Bench to Bedside: From the Science to the Practice of Addiction Medicine

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Abstract The current understanding of addiction is based on a biopsychosocial model of illness. From a neurobiological perspective, addiction can be seen as the hijacking of the pleasure-reward pathways of the brain with a concomitant weakening of its executive function. The fundamental model has been expanded to include newer concepts such as multiple levels of severity of illness, motivational circuitry, and anti-reward pathways. These neurobiological concepts can explain some of the successes and failures of addiction treatment in the second half of the 20th century and the beginning of the 21st century. Psychosocial interventions (primarily cognitive behavior therapy, mutual help groups, and motivational interviewing) and pharmacological treatments (such as agonists, antagonists, and partial agonists) form the basis of addiction treatment today.

Keywords Addiction · Toxicology · Alcohol dependence · Opioid dependence

Introduction

Drug addiction is a devastating chronic illness that continues to affect millions worldwide. The clinical presentations of alcohol and drug intoxication and withdrawal syndromes have

been described extensively in medical literature. Effective treatments have been successfully developed—and are used routinely—to combat the acute sequelae of substance use. However, our understanding of the larger problem of addiction as a chronic relapsing illness is currently evolving. New research findings are shedding light into the addictive process, both in terms of its neurobiological determinants and its clinical management.

The Fundamental Model of Addiction

The fundamental model of addiction coalesced around 2000 and is based on biopsychosocial principles. This model was proposed as a response to the old moralistic attitude that addiction was simply a disease of the morally weak. At the turn of this century, scientists proposed that addiction is a medical illness (not unlike diabetes, hypertension, and depression) with biological, psychological, and social underpinnings. According to this new formulation, addiction is caused by biological forces, mostly genetics; psychological forces, primarily the pursuit of pleasure, performance enhancement, and self-medication of anxiety, depression and other psychiatric conditions or “unacceptable affects” as psychoanalysts sometimes refer to them; and social forces, the microenvironments and subcultures in which we all live, love, work, and play.

When these forces come together in a particularly troublesome way, they alter the brain of a person who uses drugs. They turn the brain switch on. At that time, addiction develops a life of its own, largely independent of the forces that initially set it in motion. At this point, addiction hijacks the dopamine-fueled pleasure-reward pathways of the brain, overwhelms the inhibitory power and executive function of the frontal lobes, and the person loses control of her or his life over the drug of abuse. Neurobiologically, the drug war is a war between the hijacked pleasure-reward pathways of the brain and the frontal

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lobes. When the frontal lobes win, the patient is in recovery. When the hijacked pleasure-reward pathways win, the patient relapses.

Once the brain switch of addiction is turned on, it stays on for a long time, if not for the rest of a person's life. The astonishing persistence of the hijacked pleasure-reward pathways of the brain may be due to their anatomical relationships to neighboring structures: primarily the hippocampus (the memory center of the brain) and the limbic system (the emotional center). These hijacked pleasure-rewards pathways have a stronghold between memory and emotion, and thus dominate the addicted person for life. Although the majority of people who meet criteria for a substance use disorder are likely to beat the disease, the increased vulnerability upon return to the addictive agent (whether it is tobacco, alcohol, prescription pills, illicit drugs, or even addictive behaviors such as gambling and Internet gaming) is essentially permanent.

This is a powerful model, but with one major problem. Taken to its extreme, it proposes that the real causes of addiction are biological, psychological, and social vulnerabilities; thus, in the absence of such vulnerabilities, the risk of becoming addicted is nearly zero. Imagine an adolescent who does not have a genetic predisposition to addiction, does not suffer from depression or anxiety, and does not self-medicate any other psychological problem. Also assume that her or his close friends, the peer group, do not smoke cigarettes. Would it be wise to reassure the adolescent that, if she or he starts smoking cigarettes, the chances of becoming addicted to cigarettes would be negligible? While a biopsychosocial analysis does not demonstrate any vulnerabilities in this teen, "Go ahead, smoke as many cigarettes as you like because you don't seem to have any of the true causes of addiction" would be a terrible recommendation.

A very similar mistake was partially responsible for the liberal (and often aggressive) prescribing of opioid analgesics that resulted in the prescription opioid epidemic. Even experts falsely thought that the development of addiction would be exceedingly rare in people with (a) no family history of addiction, (b) no psychiatric illnesses, and (c) no social interactions with drug-infested environments.

Therefore, the model needed to be modified to account for the role of the drug itself as an independent cause that may lead a person into addiction directly, even in the absence of significant biological, psychological, or social forces.

The New Neurobiology of Addiction

In 2015, the fundamental model described above is still valid but with three significant amendments [1].

First, the brain switch is not strictly as dichotomous as it was once assumed to be. The transition from "non-addicted" substance use to "addicted" use is more nuanced. This new approach has led the fifth edition of the Diagnostic and

Statistical Manual of the American Psychiatric Association (DSM-5) to drop the hard distinction between abuse and dependence, in favor of a more continuous definition of substance use disorders and behavioral addictions using the severity specifiers of "mild," "moderate," and "severe" [2]. Neurobiologically, the addicted brain is qualitatively different from the non-addicted brain; clinically, however, the distinction between the two conditions is less clear.

The second addition to the fundamental model of addiction incorporates the motivational circuitry of the brain. Drugs of abuse do not simply hijack the pleasure-reward pathways of the brain, such as the nucleus accumbens, the hippocampus, and the amygdala. Addictive substances also have a significant effect on the more evolved, frontal part of the brain, especially the medial orbitofrontal cortex where they redirect the motivation of the person. For example, drugs of abuse cause the "stinking thinking" of addiction, celebrated for years by Narcotics Anonymous before neurobiology caught up with what people already knew to be true. An addicted person thinks that she or he uses the rational aspects of her or his frontal lobes, but in fact, it is the drug that controls the person's motivation and overall cognitive apparatus.

Finally, the anti-reward pathways of the brain (sometimes referred to as the dark side of addiction), as well as the reward pathways, are now equally appreciated. Drug use activates both systems, but, earlier in a person's trajectory through the addictive process, the reward system dominates. As addiction progresses, the dopaminergic reward pathways—the ones responsible for life's pleasure and salience—become less prominent, and the more complex anti-reward pathways—the ones that result in dysphoria, irritability, malaise, and the feeling of crawling out of one's own skin—become more prominent. Eventually, the anti-reward pathways prevail, and drug use becomes all about relief from the pain and discomfort of the now fully activated dark side of addiction, rather than the pursuit of excitement and reward.

How have these concepts influenced the development of addiction treatments? By design or by accident, substance use therapies often relate closely to key neurobiological mechanisms of addiction.

Psychoanalysis

The first medical attempt to treat addiction came through psychoanalysis. In the 1950s to 1960s, medicine had few interventions other than psychoanalysis to address any mental illness.

Psychoanalysis is most effective in "shrinking" the frontal lobes, the superego, and the inhibitions that people have. That is one of the two reasons psychiatrists are called "shrinks"—the other one is that psychiatrists "shrink" problems. By allowing the more primitive part of the brain to take over, people are allowed to have some fun and enjoy life.

In addiction, however, the task is exactly the opposite. Treatment must focus on strengthening the frontal parts of the brain, so that they can keep an eye out for emerging cravings and out-of-control drug-fueled drives derived from the more primitive limbic areas of the brain. Addicted patients undergoing classical psychoanalytic therapy did not show improvement, and the failure of psychoanalysis in the treatment of addiction gave rise to the myth that addiction has no treatment. This myth lingers even today as pockets of the population still believe that once a person is addicted there is nothing that can be done, the patient is doomed, and medicine has nothing to offer.

Boot Camps

Following the failure of psychoanalysis, a new approach emerged: the “boot camps” based on the California “Synanon” model of the 1960s. The idea was to fully reform the addicted individual through a psychological destruction and overhaul of the person’s brain, including her or his hijacked pleasure-reward pathways. The strategy was to essentially lock patients up in military-style installations (which, thankfully, are becoming less and less popular—at least in the USA); “slap” them around, sometimes physically; break down their defenses; confront their denial; and deliver them to the world reformed and drug-free. As expected, very few people completed those programs. For some of those who were able to endure such harsh and inhumane conditions, the treatment worked; however, for the vast majority of people who put their faith into these “boot camps” the results were doubly disastrous; they did not succeed in getting rid of their addictions *and* were psychologically scarred by the treatment.

The Psychosocial Interventions

Finally, starting in the 1980s, medicine began to incorporate evidence-based interventions, and patients started getting better. There are many safe and effective components to current addiction treatment (e.g., family therapy, treatment of co-occurring psychiatric disorders, contingency management, aftercare plans), but the three major ones are the following: cognitive behavior therapy (CBT), mutual help groups (such as Alcoholics Anonymous), and motivational interviewing (MI). Along with medications (discussed below), these are the cornerstones that have changed the face of addiction treatment and have helped millions heal.

The psychosocial interventions tend to strengthen the addicted person’s frontal lobes, giving patients practical tools to help them recognize early signs of relapse, identify triggers (the “people, places, and things” of AA, also known as “cues” in psychology research), avoid dangerous situations, and develop coping strategies that will keep them sober. MI seems to work on the motivational circuitry of the frontal lobes,

primarily helping people who have little interest in giving up substances explore, and eventually resolve, their ambivalence [3]. Such skills support the frontal lobes, and counteract the effects of the hijacked pleasure-reward pathways, tipping toward safety the balance of the ongoing “use, don’t use” war that rages in the addicted brain.

The Pharmacological Interventions

In terms of pharmacotherapy, addiction treatment has pursued two main strategies: an agonist approach and an antagonist approach.

In agonist therapies, the hijacked pleasure-reward pathways are tricked into believing that the addictive agent is being used. The same receptors that are activated by the drug of abuse are fully activated by the medication, the cravings for the drug are reduced, and that patient does not feel the urge to use. Classic examples of the agonist approach include the nicotine patch in the treatment of tobacco use disorder and methadone for opioid addiction.

In antagonist therapies, the target receptors are blocked. A classic example is naltrexone in the treatment of opioid addiction. By blocking the mu opioid receptors, addicted patients who try to get “high,” do not feel the effects of the drug, are discouraged, and stop using.

The remarkable development in psychopharmacology, over the past 10 to 20 years, has been the introduction of a third strategy: the partial agonists. Partial agonists block the receptors, so that people cannot get “high,” but at the same time partially activate the receptors, so that cravings are reduced—a combination of “shielding” (antagonist) and “feeding” (agonist) approaches. Varenicline for tobacco and buprenorphine for opioid addiction are partial agonists with impressive success records.

Back to Psychodynamics

Currently, addiction treatment research is examining exercise, mindfulness, and novel pharmacotherapies (e.g., N-acetylcysteine for the treatment of cannabis use disorder). Interestingly, the possible role of psychodynamic psychotherapy (a close relative of psychoanalysis in addiction treatment) is also being considered. For example, psychodynamics may be particularly helpful in exploring substance use as it relates to human sexuality. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data suggest that people most vulnerable to substance use are those who are attracted mostly—but not exclusively—to people of the opposite sex, and those who are attracted mostly—but not exclusively—to people of the same sex [4]. Perhaps the internal stress of living in one of those “greyer” zones of sexuality (being “almost” gay or “almost” straight) may translate into an increased risk of substance use. For some patients at least,

psychodynamic psychotherapy would probably be best for exploring such intra-psychic conflicts and reducing their substance use.

Conclusions

Twenty-first century neurobiology is opening the door to a deeper understanding of addiction. Such research findings have psychosocial and pharmacological treatment implications that emerge from the basic science of craving and control, the inability to resist, and the ability to recover.

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