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The science of addiction

Furthering our understanding of addiction and exploring treatment possibilities can help us better care for patients with substance use disorders.

By Kathryn Murphy, DNSc, NP

Addiction encompasses any substance or activity that results in a cycle of tolerance and dependence. According to the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), over 20 million Americans have a substance use disorder, which exacts more than $700 billion annually in healthcare, lost work productivity, and crime-related costs. And these numbers are on the rise. The total number of drug-related ED visits increased 81% from 2004 to 2009, according to the latest statistics from the SAMHSA.

Today's opioid crisis has brought substance use disorders to the forefront in our communities. According to the CDC, 42,249 Americans died as a result of opioids in 2016; deaths related to opioid overdose were five times higher in 2016 than in 1999. With these alarming rates of drug addiction, it's important to be aware of treatment modalities based on an understanding of brain science.

A complex pathophysiology

Addiction is a disease that affects the complex interactions between biological and environmental factors. Recent evidence suggests that addiction is less identified by physical dependence and withdrawal, and more as a compulsive repetition of an activity despite life-damaging consequences. The behavior reinforces the pleasurable feeling derived from the substance and causes a loss of control in limiting its use. With this way of looking at addiction, many practitioners are now focusing on other types of addictive behaviors, such as eating, shopping, technology use, sex, and gambling, that may involve the same brain chemistry and respond to similar treatment modalities.

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In the brain, the amygdala and hippocampus are part of the limbic system, which is closely linked to the prefrontal cortex. The amygdala helps identify if an experience is pleasurable or aversive, the hippocampus records the memories of the experience, and the frontal region of the cerebral cortex processes and coordinates all of the information. This interaction helps an individual decide on a

Diagram of addiction cycle neurocircuitry

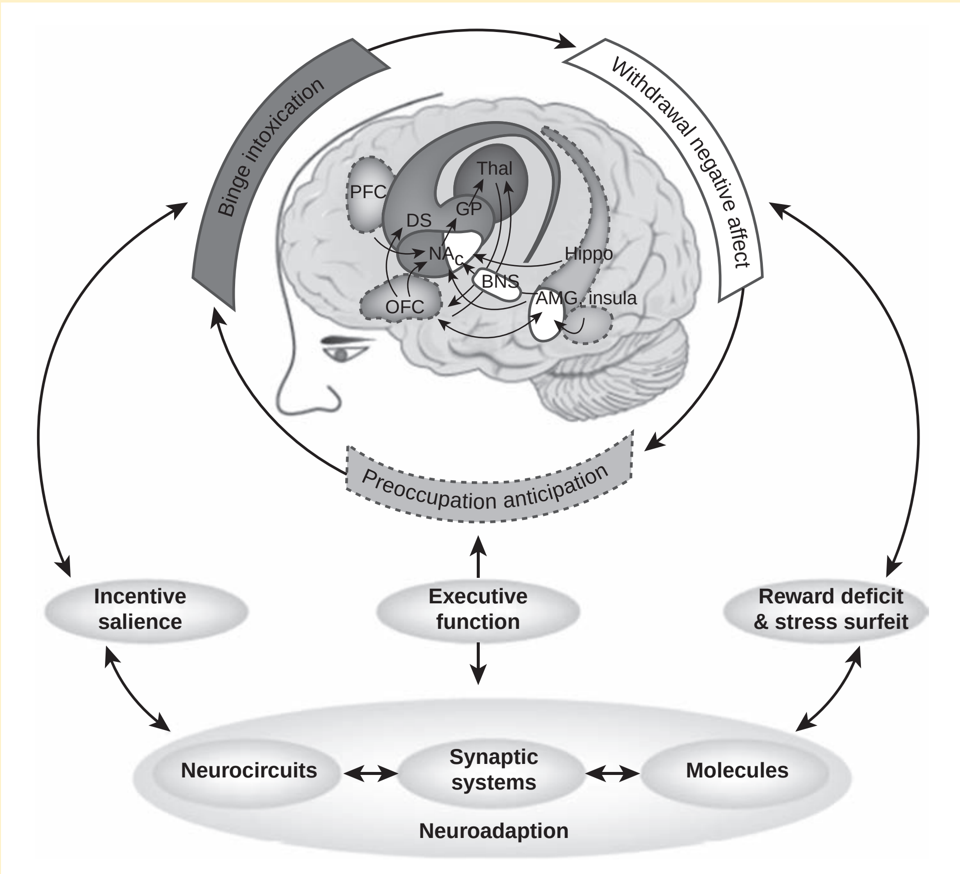

Diagram showing the neurocircuitry of the addiction cycle divided into three stages: binge/intoxication (dark gray); withdrawal/negative affect (white); and preoccupation/anticipation (light gray). The neurocircuits involved are also color-coded, with the basal ganglia, including the nucleus accumbens (NAc), dorsal striatum (DS), globus pallidum (GP), and thalamus (Thal) as key elements of the binge/intoxication stage; the extended amygdala, including the central nucleus of the amygdala (AMG), bed nucleus of the stria terminals (BNST), and a transition area in the shell of the nucleus accumbens (NAc) as key elements of the withdrawal/negative affect stage; and the frontal cortex and allocortex, including the prefrontal cortex (PFC), orbitofrontal cortex (OFC), hippocampus (Hippo), and insula (Insula) as key elements of the preoccupation/anticipation stage. Molecular, synaptic, and neurocircuitry neuroadaptations combine to render the four key elements of the transition to addiction: increased incentive salience, decreased reward, increased stress, and decreased executive function.

Source: Sadock BJ, Sadock VA, Ruiz P. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017.

response; the more rewarding an activity, the more likely the person will remember and repeat it.

When the neural circuits in the limbic system are stimulated, the neurotransmitter dopamine is released, leading to feelings of pleasure. Recent research is examining how dopamine also increases memory and attention, especially during significantly alarming events. This allows the brain to learn which activities will cause the highest rise in dopamine levels, thus increasing pleasurable feelings. In other words, the brain isn't only becoming addicted to the increased levels of dopamine and associated feelings of pleasure, but it's also learning how to become more efficient in becoming addicted.

Addictive behavior can alter brain chemistry in a distinctive way by sending dopamine levels beyond the normal range. In fact, the American Society of Addiction Medicine defines addiction as primarily a chronic disease of the neural circuits involved in reward, motivation, and memory (see *Diagram of addiction cycle neurocircuitry*). Imaging studies reveal both neurochemical and functional changes in the brains of people with substance use disorders.

A large and fast increase in dopamine is associated with reinforcing the substance's effects; dopamine levels in the brain markedly decrease after the substance has cleared. This drop may cause the person to seek the substance that increased dopamine levels. Studies have revealed a pattern of generalized prefrontal cortex dysfunction in substance-addicted people. Because the prefrontal cortex is involved in reinforcing learning, motivation, craving, and self-control, dysfunction in this area of the brain can result in more substance abuse, worsening prefrontal cortex performance, and an increased risk of relapse, thus playing a vital role in the addiction cycle.

Chronic addiction is also thought to dysregulate the neurotransmitter glutamate, increasing its activity in several receptors. Glutamate is an excitatory neurotransmitter responsible for the smooth transmission of signals between cells. It's also involved in the consolidation of memory and learning in the brain. When there's too much glutamate, the signals between cells are dysfunctional and anxiety can result.

Together, the fluctuations of dopamine and glutamate alter synaptic plasticity in the frontal cortex and increase reactivity to substance-associated cues, such as socializing with others who still use the substance. This can make a person in treatment for addiction overly responsive to environmental factors, thus increasing the risk of relapse. In addition, changes in the structure and function of the neurons involved in the pleasure response occur with chronic substance abuse. These changes can remain for weeks to years after last using the substance.

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Current therapies

Transcranial magnetic stimulation (TMS), neurofeedback (NFB), and medication-assisted treatment are current therapies focused on the brain alterations that occur in addiction. The use of acupuncture remains controversial (see *Acudetox: Yea or nay?*).

TMS

TMS is a noninvasive procedure performed in an outpatient setting such as a mental health provider's office. By stimulating the nerve cells in the brain with magnetic impulses conducted through an electromagnetic coil, it may treat symptoms of addiction.

During TMS, the provider applies alternating magnetic fields to the patient's prefrontal cortex. The magnetic pulses directly affect the prefrontal cortex about 5 cm into the brain, similar to magnetic resonance imaging. Changing the frequency and pattern of the electromagnetic pulses can increase neuron firing.

In one form of TMS, the pulses are given intermittently. It's thought that this form of stimulation may travel to the midbrain, overriding the neural circuit that's involved in substance-seeking impulses. In the second form of TMS, continuous stimulation is applied, inhibiting any communication between the cortex and midbrain, which can help decrease the patient's responses to addiction triggers.

This treatment doesn't require anesthesia or major restrictions, and there are no long-term adverse reactions. Minor adverse reactions may occur on the day of treatment, including mild headache from muscle tension on the scalp. In addition to the electromagnetic force, TMS is loud, producing an audible clinking sound that may annoy patients. The pulses can also cause the scalp muscle directly under the coil to contract, causing pain in some patients. Although infrequent, seizures may be a concern, so seizure precautions should be initiated.

Research is focusing on defining parameters for the use of TMS in addiction, such as how many pulses to deliver, at what frequency, for how long, and to what part of the brain. Each patient needs different parameters based on his or her physical composition and the substance being abused.

Acudetox: Yea or nay?

Acupuncture is the practice of inserting very thin needles into specific areas of the body to treat different diseases. The belief is that all bodily functions are controlled by a system of meridians, with a total of 365 designated acupuncture sites located on these meridians. By inserting the needles into select points, the balance of the system is corrected, thus improving the ailment.

For substance use disorders, the National Acupuncture Detoxification Association recommends a protocol called acudetox. In this form of acupuncture, the practitioner inserts five sterilized needles just under the skin at designated points on the outer ear for 30 to 45 minutes. Acudetox is thought to work by increasing the release of the body's endorphins, or natural pain relievers, which may assist the patient to not crave the substance.

However, opinions about the effectiveness of acudetox are varied and research is mixed. Therefore, acudetox shouldn't be used as a stand-alone treatment.

NFB

Addictive behavior creates neural connections in the brain. For example, if using opioids calms a person, then he or she will continue to use that coping mechanism to calm down. Over time, pathways (or "ruts") develop in the brain, leading the person to take the well-worn pathway to calmness. And the more the well-worn pathway is used, the stronger and deeper it becomes. Forming new coping mechanisms requires the "rut" in the brain to be uprooted. But changing these habits and urges becomes extremely difficult because the "ruts" have become the new normal state of the brain.

NFB is a method of monitoring the body's physiologic processes to affect psychological changes. It retrains the brain by teaching it how to be calm, focused, and relaxed. NFB can be utilized to treat the anxiety and cravings associated with addiction.

In NFB, electroencephalogram sensors that record the brain's activity to a computer are attached to the patient's head to help determine which areas of the brain indicate neural under- or overarousal and transmission. For example, a patient with anxiety aims to lower the frequency of the brain wave to elicit a calm response. A patient who's experiencing depression after stopping the use of a substance aims to increase the frequency of the brain wave to increase arousal. Overall, NFB teaches the brain to self-regulate rather than using a substance to do it.

The Bio Acoustical Utilization Device (BAUD) is an FDA-approved handheld biofeedback device that's a specialized treatment for addiction, as well as attention-deficit hyperactivity disorder, posttraumatic stress disorder, and chronic pain syndromes. The BAUD utilizes sound frequencies to disrupt the pattern of the brain in response to the particular problem. The patient using the BAUD is able to target specific issues and change the brain's response. Through stimulation of brain waves, the BAUD is thought to disrupt the reconsolidation of dysfunctional neural circuitry, usually in the limbic system.

Via the BAUD earphones, the patient listens to the sound frequencies that are common to certain brain activity. The BAUD technology utilizes a different sound frequency for each ear, from 39 to 362 Hz. The patient has control of the volume and timing of the sound in each ear. Using acoustic stimulation, the brain's neural function can be shifted back to normal, enhancing its neuroplasticity in a rapid and targeted way. Brain imaging research has confirmed the BAUD's effects on neuroplasticity.

Minor adverse reactions include headaches, temporary dizziness, and nausea in some patients.

Medication-assisted treatment

Medications currently approved by the FDA for use in addiction include buprenorphine, naltrexone, and disulfiram. Baclofen, a muscle relaxant usually used to prevent muscle spasms in patients with spinal cord injuries, is also being used as an addiction treatment.

Buprenorphine is thought to stabilize brain chemistry by reducing the euphoric effects of opioids and relieving physiologic cravings. It also blocks the effects of opioids up to a certain dose, making it hard to get high or overdose. The FDA recently approved a once-monthly I.M. dose of buprenorphine for opioid addiction, making it more difficult to be misused. Before buprenorphine can be started, the patient must go through a partial detoxification, from 12 hours to 2 days.

Naltrexone acts by blocking the effect of opioids, and to a smaller degree alcohol, making it harder to get high or overdose. It also seems to modulate the limbic system, which may decrease the desire to abuse the substance. Naltrexone can be given orally, but is usually given monthly via the I.M. route. Before naltrexone can be started, the patient must go through a full detoxification, from 3 to 10 days.

Disulfiram is an older medication used to treat alcohol addiction. It acts by

on the web

MedlinePlus:
https://medlineplus.gov/magazine/issues/spring07/articles/spring07pg14-17.html

National Center on Addiction and Substance Abuse:
www.centeronaddiction.org/what-addiction/addiction-disease

National Institute on Drug Abuse:
www.drugabuse.gov/related-topics/addiction-science

The University of Texas at Austin College of Pharmacy Addiction Science Research and Education Center:
http://sites.utexas.edu/asrec

On the horizon

In the future, the influence of genetics, and specifically epigenetics, is being explored to discover new strategies for treating addiction. Genetics involves the functional units of DNA that make up the human genome, which can be critical in the expression of diseases, such as sickle cell disease and cystic fibrosis. Epigenetics concerns changes in the regulation of gene activity and expression that aren't dependent on DNA sequencing. Epigenetic systems enable the development of different cell types in reactions to the environment; for example, when a person uses heroin, it may mark the DNA, increasing the power of the addiction in the brain. Future addiction therapy may be geared specifically to a particular patient's genetic and epigenetic composition, which will hopefully be more successful in treating substance use disorders.

causing an acute reaction following alcohol consumption by blocking the enzyme acetaldehyde dehydrogenase. This results in a series of symptoms when taken with alcohol, including flushing, throbbing headache, nausea, vomiting, sweating, thirst, chest pain, palpitations, dyspnea, syncope, blurred vision, and confusion. The hope is that these symptoms will condition the patient not to drink alcohol. However, the patient has the choice to stop taking disulfiram. Implantable disulfiram is now available, allowing the drug to be released slowly over time. Adverse reactions to this approach include infected wounds that develop either due to a reaction to the medication or from the patient trying to remove the medication to drink alcohol.

Baclofen blocks dopamine release and is purported to interfere with the reinforcing properties of ethanol. There has been some success in using this medication to treat alcohol and cocaine abuse, but more research is needed.

With our growing understanding of the neural transmitters that are altered in the addiction process, more effective prevention and treatment methods, including new targeted pharmacologic therapies, can be developed (see *On the horizon*).

Bonus content

For more information on the opioid crisis, including prevention strategies such as naloxone administration and opioid prescribing guidelines, see "Epidemic! Opioid overdose in America" at https://journals.lww.com/nursingmadeincrediblyeasy/Fulltext/2017/03000/Epidemic__Opioid_overdose_in_America.7.aspx.

Mapping brain chemistry

Nurses are involved in the care of patients with substance use disorders in the ED, on medical-surgical floors, and in mental health clinics. It's important to understand the evolving brain science of addictive behavior and stay abreast of new treatments for addiction. Ultimately, for addiction treatment to be successful, the patient has to be motivated to change. But new treatments may give hope to patients with substance use disorders and their families. ■

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