DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON DRUG ABUSE

Research on the Use and Misuse of Fentanyl and Other Synthetic Opioids

Testimony before the

House Committee on Energy and Commerce

Subcommittee on Oversight and Investigations

Wilson M. Compton, M.D.

Deputy Director, National Institute on Drug Abuse (NIDA)

March 21, 2017

Chairman Murphy, Ranking Member DeGette, and Members of the Committee: thank you for inviting the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), to participate in this important hearing to provide an overview of what we know about the role of fentanyl in the ongoing opioid overdose epidemic and how scientific research can help us address this crisis.

The misuse of and addiction to opioids – including prescription pain medicines, heroin, and synthetic opioids such as fentanyl – is a serious national problem that affects public health as well as social and economic welfare. The Centers for Disease Control and Prevention (CDC) recently estimated that the total "economic burden" of prescription opioid misuse alone in the United States is $78.5 billion a year, including the costs of health care, lost productivity, addiction treatment, and criminal justice involvement.[1] In 2015, over 33,000 Americans died as a result of an opioid overdose.[2] That year, an estimated 2 million people in the United States suffered from substance use disorders related to prescription opioid pain medicines (including fentanyl), and 591,000 suffered from a heroin use disorder (not mutually exclusive).[3]

This issue has become a public health epidemic with devastating consequences including not just increases in opioid abuse and related fatalities from overdoses, but also the rising incidence of neonatal abstinence syndrome due to opioid use during pregnancy, and the increased spread of infectious diseases, including HIV and hepatitis C.[4-6] Recent research has also found a significant increase in mid-life mortality in the United States particularly among white Americans with less education. Increasing death rates from drug and alcohol poisonings are believed to have played a significant role in this change.[7]

The Pharmacology of Fentanyl and Other Synthetic Opioids

Prescription opioids, heroin, and synthetic opioid drugs all work through the same mechanism of action. Opioids reduce the perception of pain by binding to opioid receptors, which are found on cells in the brain and in other organs in the body. The binding of these drugs to opioid receptors in reward regions in the brain produces a sense of well-being, while stimulation of opioid receptors in deeper brain regions results in drowsiness and respiratory depression, which can lead to overdose deaths. The presence of opioid receptors in other tissues can lead to side effects such as constipation and cardiac arrhythmias through the same mechanisms that support the use of opioid medications to treat diarrhea and to reduce blood pressure after a heart attack. The effects of opioids typically are mediated by specific subtypes of opioid receptors (mu, delta, and kappa) that are activated by the body's own (endogenous) opioid chemicals (endorphins, enkephalins). With repeated administration of opioid drugs (prescription or illicit), the production of endogenous opioids decreases, which accounts in part for the discomfort that ensues when the drugs are discontinued (*i.e.*, withdrawal).[8]

The rewarding effects of opioids – whether they are medications, heroin, or illicitly produced synthetic opioids – are increased when they are delivered rapidly into the brain, which is why non-medical users often inject them directly into the bloodstream.[9] Fentanyl, in particular, is highly fat-soluble, which allows it to rapidly enter the brain, leading to a fast onset of effects. This high potency and rapid onset are likely to increase the risk for both addiction and overdose, as well as withdrawal symptoms.[10] In addition, injection use increases the risk for infections and infectious diseases. Another important property of opioid drugs is their tendency, when used repeatedly over time, to induce tolerance. Tolerance occurs when the person no longer responds to the drug as strongly as he or she initially did, thus necessitating a higher dose to achieve the

same effect. The establishment of tolerance results from the desensitization of the brain's natural opioid system, making it less responsive over time.[11] Furthermore, the lack of sufficient tolerance contributes to the high risk of overdose during a relapse to opioid use after a period of abstinence whether it is intentional – for example, when a person tries to quit using – or situational – for example, if a person cannot obtain opioid drugs while incarcerated or hospitalized. Users no longer know what dose of the drug they can safely tolerate, resulting in overdoses.

While all of these opioids belong to a single class of drugs, each is associated with distinct risks. The risk of overdose and negative consequences is generally greater with illicit opioids due to the lack of control over the purity of the drug and its potential adulteration with other drugs. All of these factors increase the risk for overdose, since users have no way of assessing the potency of the drug before taking it. In the case of adulteration with highly potent opioids such as fentanyl or carfentanil, this can be particularly deadly.[12-14] Another contributing factor to the risk of opioid-related mortality is the combined use with benzodiazepines or other respiratory depressants, like some sleeping pills or alcohol.[15]

The Role of Fentanyl in the Opioid Crisis

The emergence of illicitly manufactured synthetic opioids including fentanyl, carfentanil, and their analogues represents an escalation of the ongoing opioid overdose epidemic. Fentanyl is a μ-opioid receptor agonist that is 80 times more potent than morphine *in vivo*. While fentanyl is available as a prescription – primarily used for anesthesia, treating post-surgical pain, and for the management of pain in opioid-tolerant patients – it is the illicitly manufactured versions that have been largely responsible for the tripling of overdose deaths related to synthetic opioids in

just two years – from 3,105 in 2013 to 9,580 in 2015.[2] A variety of fentanyl analogues and synthetic opioids are also included in these numbers, such as carfentanil (approximately 10,000 times more potent than morphine), acetyl-fentanyl (about 15 times more potent than morphine), butyrfentanyl (more than 30 times more potent than morphine), U-47700 (about 12 times more potent than morphine), and MT-45 (roughly equivalent potency to morphine), among others.[17]

The opioid crisis began in the mid-to late 1990's, following a confluence of events that led to a dramatic increase in opioid prescribing, including: a regulatory, policy and practice focus on opioid medications as the primary treatment for all types of pain;[18] an unfounded concept that opioids prescribed for pain would not lead to addiction;[19] the release of guidelines from the American Pain Society in 1996 encouraging providers to assess pain as "the 5th vital sign" at each clinical encounter; and the initiation of aggressive marketing campaigns by pharmaceutical companies promoting the notion that opioids do not pose significant risk for misuse or addiction and promoting their use as "first-line" treatments for chronic pain.[19-21]

The sale of prescription opioids more than tripled between 1999 and 2011, and this was paralleled by a more than four-fold increase in treatment admissions for opioid abuse and a nearly four-fold increase in overdose deaths related to prescription opioids.[22] Federal and state efforts to curb opioid prescribing resulted in a leveling off of prescriptions starting in 2012;[23] however, heroin-related overdose deaths had already begun to rise in 2007 and sharply increased from just over 3,000 in 2010 to nearly 13,000 in 2015.[2] We now know prescription opioid misuse is a significant risk factor for heroin use; 80 percent of heroin users first misuse prescription opioids.[24] While only about four percent of people who misuse prescription opioids initiate heroin use within 5 years,[24,25] for this subset of people the use of the cheaper, often easier to obtain street opioid is part of the progression of an opioid addiction.[26]

The opioid overdose epidemic has now further escalated, with the rise in deaths related to illicitly manufactured synthetic opioids. Often, the population of people using and overdosing on fentanyl looks very similar to the population using heroin. However, the drivers of fentanyl use can be complicated as the drug is often sold in counterfeit pills – designed to look like common prescription opioids or benzodiazepines (e.g. Xanax) – or is added as an adulterant to heroin or other drugs, unbeknownst to the user.[14] And there are also market forces supporting the proliferation of higher-potency opioids, as people with opioid addictions develop increasing tolerance to these drugs.[27]

History of Fentanyl Misuse

The first fentanyl formulation (Sublimaze) received approval by the Food and Drug Administration (FDA) as an intravenous anesthetic in the 1960s. Other formulations, including a transdermal patch, a quick acting lozenge or "lollipop" for breakthrough pain, and dissolving tablet and film, have since received FDA approval.[28] Misuse of prescription fentanyl was first described in the mid-1970s among clinicians,[29] and continues to be reported among the people misusing prescription opioids.[3] More recently, between April 2005 and March 2007 there was an uptick in deaths related to illicitly manufactured fentanyl that was traced to a single laboratory in Mexico. Once the laboratory shut down the rate of overdose declined.[30] However, over the last few years there has been a growing production of illicitly manufactured fentanyl, much of which is imported from China, Mexico, and Canada.[14] The increase in illicitly manufactured fentanyl availability in the U.S. is reflected by the substantial increase in seizures of fentanyl by law enforcement which jumped from under 1,000 seizures in 2013 to over 13,000 in 2015.[31]

Research shows that the increasing availability of illicitly manufactured fentanyl closely parallels the increase in synthetic opioid overdose deaths in the U.S.[32]

HHS Response and NIDA-Supported Research Related to fentanyl

Within HHS, the Office of the Assistant Secretary for Planning and Evaluation (ASPE) has been leading a targeted and coordinated policy and programmatic effort to reduce opioid abuse and overdose, including fentanyl use and overdose. The effort focuses on strengthening surveillance, improving opioid prescribing practices and the treatment of pain, increasing access to treatment for opioid addiction, expanding use of naloxone to reverse opioid overdose, and funding and conducting research to better understand the epidemic and identify effective interventions. Under this effort, NIDA is engaged in number critical activities.

NIDA supports the National Drug Early Warning System (NDEWS), which monitors emerging drug use trends to enable health experts, researchers and others to respond quickly to potential outbreaks of illicit drugs. In partnership with the NDEWS, the Northeast Node of the NIDA's Clinical Trials Network (CTN) has been funded to complete a Fentanyl Hot Spot Study in New Hampshire. In 2015, New Hampshire had the highest rate of fentanyl-related deaths in the country and this study is investigating the causes of increased fentanyl use and related deaths in this region.

In the first phase of the study, multiple stakeholders throughout the state, including treatment providers, medical responders, law enforcement, state authorities and policymakers were interviewed about their perspectives on the fentanyl crisis.[33] Many expressed that better user-level data was imperative to answer pointed questions to more accurately inform policy, such as the trajectory of fentanyl use, supply chain, fentanyl-seeking behavior versus accidental

ingestion, value of testing kits, treatment preferences, etc. The researchers reported that, "Some may seek out a certain dealer or product when they hear about overdoses because they think that it must be good stuff." According to the group leader, only approximately a third of users knowingly use fentanyl, but the number of users is slowly increasing.

The second phase of the study is conducting a rapid epidemiological investigation of fentanyl users' and first responders' perspectives, so that real-time data can inform policy in tackling the fentanyl overdose crisis.

Another ongoing NIDA funded study is characterizing the fentanyl crisis in Montgomery County, Ohio – an area experiencing one of the largest surges of illicitly manufactured fentanyl in the country. This study will explore the scope of the fentanyl crisis in this area, collecting data from postmortem toxicology and crime laboratories, and will explore active user knowledge and experiences with fentanyl. Other NIDA funded research is working to develop faster methods for screening for fentanyl and other synthetic opioids to track overdoses through emergency department screening and improve surveillance of the fentanyl threat across the country.

NIDA-supported research is also working to develop new treatments for opioid addiction, including treatments targeting fentanyl specifically. One ongoing NIDA-funded study is in the early stages of developing a vaccine for fentanyl that could prevent this drug from reaching the brain.[34]

Evidence-Based Approaches

With the emergence of very high potency opioids addressing supply becomes increasingly difficult because the quantities transported may be much lower. Thus, it is critical to address demand reduction through the deployment of evidence-based prevention and

treatment strategies to reduce the number of people developing an opioid addiction and treating the population of Americans who already suffer from this addiction.

Evidence-Based Treatments for Opioid Addiction

Three classes of medications have been approved for the treatment of opioid addiction : (1) agonists, e.g. methadone , which activate opioid receptors; (2) partial agonists, e.g. buprenorphine, which also activate opioid receptors but produce a diminished response; and (3) antagonists, e.g. naltrexone, which block the opioid receptor and interfere with the rewarding effects of opioids.[35] These medications represent the first-line treatments for opioid addiction.

The evidence strongly demonstrates that methadone, buprenorphine, and injectable naltrexone (e.g., Vivitrol) all effectively help maintain abstinence from other opioids and reduce opioid abuse-related symptoms. These medications have also been shown to reduce injection drug use and HIV transmission and to be protective against overdose.[36-40] These medications should be administered in the context of behavioral counseling and psychosocial supports to improve outcomes and reduce relapse. Two comprehensive Cochrane reviews, one analyzing data from 11 randomized clinical trials that compared the effectiveness of methadone to placebo, and another analyzing data from 31 trials comparing buprenorphine or methadone treatment to placebo, found that[38,39]:

- Patients on methadone were over four times more likely to stay in treatment and had 33 percent fewer opioid-positive drug tests compared to patients treated with placebo;
- Methadone treatment significantly improves treatment outcomes alone and when added to counseling; long-term (beyond six months) outcomes are better for patients receiving methadone, regardless of counseling received;

- Buprenorphine treatment significantly decreased the number of opioid-positive drug tests; multiple studies found a 75-80 percent reduction in the number of patients testing positive for opioid use;
- Methadone and buprenorphine are equally effective at reducing symptoms of opioid addiction; no differences were found in opioid-positive drug tests or self-reported heroin use when treating with these medications.

To be clear, the evidence supports long-term maintenance with these medicines in the context of behavioral treatment and recovery support, not short-term detoxification programs aimed at abstinence.[41] Abstinence from all medicines may be a particular patient's goal, and that goal should be discussed between patients and providers. However, the scientific evidence suggests the relapse rates are extremely high when tapering off of these medications, and treatment programs with an abstinence focus generally do not facilitate patients' long-term, stable recovery.[42,43]

Treatment Challenges

Unfortunately, medications approved for the treatment of opioid abuse are underutilized and often not delivered in an evidence based manner.[44,45] Fewer than half of private-sector treatment programs offer these medications; and of patients in those programs who might benefit, only a third actually receive it.[45] Further, many people suffering with opioid addiction do not seek treatment. Identifying the need for and engaging them in treatment is an essential element of addressing the opioid crisis. For example, recent research suggests that initiating patients on buprenorphine following an opioid overdose can increase treatment retention and improve outcomes.[46] Overcoming the misunderstandings and other barriers that prevent wider adoption of these treatments is crucial for tackling the opioid crisis.

In addition, to achieve positive outcomes, treatments must be delivered with fidelity. To be effective, methadone and buprenorphine must be given at a sufficiently high dose.[38,39] Some treatment providers wary of using methadone or buprenorphine have prescribed lower doses for short treatment durations, leading to treatment failure and the mistaken conclusion that the medication is ineffective.[38,47]

As of 2011, more than 22 percent of patients in a methadone treatment programs were receiving less than the minimum recommended dose of methadone.[48] Interestingly, a recent study identified a genetic variant near the mu opioid receptor gene associated with a higher required dose of methadone (corresponding to a need for about an additional 20 mg per day) in African American patients but not European Americans with this gene variant.[49] This highlights the need for dosing flexibility to achieve the effective dose for an individual patient. The NIH Precision Medicine Initiative and other ongoing research projects are working to define the genetic, biological, and clinical factors that influence the efficacy of treatment to help clinicians deliver care precisely tailored for a specific patient to improve outcomes.

Research has also shown that tapering off of buprenorphine can present significant risks for relapse.[43,50] A recent analysis of five studies that examined outcomes following buprenorphine taper found that on average only 18 percent (a range of 10 to 50 percent) of patients remained abstinent one to two months after tapering off of buprenorphine.[50] In addition, some state programs and insurance providers limit the duration of treatment a patient may receive. There is no evidence base to support this practice, and the available evidence suggests that it poses a significant risk for patient relapse. This is also an important consideration in the context of the two years of funding for the opioid crisis authorized through the 21st Century Cures Act. This funding will be critical for helping states address the ongoing opioid epidemic, however, opioid

addiction is a chronic condition and many patients will need ongoing treatment for many years. It will be important to develop sustainability strategies to ensure that patients do not lose access to these life-saving medications when a particular funding program is discontinued.

While users seeking treatment are on a wait list they generally continue to engage in opioid use and this may contribute to failure to enter treatment when a slot becomes available. Research has shown that providing interim treatment with medications while patients are awaiting admission to a treatment program increases the likelihood that they will engage in treatment. In one study, over 64 percent of study participants receiving interim methadone entered comprehensive care within six months, compared with only 27 percent in the control group, and the group receiving methadone had lower rates of heroin use and criminal behavior.[51] One model for interim treatment with buprenorphine would use urine testing call backs and a special medicine dispensing device to prevent diversion.[52] Implementation would require a regulatory change because take home buprenorphine is not allowed under interim regulations currently. When this model was tested, patients showed strong adherence to the interim treatment plan and reported strong satisfaction with the treatment. State regulations and payment system issues (bundled payment that does not accommodate billing for interim treatment) are often barriers to this type of program and they are not frequently used.

Fentanyl specific challenges

While specific data on treatment outcomes for patients addicted to fentanyl or other high potency synthetic opioids are not available, the same principles of treatment still apply. In addition, patients regularly using these substances and surviving would be expected to have a strong opioid dependency. At this time we are not sure how many people fit this clinical picture. In this scenario the withdrawal symptoms are likely to be severe, and could lead to life

threatening cardiac arrhythmias and seizures if untreated or if extreme opioid withdrawal is potentiated during overdose reversal.[53] There is an urgent need for more research to determine if people using fentanyl or other high potency opioids respond differently to medications for overdose reversal as well as treatment and to determine the most effective approaches for utilizing medications and psychosocial supports in this population.

In general outcomes are better predicted by the strength of the psychosocial supports around patients to support their recovery – educational or job opportunities, supportive friends and family, stable housing, access to child care – than the severity of their addiction. Providing behavioral counseling and wrap around services to address these needs is important for achieving the best outcomes.

Prevention of Opioid Misuse and Addiction

Since the majority of people who develop an opioid addiction begin by misusing prescription opioids, the Department of Health and Human Services (HHS) continues to focus efforts on improving opioid prescribing and preventing the misuse of prescription drugs as the long-run strategy to stop the opioid epidemic. NIDA supports research to understand the impact of federal and state policy changes on rates of opioid abuse and related public health outcomes. This and other federally supported research has demonstrated the efficacy of multiple types of interventions, including:

- Educational initiatives delivered in school and community settings (primary prevention)[54]
- Supporting consistent use of prescription drug monitoring programs (PDMPs)[55]
- Aggressive law enforcement efforts to address doctor shopping and pill mills[56,57]

- Providing healthcare practitioners with tools for managing pain, including prescribing guidelines and enhanced warnings on drug labels with expanded information for prescribers[58-61]

In states with the most comprehensive initiatives to reduce opioid overprescribing, the results have been encouraging. Washington State's implementation of evidence-based dosing and best-practice guidelines, as well as enhanced funding for the state's PDMP, helped reduce opioid deaths by 27 percent between 2008 and 2012.[58] In Florida, new restrictions were imposed on pain clinics, new policies were implemented requiring more consistent use of the state PDMP, and the Drug Enforcement Administration (DEA) worked with state law enforcement to conduct widespread raids on pill mills, which resulted in a dramatic decrease in overdose deaths between 2010 and 2012.[62] These examples show that state and Federal policies can reduce the availability of prescription opioids and related overdose deaths. However, the increasing supply of heroin and illicit fentanyl in the United States is undermining the effects of these improvements. While we have seen a leveling off of overdose deaths related to commonly prescribed opioids over the last few years, overdose deaths related to illicit opioids have risen dramatically during this time.

In early 2016 CDC released guidelines for prescribing opioids for chronic pain.[60] We believe they represent an important step for improving prescriber education and pain prescribing practices in our nation. NIDA is advancing addiction awareness, prevention, and treatment in primary care practices through seven Centers of Excellence for Pain Education.[63] Intended to serve as national models, these centers target physicians-in-training, including medical students and resident physicians in primary care specialties (e.g. internal medicine, family practice, and pediatrics).

Addressing the Public Health Consequences of Opioid Misuse

Other evidence-based strategies can be used to reduce the health harms associated with opioid use, including increasing access to the opioid-overdose-reversal drug naloxone.

Preventing Overdoses with Naloxone

The opioid overdose-reversal drug naloxone can rapidly restore normal respiration to a person who has stopped breathing as a result of an overdose from heroin or prescription opioids. Naloxone is widely used by emergency medical personnel and some other first responders. Beyond first responders, a growing number of communities have established overdose education and naloxone distribution programs that make naloxone more accessible to opioid users and their friends or loved ones, or other potential bystanders, along with brief training in how to use these emergency kits. Such programs have been shown to be effective, as well as cost-effective, ways of saving lives.[64,65] CDC reported that, as of 2014, more than 152,000 naloxone kits had been distributed to laypersons and more than 26,000 overdoses had been reversed since 1996.[66] In addition, the majority of states now allow individuals to obtain naloxone from retail pharmacies without a patient-specific prescription.[67]

Two naloxone formulations specifically designed to be administered by family members or caregivers have recently been developed. In 2014 the FDA approved a handheld auto-injector of naloxone, and in late 2015 the FDA approved a user-friendly intranasal formulation that was developed through a NIDA partnership with Lightlake Therapeutics, Inc. (a partner of Adapt Pharma Limited).[68]

The availability of naloxone is critical to reduce opioid-related fatalities.[69] However, research examining past fentanyl outbreaks shows that higher than typical naloxone doses were

required to reverse fentanyl overdose.[70] As the use of fentanyl and other highly potent opioids is increasing, it would be prudent to promote the use of naloxone while recognizing that multiple doses may be needed to revive someone experiencing a fentanyl overdose.[71] It is also important for first responders to know that, while fentanyl has a short duration of action (30-90 minutes), it can stay in fat deposits for hours, and patients should be monitored for up to 12 hours after resuscitation.[72] More research may be needed to develop new naloxone formulations tailored to higher-potency opioids.

Ongoing Opioid-Related Research: Implementation Science

Despite the availability of evidence based treatments for opioid abuse, we have a significant and ongoing treatment gap in our Nation. Among those who need treatment for an addiction, few receive it. In 2014, less than 12 percent of the 21.5 million Americans suffering with addiction received specialty treatment.[3] Further, many specialty treatment programs do not provide current evidence based treatments – fewer than half provide access to MAT for opioid use disorders.[45] In addition, it is clear that preventing drug use before it begins—particularly among young people—is the most cost-effective way to reduce drug use and its consequences.[73] Evidence based prevention interventions also remain highly underutilized.

Ongoing NIDA research is working to better understand the barriers to successful and sustainable implementation of evidence based practices and to develop implementation strategies that effectively overcome these barriers. This work also seeks to understand the role environment—be it social, familial, structural, or geographic—plays in preventing opioid use and in the success of prevention and treatment interventions, as well as how to tailor prevention

and treatment interventions to individuals with unique needs, including those in the criminal justice system or with HIV.

Other NIDA supported research is looking at how to improve access to treatment among other high risk populations. For example, patients with opioid addiction are at increased risk of adverse health consequences and often seek medical care in emergency departments (EDs). NIDA is also collaborating with the Baltimore County Health Department on a pilot study to explore the possibility of providing methadone through pharmacies to increase access to treatment in underserved parts of the city. In the pilot, pharmacies would be considered satellite locations of licensed methadone treatment facilities; this model has been used in Pennsylvania and New York. Discussions are underway to explore whether regulatory exceptions can be granted to make this possible. Similarly, ongoing research is examining on the impact of providing opioid addiction treatment within infectious disease clinics. This type of research is essential for translating evidence based strategies into real-world interventions that will reach the greatest number of people and get the most out of limited prevention and treatment resources.

Implementation Research to Address the Opioid Crisis in Rural Communities

Our efforts are also focused on addressing the opioid crisis in the epicenter of the epidemic – Appalachia. NIDA is partnering with the Appalachian Regional Commission (ARC) to fund one-year services planning and needs assessment research grants to provide the foundation for future intervention programs and larger scale research efforts to test interventions to address opioid misuse in rural Appalachia. Four grants were awarded in FY 2016 that will address issues related to injection drug use and associated transmission of infectious disease as well as the coordination of care for prisoners with opioid addiction as they re-enter the community.

A second funding opportunity announcement in partnership with the Substance Abuse and Mental Health Services Administration (SAMHSA), CDC, and ARC was released in October 2016 to support comprehensive, integrated approaches to prevent opioid injection and its consequences, including addiction, overdose, HIV and hepatitis C, as well as sexually transmitted diseases. High rates of injection drug use in Appalachia has led to a rapid increase in the transmission of hepatitis C, raising concern about an outbreak of HIV.[6] These projects will work with state and local communities to develop best practices that can be implemented by public health systems in the Nation's rural communities including opioid abuse treatment and other strategies to increase the testing and treatment for HIV.

HIV Testing and Treatment

NIDA supported research has helped to develop the seek, test, treat, and retain model of care (STTR) that involves reaching out to high-risk, hard-to-reach drug users who have not been recently tested for HIV; engaging them in HIV testing; engaging those testing positive in antiretroviral therapy; and retaining patients in care. Research has shown that implementation of STTR has the potential to decrease the rate of HIV transmission by half.[75]

Ongoing Opioid-Related Research: Development of Pain Treatments with Reduced Potential for Misuse

NIDA is one of multiple institutes of the NIH supporting research into novel pain treatments with reduced potential for misuse and diversion, including abuse resistant opioid analgesics, non-opioid medication targets, and non-pharmacological treatments. Some of the most promising potential therapies include:

- *Abuse Resistant Opioid Analgesics:* Efforts are underway to identify new opioid pain medicines with reduced misuse, tolerance, and dependence risk, as well as alternative delivery systems and formulations for existing drugs that minimize diversion and misuse (e.g., by preventing tampering) and reduce the risk of overdose deaths. Multiple recent NIH-funded studies have reported progress in the discovery of opioid compounds with selective analgesic effects with reduced respiratory depressive effects and reduced abuse liability.[76-78]
- *Non-Opioid Medications*: Some non-opioid targets with promising preliminary data include fatty acid binding proteins, the G-protein receptor 55, cannabinoids, and transient receptor potential cation channel A1.
- *Nervous Stimulation Therapies*: Several non-invasive nervous stimulation therapies – including transcranial magnetic stimulation and transcranial direct current stimulation, as well as electrical deep brain stimulation, spinal cord stimulation, and peripheral nerves/tissues stimulation – have shown promise for the treatment of intractable chronic pain. These devises have been approved by the FDA for treatment of other conditions but more research is needed on their effectiveness for pain.
- *Neurofeedback*: Neurofeedback is a novel treatment modality in which patients learn to regulate the activity of specific brain regions by getting feedback from real-time brain imaging. This technique shows promise for altering the perception of pain in healthy adults and chronic pain patients and may also be effective for the treatment of addiction.

Ongoing Opioid-Related Research: Accelerating Development of New Treatments for Addiction

While the three available medications have represented significant advances in the ability to treat opioid use disorders the efficacy of these medications is far from ideal. NIDA is funding research to accelerate development of new treatments. This includes development of non-pharmacological interventions including biologics – such as vaccines, monoclonal antibodies, and bioengineered enzymes designed to prevent a drug from entering the brain – and novel brain stimulation techniques – such as TMS and transcranial direct current stimulation (tDCS), that target brain circuits impaired in addiction with improved specificity and temporal and spatial resolutions, and thus, with less adverse effects. One ongoing NIDA-funded study is in the early stages of developing a vaccine for fentanyl that could prevent this drug from reaching the brain.[34]

Since the pharmaceutical industry has traditionally made limited investment in the development of medications to treat SUDs, NIDA has focused on forming alliances between strategic partners (pharmaceutical and biotechnology companies as well as academic institutions) with the common goal of advancing medications through the development pipeline toward FDA approval. NIDA conducts research to decrease the risks associated with medications development to make it more appealing for pharmaceutical companies to complete costly phase IIb and III clinical studies. An example of such a project is a partnership with US World Meds, is in late stage development of lofexidine, a medication for the treatment of opioid withdrawal symptoms that might also hold promise for the treatment of other addictions.

Conclusion

NIDA will continue to closely collaborate with other federal agencies and community partners with a strong interest in preserving public health to address the interrelated challenges posed by misuse of prescription opioids, heroin, and synthetic opioids such as fentanyl. We commend the committee for recognizing the serious and growing challenge associated with this exceedingly complex issue. Under the leadership of the Department of Health and Human Services and the Office of National Drug Control Policy, NIDA will continue to support the implementation of the multi-pronged, evidence-based strategies to improve opioid prescribing and pain management, reduce overdose deaths, and increase access to high quality opioid abuse treatment.

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