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COMMENTARY

## Beyond the opioids

### The drug epidemic of early initiation, frequent use, and a polydrug reality

**Publish date:** October 10, 2018

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# Clinical Psychiatry News<sup>®</sup>

The national opioid epidemic is one of the most important public health challenges facing the United States today. This crisis has resulted in death, disability, and increased infectious and other comorbid diseases.



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Public attention has been focused on the medical management of pain, patterns of opioid prescriptions, and use of heroin and fentanyl. But the opioid crisis is, in fact, part of a far larger drug epidemic. The foundation on which the opioid epidemic is built is recreational pharmacology – the widespread use of aggressively marketed chemicals that seductively superstimulate brain-reward producing alterations in consciousness and pleasure, often mislabeled “self-medication.”

Drugs of abuse are unique chemicals that stimulate their own taking by producing an intense reinforcement in the human brain, which tells users that they have done something monumentally good. Instead of preserving the species, this chemical stimulation of brain reward begins the process of retraining the brain and reward system to respond quickly to drugs of abuse and drug-promoting cues. Drugs of abuse do not come from one class or chemical structure, but, rather, from disparate chemical classes that have in common the stimulation of brain reward. This bad learning is accelerated to addiction when drugs of abuse are smoked, snorted, vaped, or injected, as these routes of administration produce rapidly rising and falling blood levels.

Thanks to the science of animal models, we understand drug self-administration and abstinence. However, in animals, we cannot approximate addiction beyond the mechanical because of the cultural complexity of human behavior. Most animal models are good at predicting what treatments will work for drug addiction in animals. They are less predictive when it comes to humans. Animal models are good for understanding withdrawal reversal and identifying self-administration reductions and even changes in place preference. Animal models have consistently shown that drugs of abuse raise the brain's reward threshold and cause epigenetic changes, and that many of these changes are persistent, if not permanent. In animal models, clonidine or opioid detoxification followed by naltrexone is a cure for opioid use disorder. Again, in animal models, this protocol is tied to no relapses – just a cure. We know that this is not the case for humans suffering from opioid addiction, where relapses define the disorder.

## A closer look at opioid overdoses

Opioid overdose deaths are skyrocketing in the United States. The number of deaths tied to opioid overdoses quadrupled between 1999 and 2015 (in this 15-year period, that is more than 500,000 deaths). Then, between 2015 and 2016, they further increased dramatically to more than 60,000 and in 2017 topped 72,000. This increase was driven partly by a sevenfold increase in overdose deaths involving synthetic opioids (excluding methadone): from 3,105 in 2013 to about 20,000 in 2016.

Illicitly manufactured fentanyl, a synthetic opioid 50-100 times more potent than morphine, is primarily responsible for this rapid increase. In addition, fentanyl analogs such as [acetyl fentanyl](#), [furanyl fentanyl](#), and [carfentanil](#) are being detected increasingly in overdose deaths and the illicit opioid drug supply. Drug overdose is the leading cause of accidental death in the United States, with opioids implicated in more than half of these deaths. Moreover, drug overdose is now the leading cause of death of all Americans under age 50. As if these data were not bad enough, recent analyses suggest that the number of opioid overdose deaths might be significantly undercounted. Without intervention, we would expect 235,000 opioid-related deaths (85,000 from prescription opioids and 150,000 from heroin) from 2016 to 2020; and 510,000 opioid-related deaths (170,000 from prescription opioids and 340,000 from heroin) from 2016 to 2025.<sup>1</sup> In these opioid overdose deaths, rarely is the opioid the only drug present. Data from the Florida Drug-Related Outcomes Surveillance & Tracking System show that, in that state, more than 90% of opioid overdose deaths in 2016 showed other drugs of abuse present at death, an average of 2 to 4 – but as many as 11.<sup>2</sup>

It is well-accepted that medicine – in particular the overprescribing of opioids for pain and downplaying the risks of prescription opioid use – has played a fundamental role in the exponential rise in addiction and overdose death. The prescribing of other controlled substances, especially stimulants and benzodiazepines, also is a factor in overdose deaths.

To say that the country has an opioid problem would be a simplistic understatement. It has been too easy to zero in on opioids while ignoring the ubiquity of polysubstance use by almost all individuals suffering from opioid and other substance use disorders and related drug problems, including overdose. Drug sellers are innovative, consistently adding new chemicals to the menu of available drugs. The user market keeps adding potential customers who already have trained their brains and dopamine systems to respond vigorously to drug-promoting cues and drugs. We are a nation of polydrug users without drug or brand loyalty, engaging in “recreational pharmacology.” Framing the national drug problem around opioids misses the bigger target. The future of the national drug problem is more drugs used by more drug users – not simply prescription misuse or even opioids but instead globally produced illegal synthetic drugs as is now common in Hong Kong and Southeast Asia. A focus exclusively on opioid use disorders might yield great progress in new treatment developments that are specific to opioids. But few people addicted to opioids do not also use many other drugs in other drug classes. The opioid treatments (for example, buprenorphine, methadone, naltrexone) are irrelevant to these other addictive and problem-generating drugs.

Finally, as a very recent report found, the national opioid epidemic has had profound second- and third-hand effects on those with opioid use disorders, their families, and communities, costing about \$80 billion yearly in lost productivity, treatment (including emergency, medical, psychiatric, and addiction-specific care), and criminal justice involvement.<sup>1</sup> Worse yet, missing from current discussion is the simple fact that drug users in the United States spend \$100 billion on drugs each year. The entire annual cost of all treatment – both public and private – for alcohol and other substance use disorders is \$34 billion a year. Drug users could pay for all of the treatment in the country with one-third of the money they now spend on drugs.

How much do drug users themselves spend on addiction treatment? Close to zero. The costs of both treatment and prevention are almost all carried by nondrug users. While many drug policy discussions call for “more treatment,” as important as that objective is, overlooked is the fact that 95% of people with substance use disorders do not think they have a drug problem and do not want treatment. What actions are needed now?

### Control drug supply

Illicit drug supply used to be centrally controlled and reasonably well understood by law enforcement. Today, the illegal supply of addicting chemicals is global, innovative, massive, and decentralized. More drugs, including opioids, are now manufactured and delivered to users in higher potency, at lower prices, and with greater convenience than ever before. At the same time, illegal drug suppliers are moving away from agriculturally produced drugs such as marijuana, cocaine, and heroin to purely synthetic drugs such as synthetic cannabis, methamphetamine, and fentanyl. These synthetics do not require growing fields that are difficult to conceal, nor do they require farmers, or complex, clandestine, and vulnerable modes of transportation.

Instead, these new drugs can be synthesized in small and mobile laboratories located in any part of the globe and delivered anonymously, often by mail, to the users' addresses. In addition, there remains ample illegal access to the older addicting agricultural chemicals and access to the many addicting legal chemicals that are widely used in the practice of medicine (for example, prescription drugs, including opioids). These abundant and varied sources make addicting drugs widely available to millions of Americans. Strong supply reduction efforts are needed. We must use the Drug Enforcement Administration to increase the cost of doing business in the illegal drug supply chain, and decrease access to drugs by bolstering interdiction and reducing precursor access. We can work to screen packages for drugs sent by U.S. mail or other express services.

It is gratifying to see so many of the missing pieces identified in the classic report<sup>3</sup> published in 2012 by Columbia University in New York. Health care providers and professionals-in-training are being taught addiction medicine principles and practices. The Surgeon General has helped mobilize the public response to this crisis, and rightly suggested<sup>4</sup> that everyone learn how to use and carry naloxone. Researchers are refocused on more than supply reduction.<sup>5</sup> In addition, the Substance Abuse and Mental Health Services Administration and the National Institute on Drug Abuse (NIDA) are working on delivery service improvements, developing nonopioid pain medications, and new treatments for addiction.

#### Increase access to naloxone

Increasing access to the opioid reversal medication is critical. Because of the surge in opioid overdose-related mortality, considerable resources have been devoted to emergency response and the widespread dissemination of the mu-opioid receptor antagonist naloxone.<sup>6</sup>

Naloxone should be readily available without prescription and at a price that makes access practical for emergency technicians and any concerned citizen. Administering naloxone should be analogous to CPR or cardioversion. They are similar, in that they are life-saving actions, but the target within the patient is the brain, rather than the heart. CPR education and cardioversion training efforts and access have been promoted well across the United States and can be done for naloxone.

Another comparison has been made between naloxone and giving an EpiPen to an allergic person in an anaphylaxis emergency or crisis. We need and want to rescue, resuscitate, and revive the overdosed patient and give the person another chance to make a change. We want to

administer naloxone and get the patient evaluated and into long-term treatment. Now, rapid return to drug use is common after overdose reversal. We need to use overdose reversal as a path to treatment and see that it is sustained to long-term abstinence from drug use. The most recent report on the high cost of drug use correctly points out that none of the current treatment and policy proposals can reduce substantially the number of overdose deaths.<sup>1</sup> Among 11 interventions analyzed by those researchers, making naloxone more available resulted in the greatest number of addiction deaths prevented.

The PHP system of care management demonstrates that individuals with substance use disorders can refrain from any substance use for extended periods of time with a carrot and stick approach; permitting a physician to earn a livelihood as a physician is the carrot. In medication-assisted treatment (MAT), the carrot is provided by agonist drugs and the comfort-fit they provide in the brain. They protect the patient from anxiety, and reduce stress and craving responsivity. The stick is an environment that is intolerant of continued nonmedical or addicting drug use. This can be the family, an employer, the criminal justice system, or others in a position to insist on abstinence.

PHP care management shows the way to improve all treatment outcomes; however, an even larger lesson can be learned from the millions of Americans now in recovery from addiction to opioids and other drugs. The “evidence” of what recovery is and how it is achieved and sustained is available to everyone who knows or comes into contact with people in recovery. How did that near-miraculous transformation happen? Even more importantly, how is it sustained when relapse is so common in addiction? The millions of Americans in recovery are the inspiration for a new generation of improved addiction treatment.

Addiction reprioritizes the brain toward continued drug use first, rather than family, friends, health, job, or another important remnant of the addicted person’s past having any meaningful standing. It is often a question like that raised by the AA axiom that it is easy to change a cucumber (naive or new drug user) into a pickle (an addict), but turning a pickle into a cucumber is very difficult. Risk-benefit research has shown that drugs change the ability to accurately assess risks and benefits by prioritizing drug use over virtually everything else, including the interests of the drug users themselves.

Along with judgment deficits comes dishonesty – a hallmark of addiction. The person with addictions lies, minimizes, and denies drug use, thus keeping the addictive run going. That often is the heart of addiction. The point is that once the disease is in control of the addicted brain, those around that hijacked brain must intervene – and the goal of cutting down drug use or limiting it to exclude one or another drug is not useful. Rather, it perpetuates the addiction. Freedom from addiction, that modern chemical slavery, requires no use of alcohol and other drugs, including marijuana, and a return to healthy relationships, sleep, eating, exercise, etc.

Recovery is more than abstinence from all drug use; it includes character development and citizenship. The data supporting the essential goal of recovery are found in the people who are in recovery not in today's scientific research, which generally is off-target on recovery. Just because recovering people are anonymous does not mean that they do not exist. They prove that recovery happens all the time. They show what recovery is, and how it is achieved and maintained. Current arguments over which MAT is the best in a 3-month study is too short-term for a lifetime disorder and it ignores the concept of recovery despite the millions of people who are living it. Their stories are the bedrock of our message.

Our core evidence, our inspiration, comes from asking the people in recovery from the deadly, chronic disease of addiction three questions: 1) What was your life like when using drugs? 2) What happened to get you to stop using drugs? and 3) What is your life like when not using any drugs?" Every American who knows someone in recovery can do this research for themselves. We have been doing that research for decades.

People in recovery all have sobriety dates. Few in MAT have sobriety dates. Recovery from addiction is not just not taking Vicodin but living the life of a drug-free, recovering person. How do they hold onto recovery, and prevent and deal with relapses and slips? MAT is a major achievement in addiction treatment, including agonist maintenance with buprenorphine and methadone, but it needs to build in the goal of sustained recovery and strong recovery support. That means building into MAT the 12-step fellowships and related recovery support, as is done every day by James H. Berry, DO, of the Chestnut Ridge Center at West Virginia University's Comprehensive Opioid Addiction Treatment, or COAT, program.<sup>15</sup>

MAT is good. It needs to be targeted on recovery, which can include continued use of the medicines now widely used: methadone, buprenorphine, and naltrexone. But recovery cannot include continued nonmedical drug use, and it also must include character development – with honesty replacing the dishonesty that is at the heart of addiction.

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Holding up that widely available picture of recovery and making it clear to our readers is our goal in this article. For too many people, including some of our most treasured colleagues in addiction treatment, this message is new and radical. The PHP model has put it together in a program that is now more than 4 decades old. It is real, possible, and understandable. The key to its success is the commitment to living drug free, the active and sustained testing for any use of alcohol or other drugs linked to prompt intervention to any relapse, the use of recovery support, and the long duration of active care management: 5 years. That package is seldom seen in the current approach to addiction treatment, which often is siloed out of mainstream medicine – with little or no monitoring or support after the typically short duration of treatment.

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People with addictions in recovery remain vulnerable to relapse for life, but the disease now is being managed successfully by millions of people. As dishonesty and self-centeredness were the heart of behaviors during active addiction, so honesty and caring for others are at the heart of life in recovery. This is an easily seen spiritual transformation that gives hope and guidance to addiction treatment, and inspiration to us in our work in treatment – and to all people with addictions.

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