Fentanyl as Sentinel: The Deadly Threat of Illegal Synthetic and Counterfeit Drugs

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Introduction

Over the past decade, the United States has witnessed an enormous number of drug overdose deaths. Researchers and commentators attributed the problem initially to the misuse of prescription painkillers, then to reliance on heroin as a substitute analgesic, and finally to the use of illegally manufactured fentanyl. It would be a mistake, however, to attribute today’s problem to the use of any specific drug at any particular time. The best way to understand the current drug epidemic is to realize that, at the heart of this massive public health threat, is commercialized recreational pharmacology—the widespread use of chemicals that super-stimulate brain reward for purposes of pleasure. These chemicals produce intense brain reward that over time can lead to addiction. Money paid for these chemicals in the United
States and around the world fuels an ever-increasing supply of these deadly substances.

Fentanyl is today’s demon, but it might not be tomorrow’s. If it is not, it will be because some other drug will have taken its place. The new threat may be a synthesized version or analog of an existing analgesic illicitly produced by a commercial pharmaceutical company, a clandestine or underground laboratory, or it may be a new chemical entity with psychoactive properties that is unrelated to any current pharmaceutical product. Scores of novel chemicals are introduced illicitly each year to the underground drug market. Only if we understand what is happening can we hope to get ahead of this tragic public health problem. We will not succeed if all we continue to do is focus on today’s demon drug, collect the bodies, and sweep up the detritus that each new wave of commercialized recreational pharmacology leaves in its wake.

The Story of Fentanyl: Yesterday, Today, and Tomorrow

The fentanyl story begins with opium, the gum of the poppy plant that has been used therapeutically since prehistoric times and likely was the first medicinal drug discovered and used as such. In the 19th century, morphine was identified and isolated as the key alkaloid responsible for opium’s medicinal effects. It was purified as a powerful medicine to reduce pain, treat diarrhea, and address other common disorders. In 1898, Heinrich Dreser, a chemist working at the Bayer Laboratories in Elberfeld, Germany, tweaked the morphine molecule to produce diacetylmorphine, a more powerful painkiller. The new drug was called heroin—based on the German word heroisch, meaning mighty or heroic. Heroin was hailed around the world as a powerful cough suppressant at a time when uncontrollable coughing was linked to tuberculosis and pneumonia. Although a morphine derivative, heroin was believed for a time not to be as habit-forming as morphine. That assumption, however, in short order proved not to be true.

Until 1914, Congress was content to let the states and territories deal with the control of medicinal drugs. This changed with passage of the Harrison Narcotic Tax Act of 1914, the first federal statute that regulated prescribers and dispensers of opium, morphine, heroin, codeine, and cocaine, as well as commerce in these drugs, their derivatives, and salts. A decade later, Congress banned heroin entirely by prohibiting the importation of opium for manufacturing it.

In 1929, the National Research Council (NRC), a division of the National Academy of Sciences, was tasked with developing a non-habit-forming
analgesic. Over several decades, NRC researchers synthesized many new analgesic drugs, including some that are still in use today, but they never succeeded in finding one that could meet the elusive goal. By the end of the 20th century, synthetic and semisynthetic opioids like oxycodone, methadone, and hydrocodone dominated a newly emergent medical specialty called pain management. Emphasizing the use of newly approved, long-acting opioids, the treatment of chronic pain, including chronic nonmalignant pain, became a national campaign backed by the pharmaceutical industry, patient advocacy groups, and the U.S. government. In 1999, the Veteran’s Health Administration, the largest government-run health care system in the U.S., adopted the campaign’s mantra that pain is every patient’s “Fifth Vital Sign” requiring measurement and treatment, when and if necessary, at every encounter.

While all morphine and morphine substitute chemicals produce analgesia and brain reward, prolonged use may lead to analgesic tolerance in patients treated for pain and to compulsive intake by opioid addicts. Long-term use also may produce physical dependence, a condition manifested by somatic withdrawal symptoms in the absence of the drug. Withdrawal symptoms may include pain, insomnia, and diarrhea, which are, in effect, a reversal of the drug’s therapeutic effects. Physical dependence and withdrawal symptoms can be resolved medically by gradual dose reduction over several weeks or months, and is known in the lingo as “tapering.”

More worrisome, however, is “addiction,” a serious disease referred to in the literature today as substance use disorder (SUD). This condition is often misunderstood in the discussion of chronic opioid use. Unlike physical dependence, a SUD involving opioids is not easily managed by gradual dose reduction because of a strong desire or craving that the addicted person has for the abusable substance, even following periods of forced or voluntary abstinence. Unlike tolerance or physical dependence, both of which typically respond well to medical management, a SUD is a life-threatening chronic disease characterized by compulsive use of psychoactive substances despite their harm.

Creating and Filling the Need for New Pain Drugs

Until the 1980s, the use of opioids for treating chronic pain was reserved mostly for treating malignant pain and providing end-of-life care for patients whose physical dependence on the medication was not a relevant risk factor. For several decades or more after World War II, there was growing demand in Europe and the United States for improved analgesics
and anesthesia agents, the latter for use in modern surgical procedures for which ether and morphine-based drugs were unsuited. Before and during the war, researchers on both sides of the Atlantic sought to develop synthetic analgesics in the event of a morphine shortage. One such drug that met this need was meperidine (pethidine), a synthetic opioid of the phenylpiperidine class of drugs. It was synthesized in 1932 by a German chemist and used therapeutically for the first time in 1939. Meperidine attracted the attention of Paul A. J. Janssen, a young Belgian medical doctor and researcher known affectionately by his colleagues as Dr. Paul.

Although meperidine depressed respiration less than morphine, it remained an unsuitable anesthetic for lengthy and complex surgical procedures. The drug, Dr. Paul found, did not efficiently cross the blood-brain barrier. He theorized that if the drug could be made more lipophilic, it would dissolve faster and cross the barrier more efficiently, thereby increasing its analgesic effect. Dr. Paul and his small team of researchers manipulated the meperidine molecule, specifically focusing on the piperidine ring. In a series of experiments that followed, the team synthesized a large number of new compounds, including some with important therapeutic benefits. In 1963, they synthesized fentanyl, a drug they estimated could have 100 times the potency of morphine.

In 1961, Dr. Paul carried out a merger of his company with Johnson & Johnson (J&J), the American health care giant. Under the able supervision of Dr. Paul, the new J&J division, called Janssen Pharmaceutica L.P., continued to develop a variety of new drugs. Committed to helping chronic pain patients, Dr. Paul and his J&J colleagues searched for a safe way to make fentanyl available as an outpatient drug.

In the 1970s, astronauts on their voyages to Skylab wore experimental scopolamine skin patches to address motion sickness. Dr. Paul and his J&J colleagues investigated this novel drug delivery system developed by the Alza Corporation under contract with the National Aeronautics and Space Administration. In 1990, the U.S. Food and Drug Administration (FDA) approved Janssen Pharmaceutica’s New Drug Application for Duragesic, the world’s first extended-release fentanyl transdermal drug delivery system for treating moderate to severe pain. Duragesic was manufactured by the Alza Corporation for Janssen Pharmaceuticals, Inc.

The Duragesic fentanyl patch contained enough fentanyl to provide up to 72 hours of steady and measured dosing. Its gelled formulation appeared to inhibit its misuse by people with substance use disorders. Unable to identify or safely isolate and measure the fentanyl in the gelled formulation, would-be misusers risked sudden overdose death if they exuded and
consumed or injected the high-dose contents of the patch. This risk and the knowledge of it that was spread on the Internet via underground drug fora might have kept the instances of Duragesic abuse very low for many years. This, however, would change when generic solid matrix formulations were approved in 2005. Simply cutting the solid matrix film in small portions provided an abuser with a measured—and, presumably, safe—dose of fentanyl.

The success of Duragesic accelerated the development of other forms of fentanyl for outpatient use. This included FDA-approved lozenges, sublingual films, transmucosal systems, and sprays to treat acute or breakthrough cancer pain. Most of the “new” opioids introduced in the 1980s and 1990s actually were older natural or semi-synthetic opioids repackaged and patented in extended-release formulations. Fentanyl was the only truly new analgesic drug product approved for outpatient use during this period. It quickly became known as the ultimate opioid that not only was more potent than all the others, but also produced fewer and less severe side effects than, for example, oral morphine. Unfortunately, the qualities that made fentanyl an effective pain drug also made it a popular drug among opioid abusers.

### From Plant to Pharmacy Shelf

The pathway leading from a plant-based folk medicine to isolated and purified chemicals to synthesized medicinal analogues is common for many pharmaceuticals. Nearly half of all approved drugs between 1981 and 2010 trace their origins directly or indirectly to natural substances. Many have direct medicinal application and many others have provided chemical models and templates for the design, synthesis, and semi-synthesis of novel substances for treating disease. Each synthesized analogue of the parent molecule may produce a different range of medicinal effects while generally sharing some of the major effects of the parent drug. While the science of medicinal chemistry is best known for developing beneficial medicines, it also has been used—or, more precisely, misused—by criminals to produce analogs of abusable substances, including fentanyl, to thwart the law, make money, and to enhance the psychic effects of the parent molecule.

All opioids share a common profile of effects that prominently includes reducing pain. They also share a common potential for producing overdose death by suppressing respiration when taken in high doses. They may have minor differences that determine their suitability for specific patients with specific pain conditions, but their core analgesic effects are basically
the same. Where opioids differ is in their “potency,” that is, how much of the chemical is needed to produce specific effects beyond which one may risk overdose and death. The potency of an opioid is often expressed in morphine milligram equivalents (MME). Morphine is the standard against which the potency of all other opioids is measured. It has been suggested that the labels for opioid medications be required by the FDA to list their MME-per-dosage unit to aid prescribers and patients in reducing adverse outcomes and unintentional overdoses.32

As previously mentioned, fentanyl’s potency is estimated to be as much as 100 times the potency of morphine.33 Often, this is wrongly presumed to mean that fentanyl is 100 times more powerful and, therefore, 100 times potentially more dangerous than morphine. All opioids, including fentanyl, share common analgesic actions, and, if misused, all are capable of producing serious injury, overdose, and death.

The crucial difference between fentanyl and morphine as it relates to potency is how much of each drug is needed to produce a particular effect. It takes roughly 100 times more morphine than fentanyl to produce equivalent levels of pain relief—or, for that matter, overdose death. Carfentanil (or carfentanyl), a powerful immobilizing drug used on large animals, is a fentanyl analog that is estimated to be 10,000 times more potent than morphine.34 If MMEs are equalized, all opioids, including the fentanyl drugs, are capable of producing similar dose-dependent therapeutic and adverse effects.

How Did Prescription Drugs Come to Dominate the Drug Abuse Epidemic?

The current drug abuse crisis is not unique. The heroin epidemic of the late 1960s was followed by the crack cocaine epidemic a generation later, after which came the methamphetamine epidemic. All these so-called epidemics in one form or another are still with us. In the late 1990s, the nonmedical use of prescription drugs emerged as a major public health problem that the Centers for Disease Control and Prevention (CDC) and the White House dubbed an epidemic.35 By most accounts, the epidemic began in 1996 with the introduction of an extended-release form of oxycodone (OxyContin®). More recently—at least since 2013, according to the CDC—illicitly manufactured fentanyl or IMF, a substance that often is found mixed with heroin or used as a substitute drug in counterfeited branded drugs, has dominated the non-pharmaceutical opioid market.36

The reality is that virtually all nonmedical drug use entails polydrug use. The world has changed dramatically over the past 70 years with an
ever-increasing range of manufactured psychoactive substances available to anyone with access to the Internet. Epidemiologists and others who study the drug abuse phenomenon cite lethal mixtures of pharmaceutical and non-pharmaceutical substances, including common intoxicants like marijuana and alcohol, for causing thousands of drug-related overdose deaths each year. In Florida, for example, 93 percent (1,617 of 1,743) of all fentanyl-caused overdose deaths in 2017 involved two or more drugs. In 2017, according to the CDC, more than half (50.4 percent) of all psychostimulant-involved deaths in the U.S. included opioids.

Social media can serve as a bellwether for identifying emerging trends and behaviors, especially among young people. In 2017, medical researchers and computer technicians at the University of California used unsupervised machine learning to analyze 11 million tweets filtered to identify commonly abused prescription opioid drugs (Percocet®, OxyContin®, and Oxycodone). The study yielded 2.3 million tweets (21 percent) with relevant content. Analysts reviewing the messages with relevant content noted a high degree of discussion (approximately 80 percent) about polydrug abuse involving multiple types of substances.

Fentanyl’s Future in a Post-Heroin Era

It is possible that in time fentanyl will dominate or replace the U.S. heroin market. The illicit drug trade, crude and freewheeling as it may be at times, responds reliably to market forces. While it is not in the economic interests of drug dealers to kill their customers by supplying them with lethal doses of fentanyl, paradoxically drug abusers will often flock to such dealers believing them to have “the good stuff.” Many will delude themselves into thinking they can manage the risks. Dealers, in turn, have a powerful economic incentive to protect the market, and the market, as economists have long noted, has its own survival skills. Thus, it is likely that in time these adverse outcomes will self-correct as the supply chain dynamics improve.

A similar phenomenon occurred in the 1960s when LSD burst onto the illicit drug scene. Like fentanyl, LSD is measured in micrograms, meaning just a very small amount can produce an effect. Early dealers of this drug used blotter paper, sugar cubes, and other small delivery media to market unmeasured quantities. Unable to know just how much LSD was in a single dosage unit, users risked unintentional overdoses, serious injuries, and even death from hazardous drug-induced acute psychotic behaviors. “Bad trips,” as overdoses were called, ultimately led to the demise of the LSD market—at least for several decades or until underground sources acquired the technical
means to standardize dosing levels and ensure safe trips. To illustrate how far this technology has come in the intervening years, many current users of LSD, often affluent young business entrepreneurs, calling themselves microdosers, maintain a global network of users on the Internet and claim to benefit from a typical regimen of 10 mcg of LSD taken once every three days. 41

Although bearing some similarity with the LSD market of the 1960s, today’s illicit fentanyl market poses far greater risks of sudden overdose death from the effects of the drug itself. In addition, the co-ingestion of heroin and fentanyl heightens this risk, inasmuch as the cumulative potency of the finished product is unknown by the user until consumed. As today’s fentanyl sources acquire the ability to solve the dosing problem, the market for it may increase inversely to a decline in the heroin trade. On the other hand, the pathophysiology of opiate addiction is known to drive an addict’s craving for drugs of increased potency and effect—a manifestation of the effects of tolerance and physical dependence. 42 Thus, as we learned from the LSD experience cited above, solving the fentanyl dosing problem may slow the rate of fentanyl-caused overdose deaths, but not halt it.

While criminal cartels in Mexico currently dominate the heroin-fentanyl trade in the United States, that might change if demand for heroin ultimately gives way to fentanyl. With copious supplies of unregulated pharmaceutical-grade fentanyl available for sale on the global market, domestic criminal-entrepreneurs will have little difficulty setting up illicit drug-manufacturing and distribution networks. While sharing some pharmacodynamic similarities, heroin and fentanyl differ greatly in their production and transportation costs. Fentanyl is a purely synthetic drug produced from precursor chemicals in a laboratory, whereas heroin—like morphine and codeine—is derived from opium, the resin of Papaver somniferum, a plant species commonly known as opium poppy.

Heroin is produced in clandestine makeshift labs in a relatively simple reaction process. Fentanyl traffickers may make their own supplies of the drug or, as is more common, purchase it directly from commercial pharmaceutical firms in China. 43 The cost for shipping relatively small (and falsely labeled) parcels of pharmaceutical-grade fentanyl, using international courier services, is miniscule compared with the logistics and cost of smuggling heroin.

Stocks of pharmaceutical-grade fentanyl produced in China are still available to customers around the world, including the heroin cartels in Mexico. Despite recent action by China to add fentanyl and fentanyl-related substances to its list of controlled drugs, it remains to be seen just how effective such controls are over time in closing off this important source for
pharmaceutical-grade fentanyl. Some believe China’s controls will simply drive commercial fentanyl production underground. The heightened security by federal authorities on parcels shipped directly from China has resulted in Canada and Mexico becoming transportation hubs and processing centers for Chinese fentanyl and fentanyl-laced drugs destined for the United States.

The Emerging Counterfeit Drug Phenomenon Involving Fentanyl

A separate but similarly troubling issue involving fentanyl emerged in the past decade as U.S. law enforcement authorities began discovering counterfeit controlled substances resembling well-known forms of alprazolam (Xanax®), oxycodone (OxyContin® and Percocet®), and hydrocodone (Norco®) but containing fentanyl instead of the expected active pharmaceutical ingredient (API). This phenomenon came to light after a number of victims consumed the counterfeit drugs, overdosed, and died. This caused authorities to pay close attention to the counterfeit drugs market that, until recently, involved mostly expensive lifestyle drugs and high-end chemotherapy drugs sold directly to consumers via the Internet or surreptitiously introduced into vulnerable medicinal supply chains around the world.

In 2015, according to the Drug Enforcement Administration (DEA), a confidential source reported that counterfeit prescription drugs containing fentanyl were selling “in the New York club scene” for $10 per pill. The following year, a DEA source in Florida reported that counterfeit Roxicodone® pills containing fentanyl were selling on the streets of Miami for $20 per pill. At these prices, DEA officials estimate that when processed for street sales, a kilogram of pure fentanyl could generate between $5 million and $20 million in retail sales.

The increased availability of pharmaceutical-grade API on the surface and Dark Webs (Internet) suggests that, besides the counterfeit branded drugs containing fentanyl and intended for sale to drug addicts, drug counterfeiters also have begun to manufacture well-known brand-name drugs with real API obtained from drug and chemical suppliers in China, India, and other nations where chemical and drug-making industries are poorly regulated. Two types of drug counterfeiters dominate this underground industry. One uses real but unapproved API in replicated packaging, while the other simply replicates the packaging and the appearance and logo of the branded drug but provides no API. Patients and drug addicts comprise the customer base for the former and bulk wholesalers for the latter. Authorities in India, according to a U.N. report, discovered commercial laboratories
operating as lawful producers of drugs by day, but at night they were producing “knock-off” versions of the same drugs without the labeled API.\textsuperscript{52}

In 1924, as previously mentioned, Congress outlawed pharmaceutical heroin in the United States.\textsuperscript{53} In 1931, a League of Nations convention banned its export in international commerce.\textsuperscript{54} Not long after heroin was banned by domestic American law and stricken from global commerce, underground sources in Asia and the Middle East embarked on the clandestine production and distribution of the drug to satisfy a global demand that was established long before the drug was banned. We may see a similar response as nations such as China and India are pressured by world opinion to adopt tighter controls on the lawful production and distribution of fentanyl, fentanyl analogs, fentanyl precursor substances, and other controlled precursors and APIs.

The counterfeiting of controlled substances in the U.S. has become a concern of public health and safety authorities. A modest investment in mixing equipment, a used pill-making machine, and a set of punch dies created to resemble the shapes and logos of popular drugs, are all one needs to become a do-it-yourself—albeit unlawful—pharmaceutical manufacturer.\textsuperscript{55} We briefly describe below an example of this criminal activity that was recently discovered.

In May 2017, authorities in Utah broke up a group of mostly college-aged young people who were operating a bogus pharmacy on the Dark Web. A federal indictment filed in October 2018 charged the ringleader with distribution of more than 66,000 counterfeit 30 mg oxycodone tablets containing fentanyl but made to look like a well-known generic oxycodone tablet. The indictment also charged the group with sales of more than 175,000 alprazolam tablets made to resemble a popular product (Xanax) and containing unlawfully imported alprazolam. More than $6 million in cash, gold, and Bitcoin was seized by authorities and linked to this enterprise. The group had its own pill-making machine equipped with counterfeit logo punch dies and conducted a robust business on the Dark Web.\textsuperscript{56}

What became evident as we reviewed court records in this case is that our current systems for warning about emerging drug threats like this are woefully inadequate. The federal government’s methodologies for collecting data reflect the thinking of the first half of the last century when the nation’s drug abuse problem involved mostly street drugs such as heroin, cocaine, and marijuana. By comparison, until the mid-1990s, abuse of prescription drugs was both modest and manageable. For the sake of consistency, today’s national drug surveys and the mammoth government bureaucracies that manage them continue to ask young respondents, for example, many of
the same questions they asked their parents decades ago—long before the Internet era.

These limitations came to light recently when four senior CDC analysts acknowledged that the agency’s 2016 report of prescription opioid overdose deaths was mistakenly overstated—possibly by as much as 47.3 percent. Algorithms used by the CDC’s National Vital Statistics System to code cause of death data from death certificates were not designed to distinguish deaths caused by illicitly manufactured fentanyl from those caused by pharmaceutical fentanyl and, as a result, all drug overdose deaths involving fentanyl were attributed to the prescribed form.

The CDC’s failure to distinguish IMF-related overdose deaths caused state and federal authorities to focus attention on manufacturers, wholesale distributors, prescribers, and dispensers of legitimate fentanyl medications. This, in turn, no doubt affected how chronic pain patients viewed being prescribed fentanyl. When prescribed for legitimate medical use, fentanyl has never been a serious public health problem. For those whose lives have been saved or improved by Dr. Paul’s momentous discovery, fentanyl remains nothing short of a miracle drug.

The Nation’s Drug Problem Is Not Merely a Fentanyl Problem

The best way to understand the current drug epidemic is to abandon the single demon-drug concept and, instead, recognize that this massive public health threat is commercialized recreational pharmacology—the widespread use of chemicals that super-stimulate brain reward for purposes of pleasure. This is the initial chemical lure for abusers that, in the case of drugs like fentanyl and oxycodone, eventually will cease providing them pleasure and, instead, will produce a life-threatening disorder characterized by an irressipable cravings for more drugs. These chemicals are available legally by prescription, and illegally from street and online drug dealers.

Driving this threat are the millions of Americans who eagerly spend $150 billion every year on illegal drugs. This massive and financially lucrative demand fuels the rapidly expanding and increasingly sophisticated global supply of illegal drugs used for recreational purposes. As more states liberalize their drug control policies, especially with respect to cannabis, this figure is expected to grow rapidly and be matched by a corresponding increase in related social and health costs. For comparison, the legitimate alcohol industry (wine, beer, and spirits) reported American sales of $253.8 billion in 2018, while the American tobacco industry reported $125 billion in sales.
What Should We Do Now?

In order to reduce the prevalence of fentanyl abuse, the nation must first grasp the reality that the drug problem is not just about fentanyl, the latest demon drug. Fentanyl is a sentinel calling our attention to the potential for a slew of laboratory-based drugs produced by an ever-expanding illegal global drug market to meet a growing demand. Included in this threat are the fentanyl-laced counterfeit drugs manufactured to look like well-known and trusted pharmaceutical products but containing deadly amounts of fentanyl instead of the expected API. Unrestrained by regulatory controls and labeling requirements, today’s drug trafficker-entrepreneur poses a serious threat to patients and non-patients alike. If we hope to meet these challenges successfully, we will need radically new thinking, better data systems, and improved technology to keep counterfeit drugs and deadly fentanyl analogs out of our communities and medicinal drug supplies.

Recommendations

To get this started, we offer the following recommendations:

- **Revisit regulatory guidelines.** In 2011, the FDA issued a brief guidance document on the use of physical-chemical identifiers in solid oral dosage forms of drugs to prevent counterfeiting. Because it was only a guidance document, not a regulation, drug companies generally ignored it. Conditions have changed significantly since 2011. We recommend that the FDA revisit this issue and initiate administrative rulemaking or, if necessary, seek appropriate legislation to require drug companies to implement anti-counterfeiting measures.

- **Update reporting standards.** In October 2018, following the CDC’s admission that its prescription opioid mortality figures for 2016 were flawed, Congress enacted legislation that, among other things, directs the CDC to “modernize” its system for reporting drug overdose deaths. Modernizing the CDC system is an essential first step in tracking the epidemic of drug overdose deaths. Having reliable and accurate data on drug-related morbidity and mortality is essential for addressing the current drug abuse problem. We recommend that Congress and the President undertake a complete overhaul and redesign of the nation’s drug abuse tracking and monitoring systems.
- **Reinstitute DAWN.** In the October 2018 legislation, Congress also directed the Department of Health and Human Services (HHS) to reinstitute the Drug Abuse Warning Network (DAWN) that HHS inexplicably discontinued in 2011 at the height of the prescription drug abuse epidemic. DAWN was a nationally represented public health surveillance system that continuously monitored drug-related visits to hospital emergency departments. The contract for reestablishing this vital public health program was awarded to its previous contractor, whose work was viewed as incomplete and tardy by some experts who depended upon its data for policy formulation. We recommend that HHS form an advisory committee of diverse stakeholders to advise and assist HHS on the management and direction of this vital program that monitors hospital visits for drug abuse and misuse-related emergencies.

- **Identify successful treatment protocols.** Substance use disorders and their treatment may not always be drug-specific, and a one-size-fits-all approach will not work in today’s complex drug world. The goal of any drug treatment program should be lasting recovery. Addiction treatment programs, especially those that receive public funding, should be judged on their ability to produce lasting recovery. A long-standing program successfully used by states for treating addicted physicians offers tailored strategies that improve treatment outcomes for this cohort. We recommend additional research to identify individual components of treatment protocols like this that may work across various populations and communities.

- **Merge regulatory strategies.** We need to recognize that the fundamental drug problem facing the nation today is commercialized recreational pharmacology, the use of intensely stimulating brain reward chemicals for self-directed enjoyment or “self-medication.” There are two drug markets—licit and illicit—operating simultaneously on parallel tracks to supply the growing demand for recreational neurochemicals. Currently, government control strategies address each of these markets separately. We recommend merging regulatory strategies, wherever and whenever possible, to reduce the ability of drug abusers to switch markets to acquire drugs. For example, current strategies address street drug violations using criminal provisions and most pharmaceutical drug violations using civil provisions of the Controlled Substances Act. Researchers at Harvard University...
studied regulatory law compliance and concluded that strategic and exemplary use of criminal, rather than civil, provisions of the law may achieve improved compliance.  

- **Focus on primary prevention.** We must refocus attention on the goal of primary prevention, that is, helping American youth grow up drug-free. The unique vulnerability of the adolescent brain and the knowledge that youthful drug use primes the brain for adult addictive drug use are more than sufficient reasons for why we should focus special attention on this population. The problems discussed in this paper, namely, the emergence of fentanyl and fentanyl analogs in the street drug trade and the introduction in this trade of potentially lethal counterfeit drugs greatly complicates traditional community standards and practices when it comes to addressing drug abuse. This means that the universal drug abuse prevention goal for our young people must be: “No use of alcohol, nicotine, marijuana, and other drugs for reasons of health.” On a positive note, increasing percentages of Americans have been making this choice for more than several decades. We recommend that this little-known fact be recognized, encouraged, and publicized far and wide.

**Conclusion**

The fentanyl story is an important chapter in the rapidly evolving global drug abuse epidemic—one that may foreshadow a future in which we see an increasing array of counterfeit and synthetic drugs of abuse, easily manufactured and ever-more conveniently delivered via the Internet to eager buyers in the U.S. and around the world. It also underscores the central role of money as the primary driver of those who feed this epidemic. Reducing supply, an approach from yesterday, when contraband drugs emanated from a handful of centralized locations and were smuggled into the United States for distribution by well-known criminal organizations, is anachronistic and of questionable value today in a world where anyone, anywhere, at any time can acquire the skill, equipment, and precursors to make and sell locally or online sophisticated drugs like fentanyl.

While there always will be a need for effective supply reduction, future success in reducing drug abuse will depend increasingly on identifying more effective demand-reduction strategies. The brilliance of minds like that of Dr. Paul and so many others who throughout the ages gave us life-saving and life-enhancing medicines to alleviate pain, treat, and cure our worst
ailments is living proof that turning back the uniquely human disease of drug addiction is possible.

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Endnotes

2. Ibid.
3. Ibid.
4. Ibid.
11. Ibid.
16. Ibid.
18. Ibid.
23. Ibid. The name Janssen Pharmaceuticals, Inc. is interchangeable with Janssen Pharmaceutica L.P.
25. Ibid.
26. Ibid.


50. Ibid.

51. Ibid.


55. In April 2016, the DEA conducted a brief study of Internet sources and found that various forms of fentanyl were widely available from “anonymous darknet markets,” as well as via “overtly-operated websites.” Industrial pill press machines also were available. The DEA reported that a pill press capable of producing 5,000 pills per hour was priced at $995, and die molds for oxycodone and Xanax pills were selling for $115 and $130, respectively. U.S. Drug Enforcement Administration, “Counterfeit Prescription Pills Containing Fentanyl.”


58. Ibid.


64. Support for Patients and Communities Act, Public Law No. 115–271.


68. Controlled Substances Act, Public Law No. 91–513.

