Fact Sheet:
Understanding How Treatment Medications for Opioid Use Disorder Work

Overview:

- The Role of Medication Treatment for OUD
- What are Neurons?
- Understanding the Brain's "Lock and Key" Communication System
- What is Tolerance?
- What is Physical Dependence?
- What is Withdrawal?
- What is an Agonist, Partial Agonist, and Antagonist?
- Why Medications are an Important Part of Treatment

The Role of Medication Treatment for OUD

Consider the following aspects of medication treatment for opioid use disorders (OUD):

1. There are different ways that medications for OUD can be effective for a person. In some cases, taking the medication results in rapid positive changes in a person's life, such that they no longer use opioids and return to work or school and reconnect with friends and family.
2. In other cases, the road to positive change is longer, with more twists and turns. Some people start medication treatment, but the changes in their opioid use, thoughts, behaviors and overall functioning happens at a slower pace. It is more common that people occasionally use illicit opioids even after they start medication treatment. This is simply the nature of chronic conditions and the changes in a person's brain that occur with opioid use disorders.
3. Reduction in opioid use or other substance use is not the only marker of positive change. For some individuals, positive change starts first in safer use practices. Perhaps someone is continuing to use opioids, but they are using less or making attempts to avoid injecting. Sometimes the positive changes start in the person's mind, in that they notice changes in their desire to use or reactions to use, but these changes aren't observed by others. Positive change may be a person's ability to go up to 3 days without using opioids, when before the medication treatment they used every day.
4. Medication treatment for opioid use disorders does not necessarily treat or have an effect on the use of other substances. Some individuals continue to struggle with other

substance use, such as cocaine or alcohol, while on medication treatment. This is not a reason to stop medication treatment of opioid use disorder.

5. For some, the purpose of the medications can be a tool for harm reduction. A person will never get the opportunity to see positive change if they die from an unintentional overdose. Someone who uses heroin with buprenorphine in their system has a significantly less risk of overdose and death. Having access to buprenorphine means a person can stop withdrawal symptoms and have less episodes of opioid use overall. Taking medication treatment also means they have access to treatment providers who can help them, compared to those with no connection to treatment.

What are Neurons?

Understanding how medication works starts with understanding how cells in the brain work.

- Neurons are the cells of the brain
- We have over 100 billion neurons
- Neurons are how the brain communicates to the body
- Neurons communicate to each other by sending and receiving Chemical Messengers called Neurotransmitters
- Neurons are involved in every sensation, behavior, and experience we have
- When someone uses opioids and experiences either pleasure/euphoria or withdrawal symptoms it is because of how neurons are reacting and communicating in the brain.

Understanding the Brain's "Lock and Key" Communication System

- Consider two people who are trying to communicate. In order to actually communicate something, people use a combination of facial expressions, words, and hand gestures.

- Neurons also communicate with each other. Instead of using words or hand gestures they use neurotransmitters (which are like chemical messages) that tell other neurons what to do, such as switching on certain physical changes or sensations in the brain and body.
- One of the best ways to understand how neurotransmitters work is to think of a "lock and key" system. The "lock and key" system will also help you understand how substances affect the brain.

- The key represents a message being sent from one neuron, and the lock represents a message being received by a second neuron. The keys, can be neurotransmitters from the brain, but they can also be substances put into the body, such as opioids. In other words, opioids get into the brain and act like Keys, that open certain Locks in the brain.

The lock part of a neuron is also called a Receptor - this is the location of the neuron that "receives messages". These messages can be neurotransmitters from other neurons or substances (like opioids) put in the body.

Every receptor has a dedicated job in the brain and body. When a receptor is switched on it leads to certain sensations and changes in the brain and the body.

Our brains have special receptors that attract opioids, called **opioid receptors**. We actually have 4 different types of opioid receptors, each one with a different job. This is why opioids can have different kinds of mental and physical effects.

- **For Example:** activating one type of opioid receptor allows for pain relief, anxiety reduction, a calming sensation, and euphoria. However, because the opioid also attaches to other types of receptors in other parts of the brain, it also turns down your brain's alert system which causes drowsiness, slower heart rate, slower breathing, and lower blood pressure.[1]

Substances such as opioids have an effect on our brain cells (neurons) in two ways:

1. The substance itself can attach to receptors (locks) and switch on sensations and changes.
2. The substance can also increase or decrease the brain's own neurotransmitters, which can lead to certain sensations and changes.

- **For example:** While opioids directly attach to opioid receptors in our brain, they also affect other neurotransmitters in the brain, such as **dopamine**. Dopamine is responsible for communicating to other parts of the brain saying "Hey! That felt good; do this again."[3]

Dopamine helps the brain remember the positive aspects of using a substance. Dopamine is then able to influence motivation, desire, and decision making to use again in the future. It is responsible for the strong desire or wanting to use opioids in the future.[3]

Tolerance, Physical Dependence, and Withdrawal

The following will help you understand how opioids change the brain.

<u>What is Tolerance?</u>

- Tolerance happens when a person stops experiencing the desired, positive effects of using the opioid. In order to feel the desired level of pleasure/euphoria, the person has to start taking larger doses of the opioid.

- **For example:** A person uses the same amount of heroin for a few weeks, but as time goes on, their typical dose doesn't produce the amount of pleasure/euphoria that it did the first few weeks - I starts to feel like it's a weaker dose. This is tolerance

What's Happening in the Brain with Tolerance?[1,2]

- We are not meant to be constantly switching on the opioid receptors in the brain, which is what happens with chronic opioid use.
- To create balance in the brain, the brain starts to change in response high amounts of opioids in the brain.
- The brain does this by changing how the opioid receptors (Locks) actually work. The brain weakens the opioid's ability to switch on sensations and changes. In other words, the brain starts to "ignore" the fact that the opioid is present. It's like electricity going out in a house. You can switch a light on, but nothing happens. This is what starts to happen in the brain cells when a person develops Tolerance to opioids.
- The opioid receptor (lock) still has the ability to be switched on, but to do so a person needs a larger dose of opioids in order to switch on sensations and changes in the brain and body.
- The brain can keep developing Tolerance to the new and larger amounts of opioids, which is why people start to seek stronger opioids over time.

What is Physical Dependence?

- Physical dependence is the brain making changes in response to the constant presence of opioids. The brain starts to change so that it functions **normally** when the opioid is in a person's system and starts to function **abnormally** if the opioid is taken away.
  - Changes due to physical dependence are what lead to withdrawal symptoms when opioids are not in the brain.

What's Happening in the Brain with Physical Dependence?[1,2]

- Remember, when opioids are in the brain, they are not just switching on opioids receptors associated with pleasure, they are switching on all the opioid receptors. When opioids are in the brain, they cause the slowing down of many systems in the brain and body.
- The brain knows that it's not good to be constantly suppressing certain brain functions that are causing drowsiness, slowed respiration, and low blood pressure.
- So, the brain makes changes. It starts to balance this out by becoming more active and sending stronger messages to counteract the slowing down effects of the opioids.
- Someone who has had prolonged use of opioids, will start to feel less sedated and drowsy, because the brain has adjusted and changed because of the constant presence

of the opioid. However, when the opioid is removed, those changes in the brain don't go back to normal right away. Taking away the opioid causes abnormal functioning in the brain, which leads to withdrawal symptoms.

- The brain is sending stronger messages to activate certain systems and brain functions, to counteract the opioids, in order to keep blood pressure, breathing, alertness at normal levels. However, when a person suddenly stops using opioids, the brain continues to
  activate certain brain functions TOO much - causing the person to experience symptoms of withdrawal such as jitters, anxiety, muscles cramps, and diarrhea.

What is Withdrawal?[4]

Symptoms of Opioid Withdrawal

1. Low, flat mood
2. Nausea or vomiting
3. Muscle aches
4. Tearing from the eyes or a runny nose
5. Big pupils (black center of eye), goose bumps, or sweating
6. Diarrhea
7. Yawning
8. Fever
9. Inability to fall asleep or sleep
10. Anxiety, jitters

Subjective Opioid Withdrawal Scale (SOWS):

- The Subjective Opioid Withdrawal Scale helps you assess the severity of your withdrawal symptoms. This can be used when you start medication treatment to see how your withdrawal symptoms change.
- https://www.asam.org/docs/default-source/education-docs/sows_8-282017.pdf?sfvrsn=f30540c2_2

Information about Withdrawal Symptoms:[4]

- While withdrawal symptoms can be extremely uncomfortable, they are not **directly** lifethreatening, whereas withdrawal from benzodiazepines and alcohol can directly cause death.
- However, opioid withdrawal can be **indirectly** life threatening. Due to how uncomfortable withdrawal feels some people are at risk of using more opioids to make

the extreme discomfort go away, which can increase risk of overdose and overdose death. Some individuals describe the physical and mental pain as so excruciating they experience thoughts of suicide.

The length of withdrawal symptoms depends on many factors:

- How long a person has used opioids
- How the opioid is used (needles vs. pills vs smoking)
- How strong the opioid is
- The kind of opioid (heroin vs. oxycontin)

People usually experience withdrawal symptoms beginning six to twelve hours after the last dose of the opioid and can last up to 2-4 days after.

People with **long term use** of very strong opioids report withdrawal symptoms persisting even longer, lasting weeks to months after they stop using the substances. Cravings and the experience of *wanting* opioids often persist for weeks, months, and even years.

What is an Agonist, Partial Agonist, and Antagonist?

Now let's connect the Lock and Key Communication system and the understanding of tolerance, physical dependence, and withdrawal to help you understand how medications for Opioid Use Disorder work.

Medication treatments work as Keys in the brain. There three types of "Keys" that can have an effect on opioid receptors (Locks) in the brain.

Type of Key:

1. **Agonist**
    1. This type of key fits perfectly in the receptor (lock) and opens the lock fully, which means it completely switches on whatever sensation or effect the receptor site it is responsible for. The medication treatment methadone is an agonist, but switches on the receptor very slowly vs. heroin which switches it on very fast. Methadone switches on the opioid receptor so that a person stops going into withdrawal but does not experience the euphoria/pleasure that opioids like heroin cause.
2. **Partial agonist**
    1. This type of key only partially fits in the receptor (lock) and only opens the lock part way, which means it only switches on some of the sensation or effect the receptor site it is responsible for. The medication treatment buprenorphine is a partial agonist. Buprenorphine switches on a part of the opioid receptor so that a

person stops going into withdrawal but does not experience the euphoria/pleasure that opioids like heroin cause.

3. **Antagonist**
    1. Have you ever put a key in a lock, and noticed it fit perfectly, but didn't open the lock? This is exactly what an Antagonist does. This type of key blocks a lock and does not open it. It stops anything from opening the lock and switching on that receptor sites' sensations or effects. The medication treatment naltrexone is an antagonist. It can reduce some cravings for opioids but doesn't stop withdrawal symptoms because it doesn't switch on any part of the opioid receptor. It stops other opioids such as heroin from having an effect.

Summary: Why Medications are an Important Part of Treatment

While the desire to use opioids is often initially motivated by the desire to re-experience the pleasurable or positive effects of opioids (such as pleasure/euphoria or pain or anxiety relief), over time, the need to use becomes less about feeling pleasure and euphoria and more about just feeling "normal" and preventing withdrawal symptoms. This is due to how opioids change the functioning of the brain and body and lead to Tolerance, Physical Dependence, and Withdrawal.

This is why medications like buprenorphine and methadone are helpful because they address the changes that happen in the brain due to long term opioid use. These medications stop a person from going into withdrawal, without giving the strong, euphoric feelings making these mediations less likely to be overused.

References:

1. Beveridge, T. J., Hanlon, C. A., & Roberts, D. C. (2019). The anatomy of addiction. In S. C. Miller, D. A., Fiellin, R. N., Rosenthal, & R. Saitz (Eds.), *The ASAM principles of addiction medicine (6th ed.)* (pp.48-57). Philadelphia, PA; Lippincott Williams & Wilkins.
2. Kan, D., Zweben, J., Stine, S. M., Kosten, T. R., McCance-Katz, E. F. & McCarthy, J. J. (2019). Pharmacological and psychosocial treatment for opioid use disorder. In S. C. Miller, D. A., Fiellin, R. N., Rosenthal, & R. Saitz (Eds.), *The ASAM principles of addiction medicine (6th ed.)* (pp. 805822). Philadelphia, PA; Lippincott Williams & Wilkins.
3. Berridge, K. C., & Robinson, T. E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *The American psychologist*, *71*(8), 670-679.)

4. Tetrault, J. M. & O'Connor, P. G. (2019). Management of opioid intoxication and withdrawal. In S. C. Miller, D. A., Fiellin, R. N., Rosenthal, & R. Saitz (Eds.), The ASAM principles of addiction medicine (6th ed.) (pp.741-753). Philadelphia, PA; Lippincott Williams & Wilkins.

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