Summer 2017

The Genetic Influences on Opiate Addiction

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Introduction

The effects of addiction and the present opioid crisis can not only be felt at the individual level of the addict but throughout all aspects of society. From the infant born addicted to heroin, to the family members begging their loved ones to make a change, to the medical personnel with the responsibility of caring for those with drug seeking or violent behavior needing their next fix, the drug problem in America is one that can no longer be ignored. The number of unintentional drug overdoses in Ohio has grown from 411 in 2000 to a staggering 3050 in 2015, currently averaging 8 deaths per day in Ohio alone (Ohio Department of Health [ODH], 2017).

It is the responsibility of medical personnel to not only be aware of the statistics and trends regarding this crisis, but to be knowledgeable and up to date on the current research regarding what makes an individual an addict. What differences exist, for example, between Jimmy and Sally following knee surgery that has Jimmy returning to the emergency department with drug seeking behavior while Sally's bottle sits half full on the shelf. While not all aspects of the pathophysiology behind the genetic influences of addiction are understood, much research is being completed searching for these answers. New models have also been developed that aid the provider in the accurate diagnosis of addiction and its associated behaviors (Belin-Rauscent, Fouyssac, Bonci, & Belin, 2016). These models will aid the provider in the recognition of the problem and the development of a treatment plan

Signs and Symptoms

- loss of ability to control or stop use
- trouble meeting personal, social, and work obligations
- legal/financial/marital problems
- drug seeking behaviors, spending long amounts of time to obtain opiates
- tolerance, requiring larger doses for desired effect
- withdrawal symptoms with reduced or discontinued use
- constipation
- respiratory depression
- nausea/vomiting
- slurred speech
- confusion, delayed responses
- itching or flushed skin
- euphoria
- continual use despite negative physical or psychological effects
- stupor, coma, death
- anxiety and depression
- alienation and loss of friends and family relationships
- borrowing of money, selling possessions

(National Institute on Drug Abuse, n.d.)

Nursing Implications

The treatment of opiate addiction is a life-long battle with frequent relapses and high morbidity and mortality rates. Due to these poor demographics, the efforts of containing the opiate crisis are focused on preventing further addiction. Medical providers must be educated on the risks and benefits of prescribing opiates. It is essential for prescribers to be up to date on the current recommendations and guidelines regarding opiate use and to only prescribe opiates to those that meet these guidelines. Being aware of the genetic predispositions of various ethnicities or recognizing the signs and symptoms of behaviors highly associated with various genetic alterations and addiction can aid the provider in decision making. A thorough physical and psychiatric exam and family history should be obtained on every patient prior to prescribing opiates to adequately assess the patient (Kolodny et al., 2015).

Education is also key as it has been noted that more than 75% of those who abuse prescription pain medications originally obtained the medication from a friend or family member (Center for Disease Control [CDC], 2011). Proper education regarding the risks associated with giving others these medications, especially to adolescents, is critical at preventing an addiction problem. Those who use prescription pain medications that were not prescribed to them are four to nine times more likely to abuse heroin (Martins et al., 2016).

Underlying Pathophysiology

Opioids work by binding to opioid receptors throughout the nervous and immune systems. Four major types of receptors have been identified and include mu (μ), kappa (κ), delta (δ) and OFQ/N receptors. These receptors are the binding sites for endogenous peptides, specifically enkephalins, dynorphins and endorphins. These regulate many of the important functions of the body including pain, stress, temperature, respiratory drive, the endocrine system, gastrointestinal motility, mood, and motivation. The most common opiates that are abused are mu agonists. Mu receptors, when stimulated, are responsible for the "high" felt with opiate use, feelings of euphoria, and a decrease in anxiety (Dixon et al., 2017).

The OPRM1, OPRD1, and OPRK1 genes fall into the opioid receptor category and code for their coordinating μ, δ, and κ receptors. Genetic variations in these receptors have been studied across various ethnicities. These studies have found links between these genetic variants and higher risks of developing addictions and dependence (Mistry, Bawor, Desai, Marsh, & Samaan, 2014).

The opioid receptor mu 1 (OPRM1) gene encodes for the μ-opioid receptor, which is the primary site of action for most of the commonly abused opioids. A polymorphism of the OPRM1 gene results in the replacement of asparagine residue with aspartic acid. This results in the 118G allele. Increased sensitivity to pain and a decreased response to opioid treatment are associated with this genetic variation. Studies of those with this variant have shown that participants with the 118G allele request higher doses of opiates for treatment of pain (Kreek et al., 2012).

Dopamine is a powerful neurotransmitter, responsible for the positive rewards seen with things such as finishing a full meal, sexual encounters, and receiving an award. The use of opiates creates a large amount of dopamine to be released into the "rewards center" of the brain, the nucleus accumbens, providing the "high" that is sought by addicts. The drug type, amount, and route of administration have an effect on the amount of dopamine that is released, up to ten times the normal amount seen with pleasurable experiences, thereby causing the user to seek higher doses and better quality substances (Harvard Medical School, 2012).

Dopamine release and dopaminergic receptor expression is thought to have an association with impulsive and novelty-seeking behavior. Genetic polymorphisms of the D2, D3, and D4 dopamine receptor genes have been targets of recent studies linked to opioid addiction. The DRD2 rs1800497 allele has been found to be higher in those with addition. The identification of this allele helps predict the success of methadone treatment for opiate addiction. Genetic polymorphisms of the DRD3 and DRD4 genes have been associated with an increase in sensation seeking and novelty seeking behaviors respectively as commonly seen in addicts (Mistry et al., 2014).

cAMP response element binding protein (CREB) and delta FBJ murine osteosarcoma viral oncogene homolog B (ΔFosB) are two transcription factors that have been gaining interest in the ongoing battle against addiction. CREB is activated in the nucleus accumbens by opiates where it acts to reduce the rewarding behavior seen with drug use. CREB increases the drive for seeking opiates through a negative feedback system. This occurs by reducing the addict's sensitivity to the rewards of the drug and enhances the negative experiences observed with the discontinuation of opiates. Target genes for CREB have been identified and are associated with the opioid peptide dynorphin. Dynorphin impairs reward by suppressing the transmission of dopamine to the nucleus accumbens. Addicts then seek larger, stronger doses of the drug to overcome the tolerance that has developed (Nestler, 2013).

In contrast to CREB, ΔFosB promotes drug use through positive reinforcement where users see an increase in sensitivity to the drug and the positive rewards of drug use. ΔFosB is encoded by the FOSB gene on human chromosome 19. The Fos family of transcription factors are activated during drug use and typically return to baseline levels within twelve hours. ΔFosB, however, is unusually stabile and accumulates during repeated drug use. (Nestler, 2013). ΔFosB heterodimerizes with Jun family proteins and translocates to the cell's nucleus where they bind to activator protein-1, causing gene expression. This expression, resulting in cellular and molecular changes, results in the emergence of the phenotypical changes observed in the addict. With short term use of opiates, the activation of ΔFosB returns to baseline quickly. With chronic use, however, the effects of ΔFosB can be detected months later, even after discontinuation of use. This is thought to account for the relapses that occur during treatment and rehabilitation (Ruffle, 2014).

Significance of Pathophysiology

It is thought that genetic influences account for 40-60% of one's vulnerability to addiction. These, combined with environmental influences including social, familial, work, and financial factors, help to determine the likelihood of addiction (National Institute on Drug Abuse, 2014). Having a strong knowledge of the genetic factors associated with an increased likelihood of addition can help the provider in decision making regarding treatment options. By identifying the genetic alterations and the effects they have on an individual, providers have the opportunity to provide individualized care targeted at those most susceptible to addiction (Levran, Yuferov, & Kreek, 2012).

Image retrieved from https://kleantreatmentcenters.com/explaining-the-genetics-of-addiction-to-your-kids/

Conclusion

Opiate addiction is a nationwide problem felt by the entire population. The State of Ohio has taken great steps towards containing the crisis. Prescribing guidelines have been established by the Governor's Cabinet Opiate Action Team (GCOAT) that address both acute and chronic pain control. Educational programs targeting the school age population have also been developed (ODH, 2017). While not all is known about the genetic influences surrounding addition, a thorough understanding of the current knowledge and literature by healthcare providers, combined with the actions of the state and educational systems, has the potential to not only better treat and rehabilitate those with an opiate addiction but to prevent addiction before it happens.

Image retrieved from https://www.cdc.gov/drugoverdose/epidemic/index.html

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