No End in Sight: The Abuse of Prescription Narcotics

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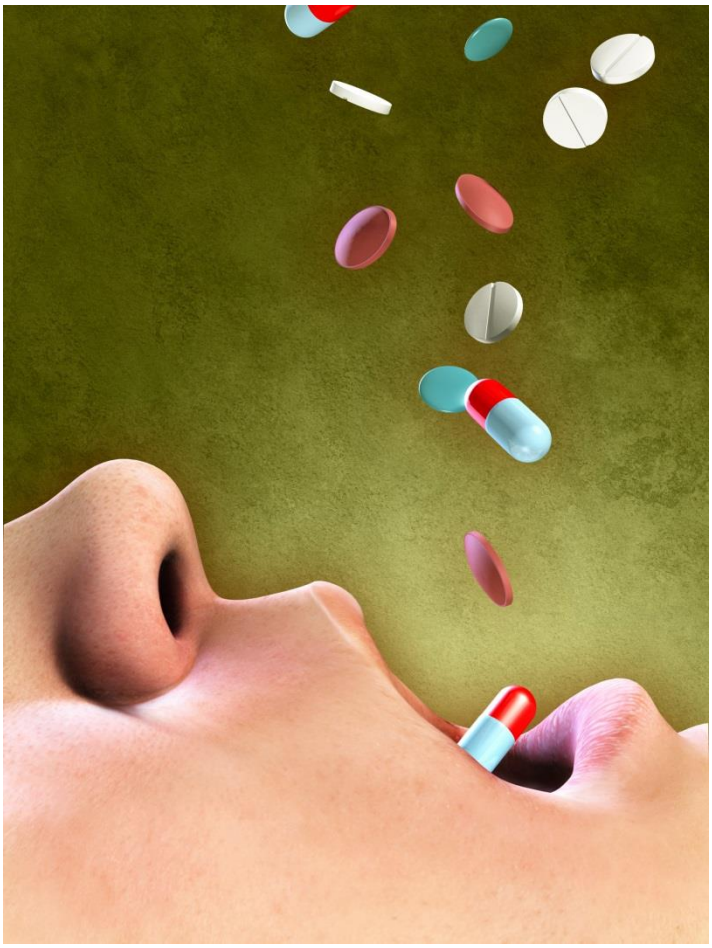

Editor's Note: From teenagers dying from heroin overdoses to crime tied to Vicodin and OxyContin addiction to road fatalities in which sedatives and muscle relaxants are involved, 20,000 deaths in the United States in 2014 were attributed to problems associated with narcotics and prescription drug use. Our author, whose research involves the neurobiological basis of drug addiction, traces the history and evolution of narcotics and leans on his clinical experience to discuss why certain drugs are powerful, addicting—and dangerous.

For centuries upon centuries, people have used opium or its components—morphine and other similar narcotics—to get "high" or feel mellow.[1,2] Opium is tied to ancient civilizations in Egypt, Persia, and China and such figures as Alexander the Great, Hippocrates, John Keats, and John Jacob Astor. Paintings portray old Chinese men relaxing and apparently deep in thought in rocking chairs, smoking pipes filled with opium, dried latex that comes from poppies grown in many regions in Asia. In countries such as Afghanistan[3] and Myanmar, opium production and exportation is the basis of their economies.

While raw opium products historically have been highly prized mood-altering drugs, one of their main active components, morphine, converts very easily, with a simple chemical step, to heroin. Users appreciate that heroin travels to the brain much more quickly and effectively than morphine. Although once in the brain heroin breaks down to morphine, heroin is the drug of choice because its high is much quicker and more intense.

In the last 200 years, opium and its derivative, heroin, has also enjoyed enormous popularity for its potent pain-relieving (analgesic) effects. The unfortunate, often unrecognized, downside of opium and heroin is that both drugs are powerfully addictive, partially because they are snorted, smoked, or injected, which produce very intense and immediate effects. Of course, our concern today is not only for opium and its derivatives, but also for the myriad of structurally related narcotic analgesics which have been developed in laboratories. Few would argue that opiate abuse is now a national crisis.

How Narcotics Work

All derivatives of the opium poppy are classified as narcotics and share common properties in the brain. All narcotics enter through the central nervous system (brain and spinal cord) to exert their effects. In the brain they bind to specific opioid "receptors" (so-called "G-protein coupled" receptors) on brain cells that use the electrochemical messenger GABA (gamma-aminobutyric acid) to communicate with one another.

There are at least three major sub-types of opioid receptors: mu, delta, and kappa. Each of these, particularly the mu receptor, have multiple sub-types (some estimates put the total number of opioid receptors at 25 to 30). Furthermore, while there is considerable overlap of receptor networks in the brain, each receptor is localized in a distinct brain region and has its own communication pathway. Why this diversity and extensive network in the brain? This is not totally known, but probably relates to the fact that "endogenous" opioids are produced by cells in the brain (as opposed to exogenous narcotic drug opioids) that regulate pleasure, pain, appetite, sexual behavior, hormonal balance, gastrointestinal activity, respiration, and other bodily functions, via effects on discrete brain areas. So, while endogenous opioids play a fundamental role in many bodily functions, narcotic drugs similarly interfere with these same systems.

Pain relief produced by opioids is facilitated primarily by mu-opioid receptors and, to a lesser extent, by delta receptors. While endogenous opioids bind to these receptors to alleviate pain, such as that arising from stress, it is primarily narcotic drugs that bind to these receptors to

relieve pain. All narcotic analgesics, arising internally or from narcotic drugs, have a high affinity for the mu-opioid receptor: the higher the affinity, the greater the response.

Narcotic analgesics work at the spinal cord level to overexcite nerve fibers so that they are poor conveyers of pain signals to the brain. These drugs also exert powerful effects in the brainstem to both transmit signals to the spinal cord to dull the transmission of pain and to lessen the conscious perception of pain.

Unfortunately, the very property of certain narcotics that makes them excellent painkillers also makes them the most rewarding and addictive drugs known to humans. Indeed, all effective opioid analgesics produce euphoria and this effect is mediated almost exclusively by mu opioid receptors, just like pain. Thus, the correlation between the potency of analgesia and euphoria is nearly perfect. This explains why it has been literally impossible to develop a narcotic drug that is useful for pain but devoid of addictive properties—despite efforts over the last one-hundred years.

The ways in which opioids produce rewarding effects is complicated, but it appears that the neurotransmitter dopamine is intrinsically involved in the rewarding properties of all drugs, especially opioids. Moreover, it has been possible to trace the reward pathway in some detail. The pathway involves perhaps a dozen or so different brain areas, several different neurotransmitters, and some stress-related factors.

It is important to note that euphoria, or rewarding pleasurable effects, are complex emotions, undoubtedly mediated by many regions in the brain. What we are trying to do is determine the molecular basis of a very elusive target; a thought or a feeling. Neuroscience has not yet reached the point where emotions can be reduced to biology.

Developing Addiction

While it is clear that many people who use opioids for pain management or to feel better handle their consumption well, others develop addictive patterns of use characterized by rapid tolerance, physical dependence, and, most importantly, craving. What happens in the brain to produce these effects? The brain adapts (develops tolerance) to the presence of high concentrations of drugs. The entire purpose of tolerance is to restore homeostasis, even in the presence of high levels of an environmental toxin, such as a drug. The downside, of course, is that more drug is required to produce the same effect, thus initiating further neuroadaptive changes. The mechanisms underlying tolerance are fairly well understood: it takes more drug to elicit a response from receptors, but the end result is that the brain is under constant assault and keeps adapting in ultimately non-productive ways to keep up with the insult produced by ever increasing drug doses.

What happens then when the brain's neuroadaptations are confronted by abrupt cessation of drug use? A withdrawal response ensues, a hyperactive reaction that is generally the opposite of the effects produced by heavy use of the narcotic: instead of drug-related constipation and elation, diarrhea and depression occur. While it was once thought that the mechanisms

underlying withdrawal were confined to hyper-excitability after the neuroadaptations were disrupted, it now appears that other brain areas that were recruited during the development of dependence are affected as well, and responses by these areas may be just as—or even more important—than the direct result of the neuroadaptive responses. One thing we know for sure is that the withdrawal response is profound and often contributes to relapse.

While obtaining relief from withdrawal probably plays an important role in addictive processes, physical dependence and drug withdrawal occur with many drugs, yet most people do not develop the craving that is associated with addiction. Craving distinguishes physical dependence from addiction. So while clearly craving must be present for a diagnosis of substance-use disorder (SUD), some other mechanism beyond physical dependence also must be involved in craving. The nature of these other mechanisms is only now being examined.

From a neurobiological perspective, the answer to why some withdrawals are worse than others is largely unknown. But we do know that the perception of the depth of withdrawal symptoms and their unpleasantness is unique to certain drugs. With opiates, the difficulty of the withdrawal response is amongst the worst.

Government Steps In

In 1914, the Harrison Narcotics Tax Act made opium and opium products illegal, unless prescribed by a physician.[6] Before that, many artists and intelligentsia used freely available opium to enhance their artistic experience, while others—such as Abraham Lincoln's wife, Mary Todd Lincoln—

famously used it to escape depression and feel better about themselves.[7] Additionally, many elixirs were sold over-the-counter or by "snake oil" salesmen at carnivals and fairs, and their use was condoned. Instead of eliminating narcotics abuse, though, the Harrison Act perpetuated an extensive black market, an underground network that still exists.

Shortly before World War II, all the way through the Reagan era, narcotics steadily gained momentum for pain relief, but abuse rates stayed relatively low.[9] When abuse occurred, heroin was mainly the drug of choice, particularly among inner-city male minorities seeking to feel better and escape their poverty and hopelessness. Despite drug wars and drug-related murders, mainstream society mostly ignored the heroin problem because the problem occurred in a marginalized segment of the population.

In the year 2000, a huge momentum shift came about when a nationally recognized non-profit health standards-setting and accrediting body, the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO),[10] released a scathing report on the undertreatment of pain. It concluded that effective narcotic analgesics were available but seldom used, and that doctors were ignoring pain management because of an irrational fear of addiction. They argued that narcotics should be more widely used, since an anecdotal report in a prestigious medical journal found that few patients abused their narcotic medications.[11] As referenced in an Institute of Medicine Committee report in 2011, the JCAHO report reasoned that pain should be the fifth vital sign, meaning that doctors should routinely ask about pain as part of any physical exam, not wait until the patient volunteers this information, and treat it accordingly. This report made headlines nationwide; *Time* magazine featured it on its cover.

The report and subsequent campaign became successful to the point that doctors began prescribing narcotics in record numbers, some probably inappropriately.[12] Inevitably, with that many new prescription drugs now in medicine cabinets and on nightstands, quantities were diverted by people who sought not pain relief but a high (or a profit on selling the drugs for such purposes). Prescription narcotic abuse quickly reached epidemic levels, fueled by drug companies that rushed to meet the new demand.

Oxycodone Arrives

New products began arriving on a fairly regular basis in the 1990s, but the most impactful of these was a novel type of product: a sustained-release drug, oxycodone, that would provide pain relief for eight to twelve hours.[13] Oxycodone is an opioid agonist with very high affinity for the mu opioid, making it an excellent pain reliever but also a powerful euphorogenic agent. The drug—marketed as OxyContin—was attractive because it needed to be taken only once or twice a day, instead of every two to four hours. The long-lasting relief was particularly beneficial for older patients who suffered from memory loss and for people with limited mobility.

The extended-release capsules work by containing copious amounts of drug that a built-in delivery device would release slowly over time. Given its slow-release properties, the Food and Drug Administration (FDA) concluded that the delay in reinforcement would dissuade abuse because addicts typically seek an immediate reward. Thus the FDA, now infamously, allowed the sponsoring company to state in the package insert or label that abuse was expected to be low.

This was an ill-informed blunder of epic proportions. What the manufacturer claimed it did not recognize, nor apparently did the FDA, was that addicts cleverly and quickly realized that they could defeat the slow-release devise by crushing pills and making large amounts of oxycodone immediately available in a form suitable for snorting or intravenous injection—an immediate rush akin to that of intravenous heroin.

The ease with which addicts could breach the slow-delivery device—with Internet "how-to" tips posted within days—makes it somewhat difficult to believe that the manufacturer and the FDA were not quickly aware of their collective blunder and did not take aggressive action to rectify a very bad design. The pharmaceutical company's lethargic response to the revised FDA mandates may explain the $635 million in fines they received for marketing strategies that failed to recognize or mention the potential for abuse.[14]

Developing Addiction

The quality of the rush or high that addicts seek, particularly after the intravenous injection of narcotics, is characterized in many ways—including, graphically, as a whole-body orgasm. This very powerful sensation is a huge part of what keeps people dependent. Why these drugs are so rewarding is elusive. What is probable is that some individuals are genetically predisposed to have a much more pleasurable response than others. Still, the precise nature of this predisposition is unknown. Several quotes from patients in our clinical research program illustrate the powerful sensation these drugs elicit and the constant yearning that ensues:[15-17]

"I found a bottle of 5mg hydrocodone tablets my dad had after knee surgery, and I took 1½ tablets. I was 18 years old and had just started smoking pot and experimenting with drugs. I went to bed, and after about an hour I felt an intense warm, fuzzy, pulsating euphoria come over my entire body. It was pure bliss and felt extremely good. I immediately always sought out opiates before any other drugs after that."

"The high or reaction to it was the first of its kind, tingly body and feeling of being in a cloud. It lasted longer than I expected. I never achieved the same feeling from them again however I continuously searched for it."

The most logical question about the surge in the abuse of prescription narcotics is why it took off in such dramatic fashion, given that narcotic analgesics and heroin had been available for years. For starters, there was a seemingly endless supply of narcotic drugs, given their widespread therapeutic use and the proliferation of "pill mills" (pain clinics that carelessly dispensed huge amounts of narcotics for profit) and disreputable "script" doctors who would write prescriptions, whether they were needed or not, for quick cash.

Second, what makes prescription narcotics acceptable in many users' minds is that they produce a good, dependable, "safe" high. Unlike heroin, the dose is known with certainty, the pill labeled clearly, and they are legal (the latter often is not true, depending on extenuating factors). To justify their use and assuage any guilt, patients also may tell themselves, "At least it's not heroin; I'm not a heroin addict."

Regarding heroin, at least, they may have a point: Heroin bought on the street is usually sold in nonsterile powder form and is rarely more than a few percent pure, and some of the powder additives (talcum powder, quinine, sugar, and sometimes other drugs, including powerful opiates such as fentanyl) that make up the rest can be very dangerous, particularly in those in whom the IV route is employed. Of course the IV route also introduces the possibility of blood borne pathogen transmission and, given the uncertainty of the purity of street-purchased heroin, there is a distinct possibility of overdose. Thus, for most narcotic drug users who administer their drugs orally, the use of heroin, at least in the beginning stages of abuse, was considered to be a degenerate, unsafe option.

However, the climate for heroin and prescription drug abuse has changed. Most new users are not impoverished minorities from inner cities, but middle-class men and women living in suburban and rural areas who find it easy to justify their use. Thus, a perfect storm has developed: legal narcotics readily available with little or no social stigma attached to their use.[18]

The Great Escape

Other than the obvious high, what purpose do these drugs serve that accounts for their popularity? It turns out that the initial potent high is not really what most users seek. Rather, narcotics relieve anxiety or depression by providing a short-lived escape from difficult circumstances. For those who become addicted, the initial high is pure bliss and something they continue to seek, often for years. But pure bliss becomes an elusive goal

and does not repair emotional dysfunction and unpleasant circumstances. More often than not, the user's life gradually disintegrates with addiction.

Several quotes from our clinical study participants are excellent representations of the utility users often find with narcotics, beyond their initial reaction:[15,16]

> *"I didn't know who I was anymore, I didn't like who I was and didn't want to be in my own skin. I would use to feel good about myself, feel comfortable, confident, beautiful. Also, just life things in general, the unknown, life is scary and using was my escape to not deal with responsibilities."*

> "*I used drugs to hide the pain of not loving/accepting myself in the beginning. Then my father passed away and I used drugs to mask the pain of grieving for many years. My life quickly spiraled out of control and I used drugs to hide how bad things really were."*

> *"It numbs pain, emotional and physical. It makes everything temporarily seem amazing, even when everything around you sucks."*

Beginning in 2010, prescription narcotic abuse began to level off[19,20] and heroin began to resurface.[21-23] The primary difference with this current surge is that it migrated from primarily an inner-city problem to the same type of users who became the norm for prescription narcotic abuse.[21-23] The reasons—as comments from our clinical research program indicate[21-23]—are surprisingly straightforward. For example:

> *"It [heroin] was most cost effective in terms of the high established over the more expensive and less effective [O]xy[C]ontin, Percocet, [V]icod[i]n, etc."*

> *"You could get more for the price. Around my area 'Southern Oregon' one [OxyContin] 80 mg (bluish green pill) goes for 70-80 bucks nowadays; used to be 50 but they are hard to find now because of changes made by the pill companies to make the [Oxy] unshootable, unsnortable and unsmokable. Heroin is always coming up from Cali … and is in high demand around here."*

In addition, and perhaps as or more important, the social stigma associated with heroin use began to dissipate:

> *"I knew I liked it [heroin] above all else, and once I had a drug dealer it became almost too easy to get, I had access to money because I am an upper middle class family and I also became close to my dealers, driving them around so I could get paid in drugs and just becoming super close, even if it meant sexually, so I could get the drug. The two dealers and the people around them that I developed that relationship with are also middle class white kids, not even kids we were all in the age range of 25-41. It just became easy, and we weren't really looked at as being addicts because everyone thinks heroin addicts are all homeless, shady looking, dirty junkies."*

What's next? Where do we go from here? It seems obvious that while we could and should do all that we can to reduce the supplies of heroin and its legal counterparts, we must also reduce the demand. The evidence shows, as outlined in part above, that narcotics satisfy—in a very harmful way—a variety of "needs" in individuals who use them. We need to find better ways to persuade users that narcotics are not the answer. There have to be, and are, better ways than entering the vicious cycle of abuse to meet those needs.

Until we make a serious effort as a society to implement those alternatives, expect to read and hear more about the devastating impact, including overdose deaths, of the continued use of legal and illegal narcotic compounds. What factors, if any, will break our centuries-old love affair with opium and other narcotics? The drug formulations may change over time, but the appetite for narcotics has persisted for a very long time, with no obvious end in sight.

Bio

Theodore J. Cicero, Ph.D., is the John P. Feighner Professor of Psychiatry at Washington University School of Medicine. After receiving his Ph.D. in 1968 from Purdue University, he joined Washington University's faculty as an assistant professor in 1970. Cicero has published more than two hundred scientific articles in the general area of substance abuse research. Much of his work has focused on neurobiological substrates of dependence and abuse of drugs (opiates and alcohol) in animal models. Over the past fifteen years, Cicero's focus has been on the epidemiology of opiate abuse, beginning with the emergence of the prescription drug problem in the 1990s and continuing with the recent transition of heroin abuse from an inner-city problem most common in poor, minority

males to an epidemic in white, middle-class male and female residents of suburban and rural locations.

Link to financial disclosure.

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