Addiction: A Complex Disease Requiring a Multifaceted Treatment Approach

Executive Summary:

The field of addiction treatment is evolving. Traditionally, addiction treatment and behavioral health have relied on subjective modalities and trial and error to diagnose and treat patients while largely ignoring the organ of interest: the human brain. Groundbreaking research in molecular genetics, imaging technology, and pharmacogenomics now offer advanced tools that provide objective information to personalize addiction treatment and improve outcomes.

Background:

Addiction is a complex chronic disease that alters the brain's reward circuitry and consequently leads to compulsive drug seeking and, if left untreated, can cause major medical, economic, and social problems. The cause of addiction is difficult to identify, and its onset is a prime example of the "nature vs. nurture" paradox. External stimuli, including the rampant availability of addictive prescription, illicit, and legal substances, are often cited as the catalyst for addiction. The framework upon which addiction is treated is also rooted in the social and behavioral aspects of the disease. Clinicians utilize evidence-based therapeutic approaches such as motivational interviewing, cognitive behavioral therapy, and counseling, in conjunction with wellness tools like physical fitness, nutrition, and environmental changes in their treatment plans. However, the genetic implications of addiction are less understood and utilized in a clinical setting despite estimates indicating that genetic factors contribute between 40-60% of the population variability in addictions involving nicotine, alcohol, or drugs [2].

To understand the role of genetics on addiction, variants in genes that encode neurotransmitters and their receptors or other mis-regulated genes whose products may be present at abnormal abundances in cells must be identified. Some genetic variants are single nucleotide polymorphisms (SNPs). These single base pair mutations in the DNA alter either the proteins encoded by a specific gene or the protein structure itself on the molecular level. Genome Wide Association Studies (GWAS) help identify these SNPs by using large sample sizes that compare genomes from individuals who do not struggle with addiction to those who do. SNPs are significant targets because some located in certain genes may control the types and amounts of chemical messengers in the brain, resulting in a specific biochemical profile that differs between an addict when compared to a healthy human.

To better understand the molecular genetics of addiction, the functioning of key cellular components must be understood. Neurotransmitters are chemical substances released at the end of a neuron fiber by a nerve impulse. By diffusing across the space between nerves known as the synapse, neurotransmitters cause the transfer of the impulse to another nerve fiber, thus relaying information from neuron to neuron. Examples of neurotransmitters are serotonin (mood receptors), gamma-aminobutyric acid (GABA – inhibitory receptors), histamine (sleep/wake receptors), and dopamine (behavior learning receptors). Other important components involved in neuron signaling are the cell receptors, which are proteins located on the surface of every cell, integrated within their membrane, that bind to external molecules. When a neurotransmitter binds to its specific receptor, a signal transduction pathway is triggered, which is the conversion

of an extracellular signal (the neurotransmitter) into an intracellular signal. This signal is then amplified within the cell and instructs it to perform a certain task. Through the lens of addiction, one example of such pathway is the opioid receptor system. Opioids change the dynamics of a nerve cell by binding to its opioid receptor companion on the cell's surface. Effects of different drugs on the brain can now be recorded via different types of live brain imaging technologies.

EEG, PET, and MRI brain scans provide new insights into the biological basis of addiction by identifying patterns of activity localized within a patient's brain and enabling comparisons between brain architectures for those who do and do not struggle with addiction. In concert with addiction genetics, functional magnetic resonance images (*f*MRI) are used to measure real time brain activity by detecting changes associated with blood flow, a reporter for the metabolic requirement of oxygenation [8]. Other methods include single photon emission computed tomography (SPECT) scans, which utilize radioactive chemical tracers to detect levels of blood flow within tissue [18] that may provide even more precision. Emerging imaging technology, like magnetoencephalography (MEG) scans, measure the magnetic fields generated by neuronal activity of the brain on a millisecond basis in a non-invasive manner [15,19]. MEG scans also produce images of high resolution with great precision over short time spans and are not affected by movement artifact [19].

Advances in Addiction Research:

1. Molecular Genetics: Identified variants and SNPs in receptors, neurotransmitters, and related neuronal proteins

Drug and alcohol addiction follow a recurring cycle made up of three stages, each driven by major neurobiological circuits. The binge/intoxication stage is driven by the basal ganglia, including the ventral tegmental and nucleus accumbens brain regions, where changes in dopamine and opioid neuropeptides, small protein-like molecules that bind to the opioid receptor, like endorphins occur. The withdrawal/negative affect stage is modulated by the extended amygdala and habenula, where there is a decrease in the dopamine function of the reward system and recruitment of brain stress neurotransmitters (ex. corticotropin and dynorphin). Finally, the preoccupation/anticipation (craving) stage is controlled by the prefrontal cortex, insula, and allocortex [3]. Several GWAS' identify SNPs in genes encoding transduction and transcription factors, specialized DNA binding proteins that activate or repress the expression of genes into their encoded products [14], that map onto these three circuits. Such correlations provide important information about the vulnerabilities, resilience, treatment, and recovery needed for addiction [3].

A timely example of this type of research involves the human OPRM1 gene and its SNP variants. Both GWAS and other allied studies support significant findings in the μ (mu)-opioid receptors (MOR) in the brain [1,4,5,6]. The MOR, encoded by the OPRM1 gene in the human genome, is activated by drugs that results in a dopamine release within the ventral striatum and prefrontal cortex of the brain, generating a reward effect [1]. These parts of the brain are responsible for the planning/moderating of complex behavior, decision making, and personal expression [11]. These variants, when found in genes expressing MOR, are strong candidates for affecting the risk of opioid use disorder. Another important example of employing GWAS to

study addiction involves the identification of SNP variants associated with heroin addiction in the dopamine receptors, metabotropic receptors (mGluR6 and mGluR8), nuclear receptors (NR4A2 and cryptochrome 1), and genes for the enzyme catechol-O-methyltransferase [6].

Contemporary molecular genetic approaches to addiction research advance to the precision of correlating types of addiction with specific genetic loci, with a special focus on genetic variants and SNPs in coding and regulatory regions for neurotransmitters, their receptors, and other neuronal protein coding regions. These genomic approaches, when combined with emergent imaging technology, provide customized and powerful resources to treat addictive behavior at the level of the individual.

2. Brain Scans: The neuroscience of fMRI, SPECT and MEG scans

A companion solution to genomics for identifying areas within the brain that are involved in addiction and/or risk of addictive behavior, are the real time brain imaging employing several types of scanning technologies. These include fMRI, SPECT, and in the near future, MEG.

SPECT scanning is a type of nuclear imaging test, where a safe radioactive tracer is injected into the patient. Metabolically active tissue absorbs more of the radioactive substance than less-active tissue [18], revealing blood flow within the patient's body. An example of what SPECT can reveal is that some individuals have a decrease in blood flow to the prefrontal cortex of the brain. This is possibly due to low levels of dopamine that can result in the subject having impulsive behavior [8]. Alternatively, overactivity observed in the anterior, middle, and posterior cingulate (top of the brain), is known to be caused by low levels of serotonin. This area of the brain is responsible for manifesting compulsive behavior [8]. Furthermore, overactivity in the basal ganglia of the brain, possibly due to low levels of GABA, may cause addicts to suffer from anxiety and depression [8]. These scans assist diagnosis by practitioners, and better understand what's going on for the patients and their families. Beyond their clinical uses, SPECT scans may also offer a destigmatizing effect. By displaying images of a brain of an individual who struggles with addiction compared to that of someone who does not, these scans may support a shift in societal perception to acknowledge that addiction is in fact a disease [8]. Amen Clinics (U.S.) has built the world's largest database of over 150,000 SPECT brain scans and is consistently expanding. This sample size enables repeated improvement of their quantitative algorithms for mapping the functional architecture of normal and diseased brains.

In contrast, fMRI scans are non-invasive and do not require an injection, but simply use a mechanism based on blood oxygen levels to investigate the status of brain regions [20]. These measurements of blood flow can be taken when the patient is in a resting state (RS-fMRI, occurring in the absence of a task or stimulus) in order to synchronize fluctuation images between regions of the brain that are spatially distinct [20].

While fMRI scans reflect the brain activity indirectly by measuring the oxygenation of blood flowing near active neurons, MEG scans provide direct measurements of the electrical activity obtained in active neurons [16]. Individual nerve cells have electrochemical properties that result in the flow of electrically charged ions generating magnetic fields. MEG scans have an advantage over fMRI scans because "MEG signals are able to show absolute neuronal activity

whereas the fMRI signals show relative activity, meaning that fMRI signal analysis has to be compared to reference neuronal activity…While fMRI measurements require the complete absence of the subject's movement during recording, MEG does not, so patients (such as children) can move their heads within the MEG helmet. Most importantly, MEG provides temporal characteristics about brain activation with sub-millisecond precision and more accurate spatial localization of neural activities" [16]. There are a few places in the world that use MEG scanning, including the University of Washington's I-Labs MEG (Magnetoencephalography) Brain Imaging Center.

One innovative avenue in the form of imaging that has a great potential to impact addiction and behavioral diagnosis and treatment, involves the restoration of neuronal networking employing personalized forms of repetitive Transcranial Magnetic Stimulation (PrTMS). PrTMS restores the neuronal synchrony in many neurocognitive and behavioral disorders, including addiction [18]. This advanced iteration, combined with electroencephalogram (EEG) scanning technology, is able to precisely modulate the Hz dose and the location in the brain during Transcranial Magnetic Stimulation (TMS) treatment.

These methods of identifying brain regions related to addiction are safe, reliable, and of a personalized nature such that treatment and rehabilitation can be customized to the individual. Neuroscience as a field is still young, and much information about the brain needs yet to be discovered, but with the combined use of multiple brain scans such as, SPECT, fMRI, and MEG scans, rapid advances in acquiring new knowledge may be within reach.

3. Pharmacology: The effects of methadone, buprenorphine, and naltrexone

Genetic and imaging research generate tools to help identify the root causes of addiction but are not treatments. Cognitive behavioral therapy and counseling have long been the standard therapeutic approaches for addiction treatment. Now, results from pharmacology research provide the foundation for the development of medicines to treat addictive behavior in addition to these treatment methods. For example, methadone is a synthetic opioid agonist that mitigates withdrawal symptoms and relieves those cravings by binding to the same opioid receptors in the brain that heroin and other opioids activate [12]. Methadone binds and activates these opioid receptors at a slower pace than heroin and other opioids so that a euphoric effect is not produced. This method of treatment has been used for more than 40 years and is only accessible for addictive patients in opioid treatment programs with doses customized to each individual.

Approved by the FDA in 2002, Buprenorphine is a partial opioid agonist that carries out the same task as methadone but activates the opioid receptors less strongly and more safely. Buprenorphine works similarly to methadone, but has the less constrained FDA approval, eliminating the need to visit specialized treatment facilities. Alternatively, naltrexone is an opioid antagonist, which blocks the activation of opioid receptors. Instead of controlling withdrawal and cravings, it prevents any opioid drug from producing euphoric effects. Some evidence to date suggests that naltrexone in the form of once a month injection, is effective in suppressing addictive behavior [12]. Although these medications significantly reduce clinical risks and physical discomfort during an individual's phase of detoxification, there is still a possibility of relapse and they do not provide a cure for the disease.

Conclusion:

Addiction is a multifaceted disorder that is confounded by nature vs. nurture components. Many variables play a role in the disease, including environmental, social, and genetical aspects. The barrier that stands between the researchers and a cure is the complex combinatorial contributions, such as epigenetics (the interaction of the genotype (x) environment etc.), that further complicate the diagnosis and treatment of addiction disorders. Compounding the problem, curing addiction involves treatment on an individual basis, and every single person has a different story and genetic makeup.

A solution to an effective and reliable treatment of addiction may involve a single treatment course or a combination of approaches. GWAS and related molecular genetic approaches have identified variants and SNPs in genes for receptors, neurotransmitters, and other neuronal-specific proteins that may correlate with addictive behavior or a high risk for it. Pharmacogenetics provide usefulness of interfering with the dangerous activity of addictive molecules in the form of medications that target the opioid receptors in the brain. Lastly, imaging technology of SPECT, fMRI, and MEG brain imaging can provide highly precise spatial information about the activity within the brain and help provide more accurate diagnoses. With this in mind, treatment therapy in the future can target with precision, and monitor progress over time in patients.

The ways in which clinical advancements impact addiction treatment is constantly evolving and comes with significant challenges, especially in terms of 3rd party reimbursement and adoption by clinicians accustomed to treating patients in a certain way. However, all of medicine is moving increasingly toward personalized, results-driven outcomes, and addiction treatment needs to embrace these technologies if it wants to provide 21st Century care. With a vision towards the future, American Addiction Centers (AAC) and the world industry of addiction research are expanding and seeking novel approaches. These highly sophisticated and effective treatments of combining genetic data with pharmacogenomics, and imaging, may possess the potential to cure the complex and multi-dimensional disease of addiction.

American Addiction Centers on Addiction Research:

According to the National Institute on Drug Abuse, 40-60% of patients with substance use disorders experience relapse after a first attempt of recovery [10]. Longitudinal outcomes studies conducted by Centerstone Research Institute on patients from AAC found that 63% of their patients remained sober two years after discharge from treatment [21].

A priority of any treatment facility is to a provide safe, holistic, and personalized treatment. At AAC's Addiction Labs, patients receive genetic testing that provides valuable information about how they respond to medications, and how their unique genetic profile may influence their susceptibility to addiction and behavioral health issues. These reports also include the risk management of medications, their potential adverse effects, and recommendations for dosing adjustments based on the patient's unique genetic makeup. This expedites treatment, mitigates guesswork with medications, helps prevent adverse drug reactions, and speeds up recovery.

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