ADDICTION: RESEARCH AND IMPLICATIONS

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Abstract

The transition from drug use to addiction is not fully understood and is debated upon within the scientific community as well as the general population. Neurobiology has demonstrated the specific neural pathways that are activated and altered due to substance use. The implications of neurobiology can serve as a basis for many theoretical models. Personality and risk factors can help understand the underpinnings of addiction. In the progression from addiction as a choice to disease explained by biopsychosocial principles, a comprehensive theory of addiction can begin to emerge. It is through this theory that stigma can begin to be addressed and reduced. Stigma has been found in all facets of society, most surprisingly within medical professions. The number one cause of stigma is ignorance. Creating a comprehensive biopsychosocial theory will aid in education, awareness, and prevention of substance use disorders. In addition, the tens of thousands of deaths caused by substances each year will begin to reduce.

Introduction

Accidental drug overdose caused 47,055 deaths in 2014 alone (CDC, 2015). While not all of these overdoses were a direct cause of addiction, many of them certainly were. In 2004 the Substance Abuse and Mental Health Services Administration (SAMHSA) approximated that 22.5 million people (9.4%) in the United States suffer from substance use disorders (SUD). A comprehensive theory must be established to prevent SUD and the deaths that are associated with these disorders. Currently there are conflicts surrounding theories for addiction both within the scientific community and the general population (Piazza & Deroche-Gamonet, 2013). It is difficult to educate the general population and attenuate stigma if there is not an agreed upon theory within the scientific community. A biopsychosocial approach must be used to understand addiction as a whole. It is through this approach that an agreed upon theory will emerge and allow for proper addiction education, prevention, and awareness.

The current theories in addiction involve: choices, behavior, personality, and neurological changes. Each of the presented theories have their strengths and weaknesses, many of which do not examine the full picture. The lack of a comprehensive theory and addiction education has caused stigma to be present in all facets of society. People facing drug addiction endure stigma from family, friends, strangers, and health care professionals. It is through this stigma that many actively avoid treatment; this avoidance plays a role in the tens of thousands of deaths that occur because of addiction. Examining the various theoretical models, risk factors associated with addiction, the basis for stigma, and the neurobiological implications of addiction will help identify a proper theory for addiction.

Neurobiology of addiction

In order to develop a comprehensive theory of addiction it is necessary to first understand how drugs affect the brain. It is important to note that not all drugs affect the brain in the same manner. A lot of what we know about the brain and addiction comes from rodent models that are exposed to cocaine. Dopamine receptors in the mesocorticolimbic system have been implicated in the involvement in drug reward reinforcement (Koob, 1992). This may be due to its involvement in emotions and emotional memory. An increase in dopamine (known as the pleasure neurotransmitter) from a drug causes a pleasant or euphoric state. This emotion is then stored as a memory and thoughts of that drug are now associated with pleasure and euphoria.

This memory can be strengthened through dopamine sensitization, the increase in pleasure from the drug over a period of time (Piazza & Deroche-Gamonent, 2013). This occurrence may cause an individual to increase their drug use. The increase in dopamine release may be due to a higher production of glucocorticoids found in some individuals. Glucocorticoid hormones are released in response to stress (Ambroggi et al., 2009). Ambroggi et al. (2009) used genetically modified mice to determine the pathway of glucocorticoid hormones in response to cocaine. In this model the glucocorticoid hormone protein found to be present on dopamine receptors were responsible for the release of dopamine which caused a change in behavior.

Combining the two processes it can be said that addiction is a neurobiologically learned behavior, in a sense. Individuals who are prone to stress have a higher production of glucocorticoids. These hormones help mediate the increased release of dopamine in response to drugs. The release of dopamine can become increased and sensitized over time which may lead to a permanent change causing addiction. However, this theory is proposed using animal models where the experimental drug was cocaine.

Dopamine receptors in the mesolimbic pathway have been implicated in alcohol reinforcement as well. Weiss et al. (1993) found that dopamine was released along this pathway both in conjunction with alcohol consumption and the anticipation of alcohol. Dopaminergic receptors do not mediate all the effects associated with alcohol dependence. Opioid molecules interact with the mesolimbic pathway enhancing the reward effects of alcohol. This effect has been successfully blocked by opioid receptor antagonists in mice models leading to the development of naltrexone, a medication used as a treatment for alcohol use disorder (Gilpin and Koob, 2008).

Alcohol also affects the GABA system, in which alcohol increases the release of GABA. GABA is a neurotransmitter involved in the regulation of emotions. An increase in GABA can lead to increased feelings of reward when consuming alcohol. Overtime, this system can become overstimulated, much like the dopamine system (Gilpin and Koob, 2008). The GABA system is implicated in the three pathway psychobiological model of addiction described below (Verheul et al. 1999).

Much like glucocorticoids being released in response to stress in the presence of opioids, corticotropin-releasing factor (CRF) is a stress molecule that is dysregulated in the presence of alcohol (Gilpin and Koob, 2008). CRF is involved in the activation of anxiety-like behavior in response to stress. When an individual is going through withdrawal from alcohol is it postulated that an increased release of CRF is present. This could potentially contribute to the increase in alcohol consumption to avoid withdrawal symptoms.

Interestingly, the same reward pathways described above (dopamine, GABA, opioid) have been discovered to be involved in social behavior. The reward processing pathway has been seen to promote

or inhibit inappropriate or risky social behavior. A dysregulation of the reward systems may promote deviant behavior which puts an individual at risk for developing a disorder (Yacubian and Buchel, 2009). For example, if an individual is inherently anxious and prone to stress then they may have a naturally high level of glucocorticoids in their system. This over activation of glucocorticoids enhances the possibility that dopamine sensitization may occur in the presence of a substance. This may cause this individual to particularly vulnerable to addiction, which may help explain why only a fraction of people develop an addiction.

Identifying the similarities and differences between drug classifications in the brain can help establish a comprehensive theory necessary for addiction education and treatment. At a neurobiological level, it becomes evident that drugs actively change the neural pathways in the brain. The change in these pathways can lead to behavioral changes that may result in addiction. However, it would appear that pathways differ depending upon the drug. With that being said, little is known from human subjects about the effects of drugs on the brain. This may be due to the stigma that surrounds addiction.

Theoretical models

Addiction has long been thought of as a cognizant choice rather than a disease. While the study of addiction has flourished over the past decades, some still view addiction as a choice. Hernstein and Prelec (1991) developed a model of behavior known as "distributed choice". This has been used to describe addiction as a set of choices over a period of time. An individual doesn't develop an addiction after once use of a substance. The individual performs a series of decisions to continue using the drug over time to eventually lead to addiction. In this context, the behaviors of the individual directly cause addiction.

Heyman and Dunn (2002) hypothesized that individuals from a drug clinic would be more likely to engage in drug related behavior when the benefit appeared to be immediate (local optimum) rather than long-term benefits of not using the drug (global optimum) as compared to healthy controls. Forty-three participants (22 drug users, 21 controls) participated in a computer run distributed choice program. Participants were instructed to choose between two options presented on the screen and they were rewarded money for each decision. Results supported the hypothesis and demonstrated that drug users were more likely than healthy controls to select the option with the most immediate reward. Behavioral psychology might support this model that addiction is caused by choices and rewards. However, addiction is multifaceted and without examining all variables a model cannot be established.

A basis for a comprehensive theory was suggested by Piazza and Deroche-Gamonent (2013), drawing from both psychology and neuroscience. The core basis of their theory is a transition from recreational sporadic drug use, to intensified, sustained, escalated drug use to a loss of control of drug intake to finally, full addiction. In this theory, an individual starts to take drugs as part of another normal recreational activity, for example being offered cocaine at a social gathering (recreational sporadic drug use phase). The person starts to enjoy the effects of the drug and engages in drug taking activities more frequently and for a longer duration than previously (intensified, sustained, escalated, phase). During this phase it is theorized that dopamine receptors along the mesolimbic pathway start to become sensitized (Piazza & Deroche-Gamonent, 2013). This sensitization causes the person to feel heightened euphoria from the drug and thus starts to crave that drug. The craving essentially leads to the loss of control phase resulting in addiction.

This theory can be used as a framework in beginning to understand addiction. It is necessary to break down each phase to start to understand addiction as a whole. First, a primary question to ask is what causes recreational drug use to increase to the intensified, sustained, escalated drug use phase which eventually leads to loss of control? It has been found that approximately 15% of people who engage in recreational drug use become addicted. Why is this the case? Wiggins (1996) developed a five-factor personality model of addiction. It was hypothesized that neuroticism, extroversion, openness to experience, agreeableness and conscientiousness were personality traits that could help predict whether an individual developed an addiction. If an individual has a propensity towards one personality trait over another it may predict whether or not they develop an addiction. Using this model, Trull and Sher (1994) discovered that individuals with a substance use disorder were more likely to associate with the traits of neuroticism and openness.

Neuroticism has also been shown to increase the likelihood of developing major depressive disorder (MDD). If an individual develops MDD then they are more likely to isolate themselves from social situations which may cause them to turn to substances as a coping strategy. The use of drugs to cope could start out recreational (smoking marijuana while watching TV), and then could increase through a sensitization of dopamine and a hyperactivity of glucocorticoid receptors. The increase in use changes several brain structures and causes increase in craving which eventually leads to a loss of control and finally addiction.

Through this example, one can begin to see how one might develop a substance use disorder (SUD). In a different environment, the above hypothetical situation may have played out differently. An individual with MDD may isolate themselves from social situations but if they were to actively seek therapy, group treatment and have a social support system, then they may not have developed a SUD. This would be particularly reasonable if this hypothetical individual had a gene for addiction.

The interplay between genetics and the environment can be seen through the research done by Raz and Berger (2010). They used a rodent model and hypothesized that rodents who were socially isolated would have higher rates of drug addiction than those who were not isolated. Adult male and female rats were separated into two groups: social housing and isolated housing. The rats were acclimated to this condition for 21 days. After 21 days the rats were then forced to consume a morphine solution for 7 days. When this stage was complete, the rats were then given a choice between water and a morphine solution for the next 7 days. Raz and Berger found that rats in the isolated situation consumed a much greater amount of morphine during both the forced and choice stages. While these results are limited for a variety of reasons one could assume that without social interaction it is easier for an animal to succumb to drug addiction. Thus supporting the hypothesis that a gene for addiction is more likely expressed in a particular (i.e. isolated) environment.

With that being said, humans are more complex than rats. While Raz and Berger's (2010) rodent model might help explain some of the variables of addiction it cannot explain addiction as whole. Neurobiology might help explain how these factors translate into addiction. The three-pathway psychobiological model (Verheul et al., 1999) uses personality types to explain three different ways an individual may crave a substance they are addicted to. The first personality type refers to introverts who seek pleasure from activation of the dopaminergic and/or opioidergic pathways. An individual with this personality type may experience reward craving (i.e., the positive feelings associated with drug use).

Someone who is experiencing relief craving may have a personality type that is prone to stress and anxiety. This person would crave a substance to activate their GABAergic/glutamatergic pathways. Through this activation they may begin to feel "normal" and their anxiety/stress may dissipate, or at least that is the anticipated effect. Someone who experiences obsessive craving may have difficulty restraining their actions or is highly impulsive. This is associated with a dysregulation of serotonin which is commonly associated with mood disorders (for example, MDD as mentioned earlier.) Through this theory we can begin to see how personality as well as neurobiology plays a role in craving and addiction.

The incentive sensitization model expands upon Piazza and Deroche-Gamonet (2013) intensified, sustained, escalated drug use phase. As briefly mentioned earlier, an increase use of a substance causes an increase of dopamine release which over time leads to an increase in sensitization of these receptors. Robinson and Berridge (1993) hypothesized that the sensitization of the dopaminergic receptors increases incentive salience, or causes that substance to become more appealing and thus increases craving. An individual may spend an increased amount of time seeking a specific drug due to this increase in craving. This in turn would support the reward seeking personality described in three-pathway psychobiological model.

Berridge and Robinson (2003) explain this increased salience as a learned condition. For example, an individual becomes conditioned to have a glass of wine every night after work. If for some reason an obstacle gets in the way of this ritual, then craving may take place (Skinner & Aubin, 2010). Depending upon the personality of that individual (reward craving, relief craving, or obsessive craving; as described previously) they may not be able to engage in avoidant behavior and thus they may enter the loss of control phase of addiction where all their goal-directed activity becomes centered on obtaining and using.

Another way to explain the development of addiction through these mechanisms is by examining the learning theory of addiction. Hogarth et al. (2013) argue that an individual goes through phases of associative learning when transitioning to addiction. An individual first engages in goal-directed drug seeking, in which they seek to use a substance unless the action has overt consequences. Overtime, drug seeking becomes habitual even in the presence of negative consequences. The individual has essentially learned that engaging in substance use evokes positive responses and has lost the ability to properly identify and deal with consequences. When looking at the diagnostic criteria for substance use disorders in the DSM-V (APA, 2013), one can begin to understand why an individual would continue to use despite knowledge of psychological or medical problems.

Engaging in continued use despite the presence of clear psychological or medical problems may be attributed to attentional bias. In other words, the inability to ignore external stimuli that provoke urges to use. The inability to ignore these external stimuli have been found to occur even when it interferes with necessary goals (Hester and Luijten, 2013). A review conducted by Jester and Luijten (2013) on fMRI studies of attentional bias in people with substance use disorders have showed an increase in activation of brain regions associated with cognitive control and emotional processing. It is suggestable that a dysfunction of these areas correlates to an increase in use despite apparent consequences.

Risk Factors

Theoretical models only help explain one piece of the puzzle. As noted previously, only approximately 15% of people who use drugs become addicted. In addition to genetics and neurobiology, risk factors including education, low socioeconomic status, psychiatric history, and adverse childhood events may contribute to the development of an addiction. Exposure to one (or more) of these risk factors may help explain why only those 15% develop a drug addiction.

Gauffin et al. (2013) used the Swedish population registry to determine whether childhood socioeconomic status and school performance were correlated to drug abuse. Those people that performed poorly in school had a higher association of drug abuse than those from a low socioeconomic background. However, individuals who lived in a low socioeconomic environment during childhood were more likely to develop a drug abuse problem in adulthood compared to those from a higher socioeconomic environment. This may be correlated to the lack of opportunities available to individuals who are less educated and who have less financial means. These results may be contributed stress that may occur due to financial situations.

Childhood trauma has also been identified as a risk factor for drug addiction. Danielson et al. (2009) interviewed 1753 young adults (age range = 18 - 26) measuring for abuse (both sexual and physical), history of PTSD, history of substance abuse, and family history of substance abuse. Of these participants, 313 were categorization as having a drug abuse problem. Drug abuse was found to have a clinically significant correlation between sexual and physical abuse and PTSD. This would appear logical due to the psychological distress that occurs because of a trauma. Drug abuse may arise by behavioral disinhibition (which is common among people with PSTD) or the lack of coping strategies.

The likelihood of childhood trauma, socioeconomic factors and school performance contributing to the onset of a substance use disorder may also be increased with comorbid psychiatric disorders. Douglas et al. (2010) predicted that adverse childhood events (such as trauma, abuse, and even low socioeconomic status) would increase the risk of a substance use disorder, particularly when comorbid with a mood of anxiety disorder. Data from a previous study was used to conduct the analyses. Douglas et al. concluded that while adverse childhood events increased the likelihood of developing a substance abuse disorder; this was more likely to occur if the individual had a preexisting psychiatric disorder.

In addition to adverse childhood events, genetics may also be used in examining the vulnerability an individual may have to drug addiction. As mentioned in the three-pathway psychobiological model of addiction, an impulsive personality may be a risk factor in developing an addiction. Specific genes have been found among individuals with highly impulsive personalities. These same genes have been found among people with alcohol use disorder (Kreek et al., 2005). The presence of these genes may cause an individual to be predisposed to developing a substance use disorder. However, limited research has been done on the subject due to the stigma that surrounds addiction (Kreek et al., 2005).

Genetics may also play a role in explaining the high comorbidity rates of substance use disorders with psychiatric disorders. Kendler et al. (2003) analyzed the pattern of genetic and environmental risk factors associated with both psychiatric and substance use disorders. Data was taken from the Virginia Twin Registry and screened for DSM-IV criteria on alcohol dependence, drug abuse and dependence, conduct disorder, personality disorders, phobia, generalized anxiety disorder, and major depression. Genetic influences were statistically significant in lifetime comorbidity of psychiatric disorders and

substance use disorders. This may suggest that vulnerability to addiction is increased with the diagnosis of another psychiatric disorder.

Genetics may also play a role in social behaviors which put an individual at risk for developing an addiction. The COMT and the DAT gene play a role in dissipating dopamine after it is released. Dysregulation in the expression of either of these genes increases the risk of developing an addiction (Yacubian and Buchel, 2009). Specifically, the dysregulation of COMT has been shown to promote aggression in mice, with the dysregulation of DAT has been shown to affect social responses to situations (Yacubian and Buchel, 2009). An individual may engage in substance use to help cope with aggression or feel comfortable in social situations. If this is the case, dopamine will stay in the system for an extended period of time because the appropriate mechanisms are not available to help reuptake the neurotransmitter.

Risk factors for addiction vulnerability are vast and may be dependent upon a number of variables. It is difficult to know if a certain personality type or socioeconomic environment will increase the likelihood of developing an addiction. Risk factors for developing any disease are variable and it is important to take that into consideration when discussing addiction. For example, a person may smoke a pack of cigarettes every day for 30 years and never develop lung cancer. Likewise, an individual may use cocaine occasionally but never transition to addiction. It is difficult to determine the outcomes but it is necessary to understand the possibilities. In this way, it is easy to discern between addiction being a choice or a disease.

Stigma

The difference in opinion over whether addiction is a disease or a cognizant choice has perpetuated the stigma associated with addiction. Heyman (2013) explains drug addiction as a choice rather than a disease due to its high rates of remission as seen through individuals stopping drug use even without intervention or treatment. Those with addiction may hesitate to seek help because of this stigma and this may be one of the causes of preventable deaths (Mundy, 2012). In order to attenuate stigma, it is necessary to educate both health care professionals as well as the general public.

Mundy (2012) shows this deficit in knowledge among nurses. Mundy hypothesizes that the judgmental errors of health care practitioners comes from a lack of knowledge on the subject. Community and District Nurses Survey (Harrison, 2007) found that 92% of nurses wanted more information about addiction to improve their job function. It is believed that because of this deficit in knowledge that stigma is perpetuated. Those who suffer from drug addiction are worried about being judged and in turn do not seek medical attention when it is necessary (Mundy, 2012). This is due to a combination of internal shame from the person with drug addiction and how people in the health care field perceive these individuals.

The deficit in knowledge on addiction can cause a difference in opinion regarding the model of addiction. Russell, Davies, and Hunter (2010) found that physicians' views on addiction as a disease versus a choice varied by country. Physicians surveyed in the United States were more likely to view addiction as a disease than physicians in the United Kingdom. This in turn affects the way the physicians treat their patients and the information they relay to these patients. For example, due to the differences in opinion among health care professionals it is no wonder that the general population has such differing views as well.

The viewpoint of addiction affects the treatment these individuals receive; this is partially because health care professionals perceive patients with SUD to be difficult and unrewarding (Luoma et al., 2014). This perception leads to a poor attitude among health care professionals which perpetuates self-stigma which ultimately leads to poor attrition in treatment programs or worse, avoidance of treatment. Luoma et al., (2014) found that patients enrolled in Acceptance and Commitment Therapy (ACT) which focused on reducing self-stigma, showed lower attrition rates than patients that did not receive this intervention. It would then appear evident that public stigma leading to self-stigma hinders the ability to recover.

One way to reduce self-stigma is through social support. However, as seen with health care providers, family members also hold their own stigma towards relatives with a SUD and this may affect the way they show support or interact with this relative. Meurk, Fraser, Weier, Lucke, Carte, and Hall (2016) interviewed people who have (or had) a relative with addiction. Participants (n = 55) were given a neurobiological explanation of addiction. They were then asked whether or not this information was useful in understanding addiction. The majority of participants (92%) agreed that the repeated use of drugs changes the way in which the brain functions, however; only 50% of participants agreed that addiction is a brain disease. The overall consensus was that understanding addiction helped participants empathize with the afflicted relative, even if they did not agree on the etiology of addiction.

Future research needs to examine the ways in which to reduce stigma and how stigma is negatively associated with treatment outcomes. In 2014 the SAMSA called for more research on this subject due to the surprising dearth in literature on stigma relating to SUD. Developing a comprehensive theory for addiction can only go so far if stigma is not reduced. Understanding stigma and developing an agreed upon theory are the necessary steps to help prevent SUD and their unfortunate deaths.

Livingston et al. (2011) conducted a review to see what kinds of interventions are currently available to reduce addiction related stigma. The interventions found were given to medical students, the general public, or former or current addicts. The interventions involved: education, acceptance and commitment therapy (ACT), self-reflection, motivation interviewing, and skills training. ACT and self-reflection showed the most reduction in stigma among current or former addicts, whereas educational communication was the most beneficial for both medical students and the general public. However, this review only contained thirteen studies which support the statement by SAMSHA in which there needs to be more research on this subject. It is difficult to determine what interventions really work without having more research on the matter.

Discussion

According to the Substance Abuse and Mental Health Services Administration (SAMHSA, 2012), approximately 22.5 million people in the United States suffer from a substance use disorder. Despite this reality, stigma still exists. This may be because a unified, comprehensive theory of addiction has yet to emerge. The lack of a comprehensive theory can be attributed to the difference in opinion over addiction as a disease versus a choice. It may be believed that addiction is a choice rather than a disease due to high rates of remission, specifically without treatment (Heyman, 2013).

However, neurobiological changes have been found due to increased exposure to substances. The increased exposure to substances may be directly correlated to specific personality traits, psychiatric comorbidities, childhood traumas, socioeconomic status, and even education. Environmental and

behavioral factors can be the direct cause of several medical conditions (e.g., lung cancer due to smoking). If these medical conditions can be considered diseases, then addiction is no different.

The development of a comprehensive theory will help attenuate stigma, aid in education, and possibly even prevention. Future research should incorporate a biopsychosocial model of addiction. Researching all three aspects within one subgroup of people may have elucidated the development of addiction. Through this process it is possible to prevent the tens of thousands of deaths caused by accidental overdose each year. ■

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