National Institute on Drug Abuse (NIDA)

Heroin

Last Updated June 2018

https://www.drugabuse.gov

Table of Contents

Overview

Heroin is a highly addictive opioid drug, and its use has repercussions that extend far beyond the individual user. The medical and social consequences of drug use—such as hepatitis, HIV/AIDS, fetal effects, crime, violence, and disruptions in family, workplace, and educational environments—have a devastating impact on society and cost billions of dollars each year.

Although heroin use in the general population is rather low, the numbers of people starting to use heroin have been steadily rising since 2007.[1] This may be due in part to a shift from misuse of prescription pain relievers to heroin as a readily available, cheaper alternative[2-5] and the misperception that pure heroin is safer than less pure forms because it does not need to be injected.

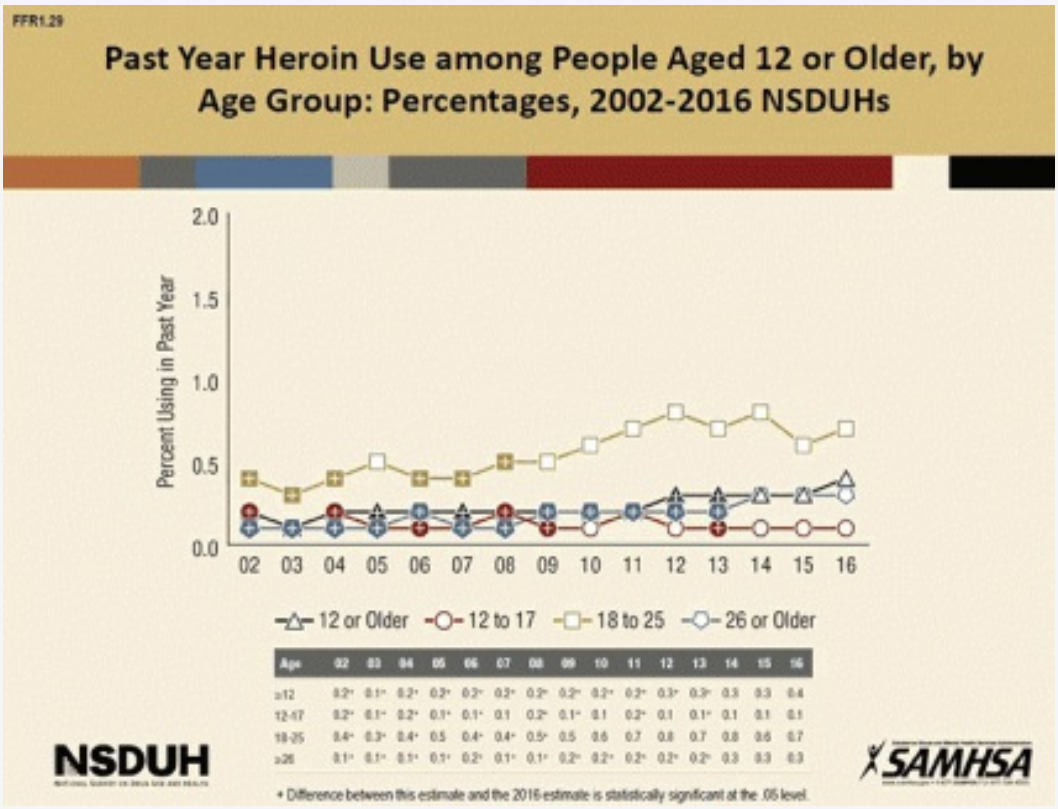
Like many other chronic diseases, substance use disorders can be treated. Medications are available to treat heroin use disorder while reducing drug cravings and withdrawal symptoms, thus improving the odds of achieving abstinence. There are now a variety of medications that can be tailored to a person's recovery needs while taking into account co-occurring health conditions. Medication combined with behavioral therapy is particularly effective, offering hope to individuals who suffer from substance use disorders and for those around them.

What is heroin and how is it used?

Heroin is an illegal, highly addictive drug processed from morphine, a naturally occurring substance extracted from the seed pod of certain varieties of poppy plants. It is typically sold as a white or brownish powder that is "cut" with sugars, starch, powdered milk, or quinine. Pure heroin is a white powder with a bitter taste that predominantly originates in South America and, to a lesser extent, from Southeast Asia, and dominates U.S. markets east of the Mississippi River.[3] Highly pure heroin can be snorted or smoked and may be more appealing to new users because it eliminates the stigma associated with injection drug use. "Black tar" heroin is sticky like roofing tar or hard like coal and is predominantly produced in Mexico and sold in U.S. areas west of the Mississippi River.[3] The dark color associated with black tar heroin results from crude processing methods that leave behind impurities. Impure heroin is usually dissolved, diluted, and injected into veins, muscles, or under the skin.

What is the scope of heroin use in the United States?

According to the National Survey on Drug Use and Health (NSDUH), in 2016 about 948,000 Americans reported using heroin in the past year,[1] a number that has been on the rise since 2007. This trend appears to be driven largely by young adults aged 18–25 among whom there have been the greatest increases. The number of people using heroin for the first time is high, with 170,000 people starting heroin use in 2016, nearly double the number of people in 2006 (90,000). In contrast, heroin use has been declining among teens aged 12–17. Past-year heroin use among the nation's 8th, 10th, and 12th graders is at its lowest levels since 1991, at less than 1 percent in each grade level.[6]



Source: National Survey on Drug Use and Health: Summary of National Findings, 2016.

It is no surprise that with heroin use on the rise, more people are

experiencing negative health effects that occur from repeated use. The number of people meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dependence or heroin use disorder increased dramatically from 214,000 in 2002 to 626,000 in 2016.[1] The fifth and the current version of the DSM, DSM-5, no longer separates substance abuse from dependence, but instead provides criteria for opioid use disorder that range from mild to severe, depending on the number of symptoms a person has.[7] Data on the scope and severity of opioid use disorder in the United States are not yet available for these new criteria.

Fentanyl

Fentanyl is a synthetic opioid that is 50 to 100 times more powerful than morphine. Recently, traces of fentanyl have been found in many other illegal drugs, including heroin. This is a public health concern because the strength of fentanyl makes overdosing more likely.

The impact of heroin use is felt all across the United States, with heroin being identified as the most or one of the most important drug use issues affecting several local regions from coast to coast. The rising harm associated with heroin use at the community level was presented in a report produced by the NIDA Community Epidemiology Work Group (CEWG). The CEWG is comprised of researchers from major metropolitan areas in the United States and selected foreign countries and provides community-level surveillance of drug use and its consequences to identify emerging trends.[3]

Heroin use no longer predominates solely in urban areas. Several suburban and rural communities near Chicago and St. Louis report increasing amounts of heroin seized by officials as well as increasing numbers of overdose deaths due to heroin use. Heroin use is also on the rise in many urban areas among young adults aged 18-25.[8] Individuals in this age group seeking treatment for heroin use

increased from 11 percent of total admissions in 2008 to 26 percent in the first half of 2012.

What effects does heroin have on the body?

The greatest increase in heroin use is seen in young adults aged 18-25.

Heroin binds to and activates specific receptors in the brain called mu-opioid receptors (MORs). Our bodies contain naturally occurring chemicals called neurotransmitters that bind to these receptors throughout the brain and body to regulate pain, hormone release, and feelings of well-being.[9] When MORs are activated in the reward center of the brain, they stimulate the release of the neurotransmitter dopamine, causing a reinforcement of drug taking behavior.[10] The consequences of activating opioid receptors with externally administered opioids such as heroin (versus naturally occurring chemicals within our bodies) depend on a variety of factors: how much is used, where in the brain or body it binds, how strongly it binds and for how long, how quickly it gets there, and what happens afterward.

What are the immediate (short-term) effects of heroin use?

Once heroin enters the brain, it is converted to morphine and binds rapidly to opioid receptors.[11] People who use heroin typically report feeling a surge of pleasurable sensation—a "rush." The intensity of the rush is a function of how much drug is taken and how rapidly the drug enters the brain and binds to the opioid receptors. With heroin, the rush is usually accompanied by a warm flushing of the skin, dry mouth, and a heavy feeling in the extremities. Nausea, vomiting, and severe itching may also occur. After the initial effects, users usually will be drowsy for several hours; mental function is clouded; heart function slows; and breathing is also severely slowed, sometimes enough to be life-threatening. Slowed breathing can also lead to coma and permanent brain damage.[12]

Opioids Act on Many Places in the Brain and Nervous System

- Opioids can depress breathing by changing neurochemical activity in the brain stem, where automatic body functions such as breathing and heart rate are controlled.
- Opioids can reinforce drug taking behavior by altering activity in the limbic system, which controls emotions.
- Opioids can block pain messages transmitted through the spinal cord from the body.

What are the long-term effects of heroin use?

Repeated heroin use changes the physical structure[13] and physiology of the brain, creating long-term imbalances in neuronal and hormonal systems that are not easily reversed.[14,15] Studies have shown some deterioration of the brain's white matter due to heroin use, which may affect decision-making abilities, the ability to regulate behavior, and responses to stressful situations.[16-18] Heroin also produces profound degrees of tolerance and physical dependence. Tolerance occurs when more and more of the drug is required to achieve the same effects. With physical dependence, the body adapts to the presence of the drug, and withdrawal symptoms occur if use is reduced abruptly.

Withdrawal may occur within a few hours after the last time the drug is taken. Symptoms of withdrawal include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps ("cold turkey"), and leg movements. Major withdrawal symptoms peak between 24–48 hours after the last dose of heroin and subside after about a week. However, some people have shown persistent withdrawal signs for many months. Finally, repeated heroin use often results in heroin use disorder—a chronic relapsing disease that goes beyond physical dependence and is characterized by uncontrollable drug-seeking, no matter the consequences.[19] Heroin is extremely addictive no matter how it is administered, although routes of administration that allow it to reach the brain the fastest (i.e., injection and smoking) increase the risk of developing heroin use disorder. Once a person has heroin use disorder, seeking and using the drug becomes their primary purpose in life.

How is heroin linked to prescription drug misuse?

Photo by ©istock.com/smartstock

Harmful health consequences resulting from the misuse of opioid medications that are prescribed for the treatment of pain, such as Oxycontin®, Vicodin®, and Demerol®, have dramatically increased in recent years. For example, almost half of all opioid deaths in the U.S. now involve a prescription opioid. People often assume prescription pain relievers are safer than illicit drugs because they are medically prescribed; however, when these drugs are taken for reasons or in ways or amounts not intended by a doctor, or taken by someone other than the person for whom they are prescribed, they can result in severe adverse health effects including substance use disorder, overdose, and death, especially when combined with other drugs or alcohol. Research now suggests that misuse of these medications may actually open the door to heroin use. Some also report switching to heroin because it is cheaper and easier to obtain than prescription opioids.[2-4]

What are the medical complications of chronic heroin use?

No matter how they ingest the drug, chronic heroin users experience a variety of medical complications, including insomnia and constipation. Lung complications (including various types of pneumonia and tuberculosis) may result from the poor health of the user as well as from heroin's effect of depressing respiration. Many experience mental disorders, such as depression and antisocial personality disorder. Men often experience sexual dysfunction and women's menstrual cycles often become irregular. There are also specific consequences associated with different routes of administration. For example, people who repeatedly snort heroin can damage the mucosal tissues in their noses as well as perforate the nasal septum (the tissue that separates the nasal passages).

Medical consequences of chronic injection use include scarred and/or collapsed veins, bacterial infections of the blood vessels and heart valves, abscesses (boils), and other soft-tissue infections. Many of the additives in street heroin may include substances that do not readily dissolve and result in clogging the blood vessels that lead to the lungs, liver, kidneys, or brain. This can cause infection or even death of small patches of cells in vital organs. Immune reactions to these or other contaminants can cause arthritis or other rheumatologic problems.

Sharing of injection equipment or fluids can lead to some of the most severe consequences of heroin use—infections with hepatitis B and C, HIV, and a host of other blood-borne viruses, which drug users can then pass on to their sexual partners and children.

Why does heroin use create special risk for contracting HIV/AIDS and hepatitis B and C?

Photo by ©istock.com/sjenner13

Heroin use increases the risk of being exposed to HIV, viral hepatitis, and other infectious agents through contact with infected blood or body fluids (e.g., semen, saliva) that results from the sharing of syringes and injection paraphernalia that have been used by infected individuals or through unprotected sexual contact with an infected person. Snorting or smoking does not eliminate the risk of infectious disease like hepatitis and HIV/AIDS because people under the influence of drugs still engage in risky sexual and other behaviors that can expose them to these diseases.

People who inject drugs (PWIDs) are the highest-risk group for

acquiring hepatitis C (HCV) infection and continue to drive the escalating HCV epidemic: Each PWID infected with HCV is likely to infect 20 other people.[21] Of the 30,500 new HCV infections occurring in the United States in 2014, most cases occurred among PWID.[22]

Hepatitis B (HBV) infection in PWIDs was reported to be as high as 25 percent in the United States in 2014,[22] which is particularly disheartening since an effective vaccine that protects against HBV infection is available. There is currently no vaccine available to protect against HCV infection.

Drug use, viral hepatitis and other infectious diseases, mental illnesses, social dysfunctions, and stigma are often co-occurring conditions that affect one another, creating more complex health challenges that require comprehensive treatment plans tailored to meet all of a patient's needs. For example, NIDA-funded research has found that substance use disorder treatment, along with HIV prevention and community-based outreach programs, can help people who use drugs change the behaviors that put them at risk for contracting HIV and other infectious diseases. They can reduce drug use and drug-related risk behaviors such as needle sharing and unsafe sexual practices and, in turn, reduce the risk of exposure to HIV/AIDS and other infectious diseases.

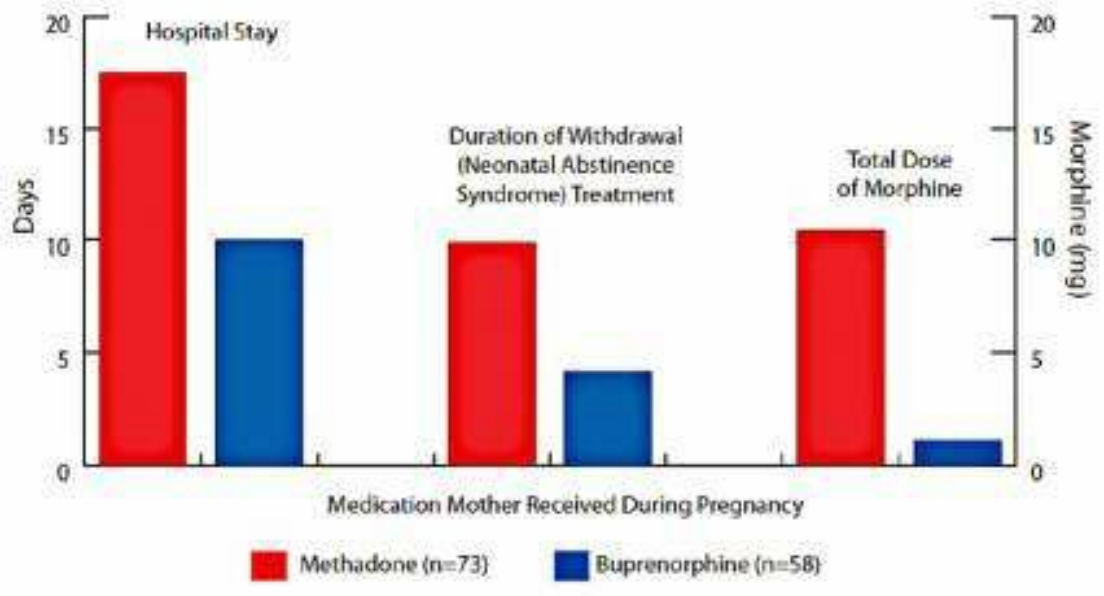
How does heroin use affect pregnant women?

Photo by morgueFile.com

Heroin use during pregnancy can result in neonatal abstinence syndrome (NAS). NAS occurs when heroin passes through the placenta to the fetus during pregnancy, causing the baby to become dependent, along with the mother. Symptoms include excessive crying, fever, irritability, seizures, slow weight gain, tremors, diarrhea, vomiting, and possibly death. NAS requires hospitalization and treatment with medication (often morphine) to relieve symptoms; the medication is gradually tapered off until the baby adjusts to being opioid-free. Methadone maintenance combined with prenatal care and a comprehensive drug treatment program can improve many of the outcomes associated with untreated heroin use for both the infant and mother, although infants exposed to methadone during pregnancy typically require treatment for NAS as well.

A NIDA-supported clinical trial demonstrated that buprenorphine treatment of opioid-dependent mothers is safe for both the unborn child and the mother. Once born, these infants require less morphine and shorter hospital stays compared to infants born of mothers on methadone maintenance treatment.[23] Research also indicates that buprenorphine combined with naloxone (compared to a morphine taper) is equally safe for treating babies born with NAS, further reducing side effects experienced by infants born to opioid-dependent mothers.[24,25] A NIDA-funded study found that treating NAS babies with sublingual buprenorphine resulted in a shorter duration of treatment than oral morphine, and also resulted in a shorter length of hospital stay, with similar rates of adverse events.[26]

Mothers' Buprenorphine Treatment During Pregnancy Benefits Infants



A NIDA-funded clinical trial[24] found buprenorphine to be a safe and effective alternative to methadone for treating opioid dependence during pregnancy. Buprenorphine was also found to be effective in reducing neonatal abstinence syndrome in newborns born to opioid-dependent mothers.

What can be done for a heroin overdose?

Overdose is a dangerous and deadly consequence of heroin use. A large dose of heroin depresses heart rate and breathing to such an extent that a user cannot survive without medical help. Naloxone (e.g., Narcan®) is an opioid receptor antagonist medication that can eliminate all signs of opioid intoxication to reverse an opioid overdose. It works by rapidly binding to opioid receptors, preventing heroin from activating them.[27] Because of the huge increase in overdose deaths from prescription opioid misuse, there has been greater demand for opioid overdose prevention services. Naloxone that can be used by nonmedical personnel has been shown to be cost-effective and save lives.[28] In April 2014, the U.S. Food and Drug Administration (FDA) approved a naloxone hand-held auto-injector called Evzio®, which rapidly delivers a single dose of naloxone into the muscle or under the skin, buying time until medical assistance can arrive. In 2015, the FDA approved a Narcan® nasal spray that is sprayed directly into one nostril. Since Evzio® and Narcan® can be used by family members or caregivers, it greatly expands access to naloxone.[29]

In addition, the Substance Abuse and Mental Health Services Administration (SAMHSA) continually updates its Opioid Overdose Prevention Toolkit that provides helpful information necessary to develop policies and practices to prevent opioid-related overdoses and deaths. The kit provides material tailored for first responders, treatment providers, and individuals recovering from an opioid overdose. Learn more about naloxone in NIDA's policy brief.

What are the treatments for heroin use disorder?

A variety of effective treatments are available for heroin use disorder, including both behavioral and pharmacological (medications). Both approaches help to restore a degree of normalcy to brain function and behavior, resulting in increased employment rates and lower risk of HIV and other diseases and criminal behavior. Although behavioral and pharmacologic treatments can be extremely useful when utilized alone, research shows that for many people, integrating both types of treatments is the most effective approach.

Photo by ©istock.com/megaflopp

Pharmacological Treatment (Medications)

Scientific research has established that pharmacological treatment of opioid use disorder increases retention in treatment programs and decreases drug use, infectious disease transmission, and criminal

activity.

When people addicted to opioids like heroin first quit, they undergo withdrawal symptoms (pain, diarrhea, nausea, and vomiting), which may be severe. Medications can be helpful in this detoxification stage to ease craving and other physical symptoms that can often prompt a person to relapse. The FDA approved lofexidine, a non-opioid medicine designed to reduce opioid withdrawal symptoms. While not a treatment for addiction itself, detoxification is a useful first step when it is followed by some form of evidence-based treatment.

Medications developed to treat opioid use disorders work through the same opioid receptors as the addictive drug, but are safer and less likely to produce the harmful behaviors that characterize a substance use disorder. Three types of medications include: (1) agonists, which activate opioid receptors; (2) partial agonists, which also activate opioid receptors but produce a smaller response; and (3) antagonists, which block the receptor and interfere with the rewarding effects of opioids. A particular medication is used based on a patient’s specific medical needs and other factors. Effective medications include:

- Methadone (Dolophine® or Methadose®) is a slow-acting opioid agonist. Methadone is taken orally so that it reaches the brain slowly, dampening the "high" that occurs with other routes of administration while preventing withdrawal symptoms. Methadone has been used since the 1960s to treat heroin use disorder and is still an excellent treatment option, particularly for patients who do not respond well to other medications. Methadone is only available through approved outpatient treatment programs, where it is dispensed to patients on a daily basis.
- Buprenorphine (Subutex®) is a partial opioid agonist. Buprenorphine relieves drug cravings without producing the "high" or dangerous side effects of other opioids. Suboxone® is a novel formulation of buprenorphine that is taken orally or sublingually and contains naloxone (an opioid antagonist) to prevent attempts to get high by injecting the medication. If a person with a heroin use disorder were

to inject Suboxone, the naloxone would induce withdrawal symptoms, which are averted when taken orally as prescribed. FDA approved buprenorphine in 2002, making it the first medication eligible to be prescribed by certified physicians through the Drug Addiction Treatment Act. This approval eliminates the need to visit specialized treatment clinics, thereby expanding access to treatment for many who need it. Additionally, the Comprehensive Addiction and Recovery Act (CARA), which was signed into law in July 2016, temporarily expands prescribing eligibility to prescribe buprenorphine-based drugs for medication-assisted treatment to qualifying nurse practitioners and physician assistant through October 1, 2021. In February 2013, FDA approved two generic forms of Suboxone, making this treatment option more affordable. The FDA approved a 6-month subdermal buprenorphine implant in May 2016 and a once-monthly buprenorphine injection in November 2017, which eliminates the treatment barrier of daily dosing.

- Naltrexone (Vivitrol®) is an opioid antagonist. Naltrexone blocks the action of opioids, is not addictive or sedating, and does not result in physical dependence; however, patients often have trouble complying with the treatment, and this has limited its effectiveness. In 2010, the injectable long-acting formulation of naltrexone (Vivitrol®) received FDA approval for a new indication for the prevention of relapse to opioid dependence following opioid detoxification. Administered once a month, Vivitrol® may improve compliance by eliminating the need for daily dosing.

Behavioral Therapies

The many effective behavioral treatments available for opioid use disorder can be delivered in outpatient and residential settings. Approaches such as contingency management and cognitive-behavioral therapy have been shown to effectively treat heroin use disorder, especially when applied in concert with medications. Contingency management uses a voucher-based system in which patients earn "points" based on negative drug tests, which they can exchange for items that encourage healthy living. Cognitive-behavioral therapy is designed to help modify the patient’s expectations and

behaviors related to drug use and to increase skills in coping with various life stressors. An important task is to match the best treatment approach to meet the particular needs of the patient.

Where can I get further information about heroin?

To learn more about heroin and other drugs of misuse, visit the NIDA Web site at **www.drugabuse.gov** or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

What's on the NIDA Web Site

- Information on drugs of misuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals
- Funding information (including program announcements and deadlines)
- International activities
- Links to related Web sites (access to Web sites of many other organizations in the field)

NIDA Web Sites

- www.drugabuse.gov
- www.teens.drugabuse.gov
- www.drugabuse.gov/drugs-abuse/heroin
- www.easyread.drugabuse.gov

Other Resources

Information on heroin and substance use disorders is also available through these other Web sites:

- Medication-Assisted Treatment for Opioid Addiction
- Prescription Drugs

References

1. Substance Abuse Center for Behavioral Health Statistics and Quality. Results from the 2016 National Survey on Drug Use and Health: Detailed Tables.
   SAMHSA. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.htm. Published September 7, 2017. Accessed March 7, 2018.

2. Cicero, T.J.; Ellis, M.S.; and Surratt, H.L. Effect of abuse-deterrent formulation of OxyContin. *N Engl J Med* 367(2):187–189, 2012.

3. National Institute on Drug Abuse. Epidemiologic Trends in Drug Abuse, in *Proceedings of the Community Epidemiology Work Group*, January 2012. Bethesda, MD: National Institute on Drug Abuse, 66.

4. Pollini, R.A.; Banta-Green, C.J.; Cuevas-Mota, J.; Metzner, M.; Teshale, E.; and Garfein, R.S. Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Subst Abuse Rehabil* 2(1):173–180, 2011.

5. Lankenau, S.E.; Teti, M.; Silva, K.; Jackson Bloom, J.; Harocopos, A.; and Treese, M. Initiation into prescription opioid misuse amongst young injection drug users.*Int J Drug Policy* 23(1):37–44, 2012.

6. Johnston, L.D.; Meich, R.A., O'Malley, P.M.; Bachman, J.G.; Schulenberg, J.E.; and Patrick, M.E. *Monitoring the Future National Results on Adolescent Drug Use: 1975-2017. Overview, Key Findings on Adolescent Drug Use.* Ann Arbor: Institute for Social Research, The University of Michigan. Available at: www.monitoringthefuture.org

7. American Psychiatric Association. *Substance-Related and Addictive Disorders, in Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Washington, DC: American Psychiatric Publishing, 540–550, 2013.

8. National Institute on Drug Abuse, Community Epidemiology Working Group. Epidemiologic Trends in Drug Abuse, in *Proceedings of the Community Epidemiology Work Group*, January 2014, Bethesda, MD:

National Institute on Drug Abuse. In preparation.

9. Waldhoer, M.; Bartlett, S.E.; and Whistler, J.L. Opioid receptors. *Annu Rev Biochem* 73: 953–990, 2004.

10. Johnson, S.W.; and North, R.A. Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J Neurosci* 12(2):483–488, 1992.

11. Goldstein, A. Heroin addiction: neurobiology, pharmacology, and policy. *J Psychoactive Drugs* 23(2):123–133, 1991.

12. National Library of Medicine. *Cerebral hypoxia*. Available at: https://medlineplus.gov/ency/article/001435.htm. Updated March 5, 2018. Accessed March 17, 2018.

13. Wang, X.; Li, B.; Zhou, X.; Liao, Y.; Tang, J.; Liu, T.; Hu, D.; and Hao, W. Changes in brain gray matter in abstinent heroin addicts. *Drug Alcohol Depend* 126(3):304–308, 2012.

14. Ignar, D.M.; and Kuhn, C.M. Effects of specific mu and kappa opiate tolerance and abstinence on hypothalamo-pituitary-adrenal axis secretion in the rat. *J Pharmacol Exp Ther* 255(3):1287–1295, 1990.

15. Kreek, M.J.; Ragunath, J.; Plevy, S.; Hamer, D.; Schneider, B.; and Hartman, N. ACTH, cortisol and beta-endorphin response to metyrapone testing during chronic methadone maintenance treatment in humans. *Neuropeptides* 5(1-3):277–278, 1984.

16. Li, W.; Li, Q.; Zhu, J.; Qin, Y.; Zheng, Y.; Chang, H.; Zhang, D.; Wang, H.; Wang, L.; Wang, Y.; Wang, W. White matter impairment in chronic heroin dependence: a quantitative DTI study. *Brain Res* 1531:58-64, 2013.

17. Qiu, Y.; Jiang, G.; Su, H.; Lv, X.; Zhang, X.; Tian, J.; Zhou, F. Progressive white matter microstructure damage in male chronic heroin dependent individuals: a DTI and TBSS study. *PLoS One* 8(5):e63212, 2013.

18. Liu, J.; Qin, W.; Yuan, K.; Li, J.; Wang, W.; Li, Q.; Wang, Y.; Sun, J.; von Deneen, K.M.; Liu, Y.; Tian, J. Interaction between dysfunctional connectivity at rest and heroin cues-induced brain responses in

male abstinent heroin-dependent individuals. *PLoS One* 6(10):e23098, 2011.

19. Kreek, M.J.; Levran, O.; Reed, B.; Schlussman, S.D.; Zhou, Y.; and Butelman, E.R. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. *J Clin Invest* 122(10):3387–3393, 2012.

20. Chen, L.H.; Hedegaard, H.; and Warner, M. QuickStats: Number of Deaths from Poisoning, Drug Poisoning, and Drug Poisoning Involving Opioid Analgesics - United States, 1999–2010. *Morbidity and Mortality Weekly Report* 234, 2013.

21. Magiorkinis, G.; Sypsa, V.; Magiorkinis, E.; Paraskevis, D.; Katsoulidou, A.; Belshaw, R.; Fraser, C.; Pybus, O.G.; and Hatzakis, A. Integrating phylodynamics and epidemiology to estimate transmission diversity in viral epidemics. *PLoS Comput Biol* 9(1):e1002876, 2013.

22. Centers for Disease Control and Prevention. *Surveillance for Viral Hepatitis - United States*, 2014. Atlanta, GA: Centers for Disease Control and Prevention, 2014.

23. Jones, H.E.; Kaltenbach, K.; Heil, S.H.; Stine, S.M.; Coyle, M.G.; Arria, A.M.; O'Grady, K.E.; Selby, P.; Martin, P.R.; and Fischer, G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 363(24):2320–2331, 2010.

24. Kraft, W.K.; Dysart, K.; Greenspan, J.S.; Gibson, E.; Kaltenbach, K.; and Ehrlich, M.E. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. *Addiction* 106(3):574–580, 2010.

25. Lund, I.O.; Fischer, G.; Welle-Strand, G.K.; O'Grady, K.E.; Debelak, K.; Morrone, W.R.; Jones, H.E. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. *Subst Abuse* 7:61–74, 2013.

26. Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome. N Engl J Med. 376(24):2341-2348, 2017.

27. Boyer, E.W. Management of opioid analgesic overdose. *N Engl J Med* 367(2):146–155, 2012.

28. Coffin, P.O.; and Sullivan, S.D. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann Intern Med* 158(1):1–9, 2013.

29. U.S. Food and Drug Administration. FDA approves new hand-held auto-injector to reverse opioid overdose. *FDA News Release*. April 3, 2014.