

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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What Science Tells us About Opioid Abuse and Addiction

Testimony before the House Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

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Good Morning, Mr. Chairman, Ranking Member DeGette, and Members of the Subcommittee. 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 and provide an overview of what science tells us about the growing and intertwined problems of non-medical use of prescription pain medicines and use of heroin in our Nation.

Background

The misuse of and addiction to opioids such as heroin, morphine, and other prescription pain medicines is a serious national problem that affects public health as well as social and economic welfare. An estimated 1.9 million people in the United States suffered from substance use disorders related to prescription opioid pain medicines in 2013 and 517,000 suffered from a heroin use disorder.ⁱ This issue has become a public health epidemic with devastating consequences including not just opioid use disorders and related overdoses, but also the rising incidence of newborns who experience neonatal abstinence syndrome because their mothers used these substances during pregnancy; and increased spread of infectious diseases including HIV and hepatitis C (HCV).

Existing evidence based prevention and treatment strategies are highly underutilized across the United States. The recently announced initiative of the Secretary of Health and Human Services to address the complex problem of prescription opioid and heroin abuse in this country emphasizes the implementation of these evidence based prevention and treatment strategies which include not only better prescription practices but also deployment of medication to combat overdoses and medication-assisted treatment (MAT) to treat opioid use disorders. NIDA is an active partner in this initiative and will focus on supporting research and disseminating findings to improve opioid prescribing practices, to expand the use of the opioid overdose reversal drug naloxone, to improve the integration of pharmacotherapies into treatment services in specialty care and primary care, and to develop pain treatments with reduced potential for misuse and diversion.

The Effects of Opioids on the Brain and Body

Both prescription opioid drugs (such as oxycodone and hydrocodone) and heroin work through the same mechanism of action. Opioids reduce the perception of pain by binding to

opioid receptors, which are found on nerve cells in the brain and periphery (as well as 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 that can lead to respiratory depression, which can lead to overdose deaths. Presence of opioid receptors in other tissues is responsible for side effects such as constipation and cardiac arrhythmias. The effects of opioids are typically 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 heroin) the production of endogenous opioids decreases, which accounts in part for the discomfort that ensues when the drugs are discontinued (*i.e.*, withdrawal).

People who use opioids non-medically may seek to intensify their experience by taking the drug in ways that deliver the drug more rapidly to their brain. For example, extended-release oxycodone is designed to release slowly and steadily into the bloodstream when taken orally, which minimizes its euphoric effects. People who use pills for their mood elevating effects may crush them to snort or inject the drug, which not only increases the euphoria but also increases the risk for serious medical complications, such as respiratory arrest, coma, and substance use disorder. When people tamper with long-acting or extended-release medicines, which typically contain higher doses because they are intended for release over long periods, the results can be particularly dangerous, as all of the medicine can be released at once. Taking opioids through nasal, smoked, or intravenous routes enhances risks both because of the higher than manufacturer intended dose and the quicker onset.

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 ability of opioids to desensitize the brain's own natural opioid system, making it less responsive over time.ⁱⁱ This 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 whether it is situational, for example if a user cannot obtain opioid drugs while incarcerated or hospitalized. Users who do not realize they have lost their tolerance during periods of abstinence may initially take the high dosages

that they previously had used before quitting, thus producing overdoses. Another contributing factor to the risk of opioid-related morbidity and mortality is the combined use of benzodiazepines (BZDs) or other central nervous system (CNS) depressants like some sleeping pills, even if these agents are used for the correction indication. Thus, patients with chronic pain who use opioid analgesics along with BZDs are at higher risk for overdose. Similar risks are observed when opioids are combined with alcohol.ⁱⁱⁱ Indeed, the label for these drugs often state, for example, that they should not be used in combination with alcohol and that they should be started at lower doses when used in combination with sedatives. Also, existing and model clinical guidance on opioid prescribing often suggest opioids should not be used with other BZDs.^{iv,v} Unfortunately in many cases practitioners fail to heed practice guidelines and recommendations with respect to co-use.^{vi,vii}

The public-health consequences of opioid misuse are broad and worrisome. For example, use of opioids by pregnant women can result in a withdrawal syndrome in newborns, referred to as neonatal abstinence syndrome, which increased by almost 300 percent in the United States between 2000 and 2009.^{viii} This increase was driven in part by the high rate of opioid prescriptions being given to pregnant women. An estimated 14.4 percent of pregnant women in the United States are prescribed an opioid during their pregnancy.^{ix} Despite producing neonatal abstinence syndrome, methadone has been the acknowledged gold standard for use during pregnancy and there is a growing literature on the use of buprenorphine in pregnant women. These treatments, in combination with behavioral treatment (*e.g.*, MAT), remain highly underused and present the best opportunities to treat opioid use disorder in pregnancy.

Another concern is the transmission of infectious diseases such as HIV and HCV due to injection of heroin or prescription opioids, which has risen along with the increases in individuals injecting opioids. The high prevalence of opioid use also impacts public safety; from 1999-2010, there was a six-fold increase in positive opioid tests among drivers who died within one hour of a crash.^x

Research on National Efforts to Curb the Prescription Opioid Epidemic

Significant efforts have been undertaken across the United States to reduce diversion and misuse of prescription opioids and to reduce opioid overdoses and related deaths. NIDA supports research to understand the impact of these policy changes on rates of opioid misuse, use

disorders, and related public health outcomes. This research has demonstrated the efficacy of multiple types of interventions including:

- Educational initiatives delivered in school and community settings (primary prevention)^{xi}
- Supporting consistent use of prescription drug monitoring programs (PDMPs)^{xii}
- Implementation of overdose education and naloxone distribution programs to issue naloxone directly to opioid users and potential bystanders^{xiii}
- Aggressive law enforcement efforts to address doctor shopping and pill mills^{xiv}
- Diverting individuals with substance use disorders to Drug Courts^{xv}
- Expansion of access to MAT^{xvi}
- Abuse-deterrent formulations for opioid analgesics^{xvii}

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 and enhanced funding for the state's PDMP helped reduce opioid deaths by 27 percent between 2008 and 2012.^{xviii} 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 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.^{xix} These examples show that state and Federal policies can reduce the availability of prescription opioids and overdose deaths.

Relationship between Prescription Opioids and Heroin Abuse

While the initiatives discussed above are beginning to show successes in the form of decreasing availability of prescription opioid drugs and a decline in overdose deaths in states with the most aggressive policies, since 2010, overdose deaths related to heroin have started to increase (as detailed in the testimony from CDC). There is some concern that the increase in heroin-related overdoses may be an unintended consequence of reducing the availability of prescription opioids. Research has shown that prescription opioid use is a risk factor for heroin use. The incidence of heroin initiation is 19 times higher among those who report prior non-medical pain-reliever use than among those who do not (0.39 percent vs. 0.02 percent).^{xx} However, heroin use is rare in prescription drug users. According to the National Survey on Drug Use and Health, less than four percent of people who had used prescription painkillers non-

medically started using heroin within five years of their initiation of non-medical use of pain medication.^{xviii}

Heroin and prescription opioid pain relievers belong to a single class of drugs—but each are associated with distinct risks. The risk of overdose and negative consequences is even greater with heroin due to the lack of control over the purity of the drug and its possible contamination with other drugs (such as fentanyl, originally a potent prescription opioid but now variants of which are often produced in clandestine labs). All of these factors increase the risk for overdose since users have no way of assessing the potency of the drug before taking it and because in the case of fentanyl contamination, users typically have no opportunity to become tolerant.

There also has been a shift in the demographic of opioid users over the last few decades. In the 1960s, more than 80 percent of people who began using opioids initiated with heroin; in the 2000s, 75 percent of opioid users reported that their first regular opioid was a prescription pain reliever.^{xxii} It also has been reported that current heroin users are more likely to be white, middle-class, and live in more suburban and rural areas; this is consistent with the population of people who report the largest increases in non-medical use of opioid pain relievers over the last decade.^{xxi}

The transition from misusing prescription opioids to using heroin may be part of the natural progression of disease in a subset of users. Evidence from interviews with individuals with heroin use disorder suggest that market forces, including the accessibility, cost, and high potency of heroin are driving increased use of and transition from prescription opioids.^{xxii}, ^{xxiii} Some individuals who have developed dependence on prescription opioids, when faced with the increasing difficulty in obtaining these medications through their providers and the cost of obtaining them illegally, have initiated heroin use, which is cheaper and in some communities easier to obtain than prescription opioids.

In aggregate, these data suggest that preventing the initiation of prescription opioid misuse is a crucial component of efforts to prevent heroin use.

NIDA Efforts to Stem the Tide of Prescription Opioid and Heroin Abuse

NIDA first launched its prescription drug abuse public health initiative in 2001 using evidence-based strategies to (1) enhance our understanding of pain and its management; (2) prevent overdose deaths; and (3) effectively treat opioid use disorders.

Research on Pain and Next Generation Analgesics

Although opioid medications have a legitimate role in the treatment of acute pain and some chronic pain conditions, it is clear that they often are overprescribed or are prescribed without adequate safeguards and monitoring and that their misuse can have devastating effects. This presents a dilemma for healthcare providers who seek to relieve suffering while preventing drug abuse and addiction. As summarized in a recent report from the NIH Pain Consortium,^{xxiv} there is a pressing need for more research on the effectiveness and safety of using opioids to treat chronic pain as well as on optimal management and risk mitigation strategies. As noted, there are some patients for whom opioids are the best treatment for their chronic pain (*e.g.*, cancer-related pain). However, many other chronic pain patients are inappropriately prescribed opioid medications that may be ineffective or even harmful, often due to lack of adequate clinician education on pain management and screening for substance use disorder risk. This is partially the result of inadequate research on the best approaches to treat various types of pain, but it also is because clinicians may find prescribing opioids to be the easiest and least expensive course for addressing pain. The challenge is to identify the patients for whom opioids are the most appropriate treatment, to identify the best alternative treatments for those who are unlikely to benefit from opioids, and to define the best approach to ensuring that every patient's individual needs are met by a patient-centered health care system.

To better understand these issues, NIDA launched a research initiative on "Prescription Opioid Use and Abuse in the Treatment of Pain." This initiative encourages a multidisciplinary approach using both human and animal studies to examine factors that predispose or protect against opioid abuse and addiction. Funded grants cover clinical neurobiology, genetics, molecular biology, prevention, treatment, and services research. This type of information will help develop screening and diagnostic tools that physicians can use to assess the potential for prescription drug misuse in their patients.

Another important initiative pertains to the development of new approaches to treat pain. NIDA has initiated multiple strategic partnerships to advance development of medications for

pain, leveraging NIDA funds with the strengths and resources of outside organizations, including academic institutions, pharmaceutical and biotechnology companies, private and public foundations, and small businesses. This includes research to identify new pain medicines with reduced abuse, tolerance, and dependence risk, as well as devising alternative delivery systems and formulations for existing drugs that minimize diversion and non-medical use (*e.g.*, by preventing tampering) and reduce the risk of overdose deaths. For example, a partnership with Signature Therapeutics is working to develop an abuse deterrent formulation of oxycodone that uses prodrug technology—attaching an extension to the opioid molecule that renders it inactive if injected, snorted, or smoked; instead it must pass through the digestive system to begin the process of releasing the opioid. Early phase trials have supported safety, dose proportionality, and a clinically beneficial extended release profile.

In addition, new compounds are being developed that exhibit novel properties as a result of their combined activity on two different opioid receptors (*i.e.*, mu and delta). Preclinical studies show that these compounds can induce strong analgesia without producing tolerance or dependence.^{xxv} Researchers are also getting closer to developing a new generation of non-opioid-based medications for severe pain that would circumvent the brain reward pathways, thereby greatly reducing abuse potential. This includes compounds that work through a type of cannabinoid receptor found primarily in the peripheral nervous system.

Education is another critical component of any effort to curb the abuse of prescription medications and must target every segment of society, including healthcare providers (doctors, nurses, dentists, pharmacists). NIDA is advancing addiction awareness, prevention, and treatment in primary care practices through four Centers of Excellence for Physician Information. 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). NIDA also has developed, in partnership with the Office of National Drug Control Policy, two online continuing medical education courses on safe prescribing for pain and managing patients who abuse prescription opioids. To date, these courses have been completed by over 100,000 clinicians combined.

Developing More Effective Means for Preventing Overdose Deaths

The opioid overdose-reversal drug naloxone can rapidly restore normal respiration to a person who has stopped breathing as a result of overdose from heroin or prescription opioids. Naloxone is widely used by emergency medical personnel and some first responders. Beyond first responders, some communities have established overdose education and naloxone distribution programs that issue naloxone directly 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. CDC reported that, as of 2010, lay-distributed naloxone had resulted in more than 10,000 overdose reversals nationwide since 1996.^{xxvi}

For many years, naloxone was available only in an injectable formulation that was generally carried only by medical emergency personnel. However, FDA recently approved a new hand-held auto-injector of naloxone to reverse opioid overdose that is specifically designed to be given by family members or caregivers. NIDA and other agencies are working with the FDA and drug manufacturers to support the development and approval of a user-friendly intranasal formulation that would match the pharmacokinetics (*i.e.*, how much and how rapidly the drug gets into the body) of the injectable version. More market competition is expected to help bring down the cost of naloxone products.

Research on the Treatment of Opioid Addiction

There are a number of medications available for the treatment of opioid use disorders, both for patients in acute withdrawal and to support long term recovery. Medications have become an essential component of an ongoing treatment plan, enabling opioid-addicted persons to regain control of their health and their lives. Agonist medications developed to treat opioid addiction work through opioid receptors but are safer and less likely to produce the harmful behaviors that characterize addiction, because the rate at which they enter and leave the brain is slower. The three classes that have been developed to date include (1) agonists, *e.g.* methadone (Dolophine or Methadose), which activate opioid receptors; (2) partial agonists, *e.g.* buprenorphine (Subutex, Suboxone, Zubsolve), which also activate opioid receptors but produce a diminished response; and (3) antagonists, *e.g.* naltrexone (Vivitrol), which block the receptor and interfere with the rewarding effects of opioids. Physicians can select from these options on the basis of a patient's specific medical needs. The evidence strongly demonstrates that

methadone, buprenorphine, and injectable naltrexone (*e.g.*, Vivitrol), when administered in the context of an addiction treatment program, all effectively help maintain abstinence from other opioids, reduce opioid use disorder-related symptoms, and reduce the risk of infectious disease and crime.^{xxvii} 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,^{xxviii,xxix} found that:

- 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 opioid use; 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.^{xxx} 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 high when tapering off of these medications and treatment programs with an abstinence focus generally do not facilitate patients' long term, stable recovery. It is often the case that patients with good long-term outcomes are the ones who engaged in MAT although cycling in and out of treatment is not unusual in the path to a stable recovery.^{xxxi} Maintenance treatments have also been shown to be protective against injecting and overdose.^{xxxii, xxxiii}

Ongoing NIDA research is working to develop improved strategies for the implementation of these evidence-based interventions. This includes research to better

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

Conclusion

NIDA will continue its close collaborations with other Federal Agencies and community partners with a strong interest in preserving public health to address the ongoing challenge posed by abuse of prescription and non-prescription opioids in this country. We commend the Subcommittee for recognizing the serious and growing challenge associated with this exceedingly complex issue. Indeed, prescription opioids, like other prescribed medications, do present health risks but they are also powerful clinical tools for the treatment of pain. It is imperative that we strive to achieve a balanced approach to ensure that people suffering from pain can get the relief they need while minimizing the potential for negative consequences. We support the development and implementation of multipronged, evidence-based strategies that minimize the intrinsic risks of opioid medications and make effective, long term treatments more widely available.

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