids are still in the patient's system. The risk of opioid overdose death declines immediately when patients start taking buprenorphine.

The most widely available forms of buprenorphine in the United States are combined with naloxone in a 4:1 ratio in the form of sublingual tablets or films (Trade names include Suboxone, Zubsolv and Bunavail. Generics do exist for tablets and film). Naloxone is added for the sole purpose of decreasing diversion as the naloxone is not absorbed sublingually but will put a patient in precipitated withdrawal if injected. Buprenorphine is also available as a monthly extended release subcutaneous injection (Sublocade) and in an implantable formulation (Probuphine). The buprenorphine mono product (Subutex) is usually reserved for pregnant patients due to the unknown effects of naloxone on the fetus, although studies exist showing similar efficacy and outcomes between both formulations in pregnant patients. Although methadone is still considered the gold standard for pregnant patients, numerous studies exist that demonstrate less severe neonatal opioid withdrawal syndrome with mothers who are taking buprenorphine versus methadone for OUD.¹²

Extended-release naltrexone is not an opioid but rather is a full antagonist at the mu-opioid receptor and completely blocks the euphoric and analgesic effects of all opioids. If the euphoric effect cannot be felt by a person with OUD who uses an opioid after an injection of naltrexone, the thought is that the patient is much less likely to use opioids again in the future. Although an oral pill form of the medication that is given daily is available, evidence shows that the outcomes with that formulation are no different than placebo. Extended-release naltrexone is complicated by its mechanism and long duration of action. Because naltrexone can trigger severe withdrawal symptoms, initiation typically requires 4-7 days without the use of opioids. As this is one of the most difficult times for patients with opioid use disorder due to the severity of withdrawal symptoms that are experienced in this length of time, many are unable to make it through the withdrawal that is required to initiate the medication. After the first injection, however, outcomes are similar to patients that are prescribed buprenorphine for OUD. Thus, only the extended-release depot injection is approved for OUD by the FDA. Any provider can prescribe extended-release naltrexone and no special training is required. Treatment can be limited by the expense of this medication and may require prior authorization and discussions with insurance companies to accommodate payment. Depression is a relatively rare adverse effect of naltrexone and not a contraindication to its use.

Buprenorphine-naloxone and naltrexone are the only medications that can be prescribed in a physician's office, and buprenorphine-naloxone can only be prescribed by a provider (physician, physician assistant or nurse practitioner) who has received special training, submitted an intent to treat form to SAMHSA and given an "X" license or waiver to prescribe buprenorphine-naloxone for opioid use disorder.

So, with all the evidence showing the effectiveness of these medications in reducing morbidity and mortality, the increase in treatment retention, and improved well-being for folks with OUD, what keeps patients from receiving this life saving treatment? Studies show that less than 35%

of adults with OUD had received treatment for OUD in the past year.¹³ Also, there is no good data to help us see the number of those patients who had received one of the three U.S. FDA approved medications. Finally, evidence shows that there is a delay in the range of 4-7 years from the onset of OUD to when a patient receives treatment.¹⁴ Some of the barriers that prevent broader access to life-saving medications include stigma, inadequate professional education and training, delivery system fragmentation, regulatory and legal barriers, barriers to insurance payment, and adequate reimbursement for high-value evidence-based care for OUD.

Despite all the efforts by the medical field, the press, and education of the public about the disease model of addiction, high levels of stigma still exist toward persons with OUD and toward medications to treat OUD. This stigma exists in both the general public, but also among professionals in key segments that commonly are engaged with people with OUD. Stigma exists “when elements of labeling, stereotyping, separation, status loss and discrimination occur together in a power situation that allows them.” People are stigmatized when “the fact that they are labeled, set apart and linked to undesirable characteristics leads them to experience status loss and discrimination.”¹⁵ In a 2016 national survey, more than three-quarters of respondents reported viewing people with OUD as to blame for their substance use, and also characterized people with OUD as lacking self-discipline.¹⁶

Stigmatizing attitudes among health professionals have been shown to be widespread. This can have detrimental effects for connecting patients with OUD to treatment. These attitudes have been shown to be similar to the stigmatizing attitudes seen in the general public. This stigma leads professionals to treat patients differently than patients with mental illness or other medical conditions. Professionals who see patients with OUD as having a weak will or poor character are more likely to see those patients as people who need to be punished rather than as sick patients who need to be made well. This stigma extends to the medications used to treat OUD as well, with the prevailing idea being that the medications are just substituting one drug for another. As noted above, the use of drugs in a person with opioid use disorder destroys lives and medications for treatment of opioid use disorder builds and saves lives. Continued education about the brain disease model of addiction along with time and experience treating patients with OUD leads to more positive perceptions about the role of medications in effective treatment. There has also been a push to look at language as stigmatizing. Terms such as “substance abuser” have been shown to increase stigma relative to person centered terms such as “person with substance use disorder.” The word “abuse” has many negative connotations, such as child abuse, spouse abuse, physical abuse, and sexual abuse. These later terms are used when a person is the victim which is not true of a substance user. Subsequently, substance “use or misuse” are terms that are preferred to “substance abuse” and have less of a negative connotation. The key to reducing stigma and improving treatment access for patients with OUD is education and training. Many avenues exist for providers already in practice to receive the training to gain the knowledge and skills to treat patients with OUD. These include the PCSSNow.org website¹⁷ with access to local mentors through this resource, the Opioid Response Network (ORN)¹⁸ which also gives providers access to local mentors, and local in-person training opportunities. Nebraska has a web-based educational opportunity for all providers in practice called “Pain and Substance Use Disorder ECHO (Extension for Community

Healthcare Outcomes). These are all free resources and provide opportunities to receive free CME credits.

In summary, I would say that treating patients who have OUD with buprenorphine-naloxone is one of the most valued skills I have as an addiction medicine physician. To watch patients move through the stages of suffering from opioid withdrawal to almost total relief of that suffering in a matter of an hour after buprenorphine induction is great. It does take effort to understand some of the neurobiology and pharmacology, as well as to prepare an office to treat patients with OUD. These preparations include finding the persons in an office that are willing to take a lead on developing policy and procedures, making forms that can be used as agreements between the patients and providers in this venture, and making connections with therapists who are comfortable and willing to provide psychosocial support to clients with OUD receiving medication based treatment for OUD. There will never be enough addiction medicine physicians to treat all the patients in Nebraska with opioid use disorder. This is where primary care providers step in to do what they do best...care for the people in their community no matter the problem.

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