HEROIN USE DISORDER: THE EVOLVING ROLE OF THE PHARMACIST

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ACPE no. 0120-0000-16-031-H04-P
1.5 Contact Hour (.15 CEU's)
This is a knowledge based activity.
See the end of the article for CE details. Target Audience: Pharmacists
Faculty Disclosure: Faculty have no conflicts of interest to disclose

Goal:
To improve the pharmacist's awareness and knowledge of current heroin use in Indiana and detail treatment options for the management of heroin use disorder.

Learning Objectives:
Upon completion of this article the learner should be able to:

1. Summarize the current national and Indiana trends and prevalence of heroin use.
2. Describe the origin, history, and pharmacology of heroin.
3. Describe the routes of heroin administration and the risks associated with each route.
4. Identify signs and symptoms of heroin use disorder.
5. Detail long-term consequences of heroin use disorder.
6. Discuss treatment options for heroin use disorder.
7. Discuss the clinical presentation and acute management of a heroin overdose.

INTRODUCTION

The past several years have seen an increasing national trend in heroin use and abuse, with the Midwest suffering the highest increase in the rate of heroin-related deaths.[1] According to the Centers for Disease Control and Prevention (CDC), in 2011, over 4,000 Americans died from heroin overdose.[2] What is even more concerning is that the number of deaths has been rising each year, especially in adults between the ages of 25 and 44[1]; in 2013, 8,257 deaths were attributed to heroin, nearly double the number in 2011.[2] Between 2000 and 2013, the age-adjusted rate for heroin-related drug poisoning deaths increased almost 11-fold in the Midwest.[1] These are but a few of the reasons why pharmacists, particularly those practicing in the Midwest, should be aware of the signs and symptoms of heroin use and overdose and have an understanding of available treatment options. Furthermore, pharmacists should be able to

provide information to those who require assistance with heroin use disorder.

TRENDS AND PREVALENCE

National Statistics

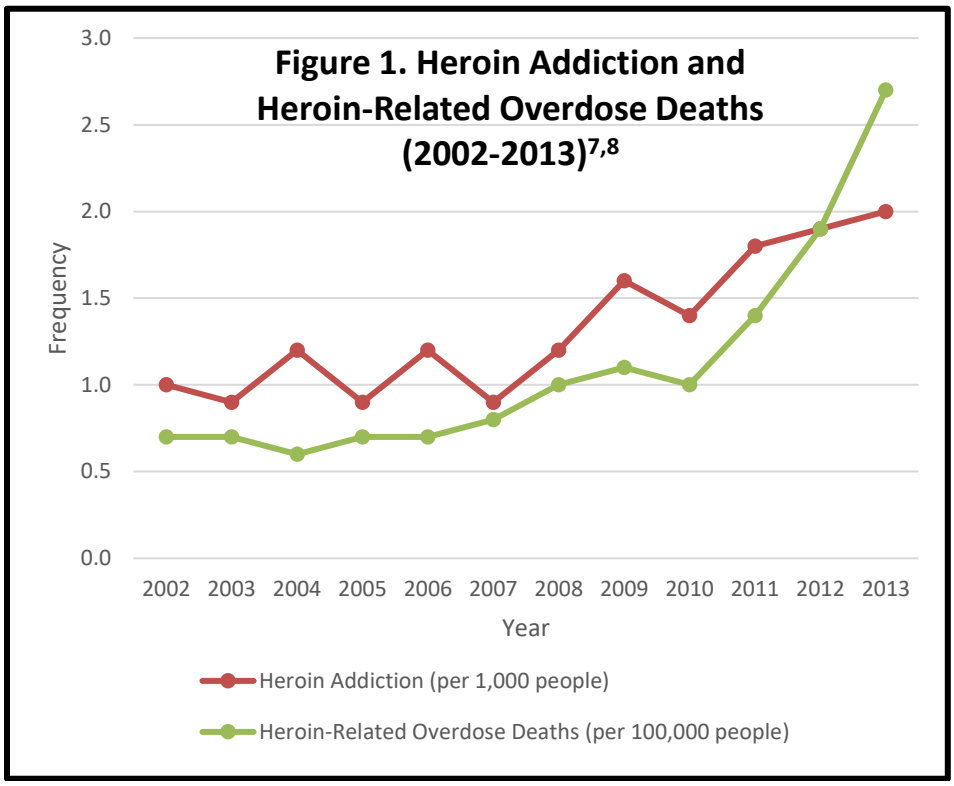
Heroin is a highly addictive opioid that is illegal and has no accepted medical use in the United States.[3] However, despite the many dangers associated with heroin, its use has increased in the nation's population. The National Survey on Drug Use and Health (NSDUH), which serves as the federal government's primary source of national and state data on the use of tobacco, alcohol, and illicit drugs (including non-medical use of prescription drugs), provides data in this regard.[4] For instance, NSDUH's *past year use* data shows that of Americans aged 12 years or older, 0.3% reported using heroin in 2013 (681,000 people) and in 2014 (914,000 people).[5] Similarly, *past month use* data of that population shows that 0.1% reported using heroin in 2013 (289,000 people), and 0.2% reported using the drug in 2014 (435,000 people). In comparison, 2014 *past year use* data shows that 13.2% of people aged 12 or older (35 million people) used marijuana, 3.9% (10 million people) used prescription opioids non-medically, and 1.7% (4 million people) used cocaine. Although the number of heroin users is lower than the number of users of other substances, use of heroin in 2014 was statistically significantly higher than in 2013 and also higher than one decade ago.

Furthermore, according to the Drug Enforcement Administration (DEA), the number of heroin users is increasing at a much faster rate than that of any other drug of abuse.[6] Indeed, heroin use in the United States increased 63% from 2002-2013; this increase occurred among a broad range of demographics, including males and females, most age groups, and all income levels.[7] Notably, according to the CDC, the following demographics are at an increased risk for heroin use: 18-25 year olds, non-Hispanic whites, those with an annual income less than $20,000, those living in a large metropolitan area, Medicaid recipients, and the uninsured.

Still more concerning results from 2014 showed that young adults (aged 18-25) were more likely to have used heroin in the past year, followed by adults (aged 26 or older) and adolescents (aged 12-17).[5] In the past decade, heroin use among young adults has more than doubled.[7] Additionally, heroin is often abused with other substances (e.g., marijuana, cocaine, alcohol, and prescription opioids) as about 90% of those who use heroin also abuse at least one other drug. Indeed, approximately 45% of those who use heroin are also addicted to prescription opioids.

As heroin use has increased, so too have heroin-related overdose deaths. From 2002-2013, the rate of heroin-related overdose deaths nearly quadrupled from 0.7 to 2.7 deaths per 100,000 population, with the increase nearly doubling from 2011-2013.[7] Although cocaine users outnumbered heroin users by a factor of five in 2013, heroin overdose deaths were almost twice those of cocaine.[6] Importantly, frequencies of heroin abuse or dependence are strongly positively correlated with rates of heroin-related overdose deaths (see Figure 1).[8] In 2013, an estimated 517,000 persons across the nation reported past-year heroin abuse or dependence, a nearly 150% increase since 2007. From 2011-2013, past-year heroin abuse or dependence was highest among those with past-year cocaine or prescription opioid abuse or dependence. According to the National Institute on Drug Abuse (NIDA), 23% of individuals who use heroin become dependent on it.[9]

The increase in prescription opioid use and rates of opioid addiction along with the increase in heroin supply appear to be driving the increase in heroin overdoses.[10] While the majority of prescription opioid users do not become heroin users, research shows that about 75% of new heroin users report having abused prescription opioids prior to using heroin; this is because heroin acts via the same receptors in the brain, often costs less than prescription opioids, and is increasingly available. Notably, based on law enforcement reporting, availability levels of heroin are highest in the Northeast and Midwest



areas of the United States.[6] In keeping with the increase in supply of the illicit drug, heroin seizure amounts in the United States have nearly doubled since 2010.

Indiana Statistics

Indiana State Police (ISP) report that troopers are extremely alarmed at the rate at which heroin is showing up on Hoosier streets.[11] In 2011, heroin was second only to marijuana in terms of purchases by undercover ISP officers. Analysis of ISP data indicates that heroin cases increased by 294% (from 354 to 1,396) from 2008-2013. As well, ISP drug enforcement data also shows an increase of 126% in heroin cases in 2014 as compared to 2010.[11,12]

Since 2010, the number of heroin-related deaths in Indiana has tripled.[11] Indeed, treatment providers in Indiana have reported a dramatic increase in clients seeking services for heroin addiction. The Treatment Episode Data Set (TEDS), which is maintained by the Center for Behavioral Health Statistics and Quality and includes records for approximately 1.5 million substance abuse treatment admissions annually, provides a significant amount of data related to such increases.[13] In 2014 (the most recent TEDS data for Indiana), substance abuse treatment admissions in the state totaled 25,676; of these, 12.3% (or 3,147 admissions) indicated heroin as the primary substance of abuse.[14] In comparison, 35% indicated alcohol (only or in combination) as the primary substance of abuse, 20.8% indicated marijuana as the primary substance of abuse, and 12% indicated opioids other than heroin as the primary substance of abuse. Of the treatment admissions in Indiana where heroin was the primary substance of abuse, 75.2% of the patients were in the 21-35 years age group, 88.7% were white, and 52.6% were male. According to George Fields, program director at Next Step Recovery Center in Terre Haute, Indiana, “heroin use among high school seniors in Indiana on a monthly basis is more than twice as high as the national rate” (0.8% versus 0.3%, respectively).[12]

Of Indiana's 92 counties, only 27 did not report any heroin cases to the ISP in 2013.[15] Unfortunately, it is difficult to explain why some counties in Indiana have more heroin cases than others, or to predict where heroin use might emerge next. In an August 2014 interview, Noel Houze, an ISP sergeant, stated, "We've seen heroin in almost every county [in Indiana], but it's primarily in those counties where the interstate runs through that we're finding it more and more. Heroin comes primarily from foreign countries, so it's going to be trafficked more on the interstate." In keeping with this information, the Indianapolis Metropolitan Police Department reported that Indianapolis is known as "the hub" for Mexican drug cartels due to the city's multiple intersecting interstates.[11] Indiana's heroin overdose rate rose 500% from 1999-2009 and by 2013, Indiana's overdose rate was the 16th highest in the nation. In 2014, Marion County reported 154 heroin overdose deaths.[16] Within a two-week period in early 2015, Tippecanoe County suffered seven heroin overdoses, of which five were fatal.

OVERVIEW OF HEROIN: ORIGIN, HISTORY, AND PHARMACOLOGY

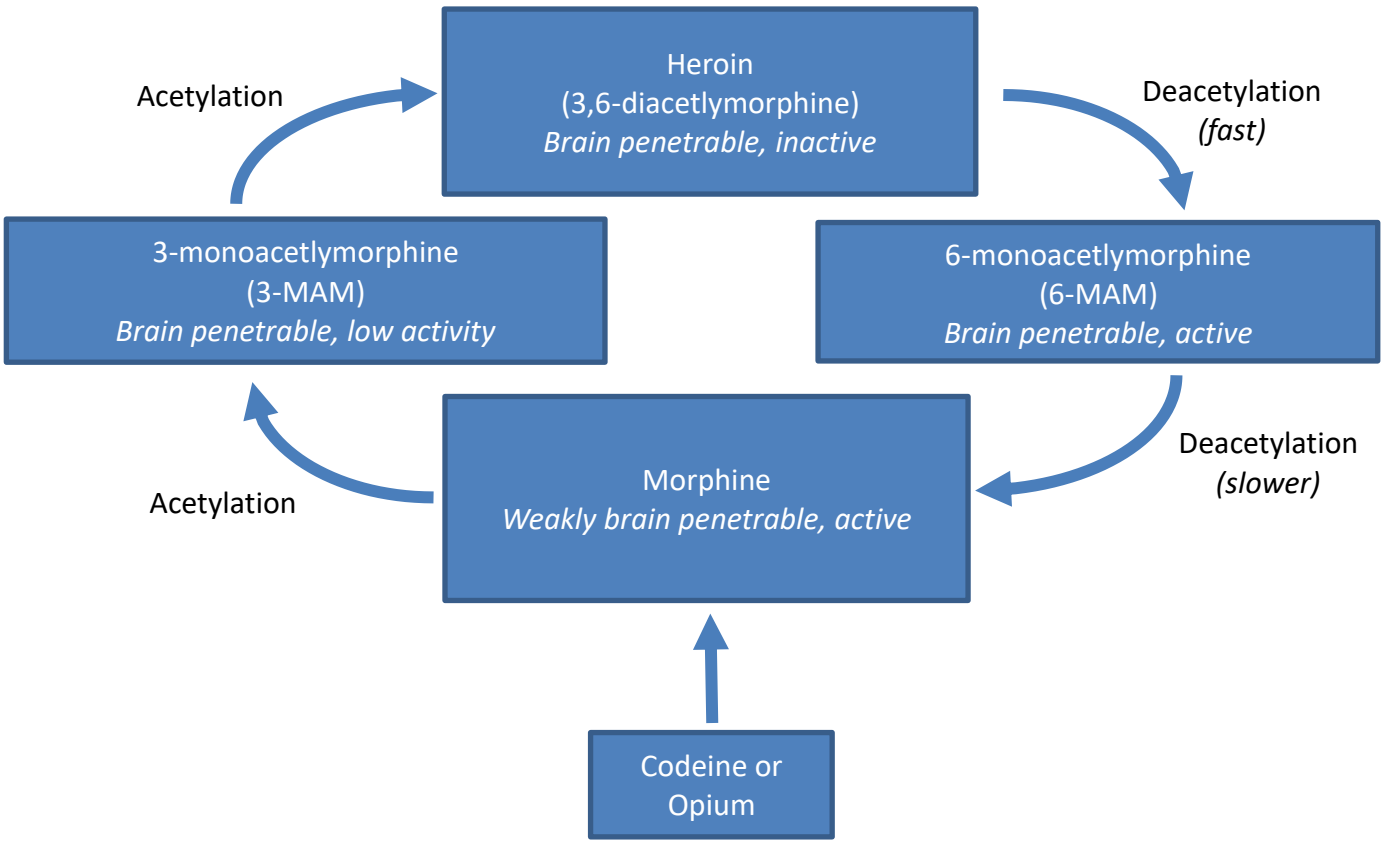
Heroin, also referred to by its chemical name of diacetylmorphine, was first synthesized in the second half of the 19th century from morphine using acetic anhydride.[17] As the more formal name implies, in order to obtain heroin, morphine must be acetylated twice; the first acetylation produces 3-monoacetylmorphine, or 3-MAM, and the second produces 3,6-diacetylmorphine, the classic white powder heroin[18], as illustrated in Figure 2.

Heroin itself is inactive and can be considered a prodrug.[19] The benefit for users of heroin over morphine lies in the increased lipophilicity of the illicit parent drug[20]; this is due to the fact that the acetyl groups on heroin are less polar than the hydroxyl groups on morphine, which allows heroin to cross the blood-brain barrier much more rapidly than morphine.[21] Once in the body, heroin has a half-life of 3 minutes in the blood and brain.[22,23,24,25] IV administration of heroin yields a half-life ranging from 1.3-7.8 minutes, on average.[26] It is rapidly deacetylated by serum and liver esterases to 6-monoacetylmorphine, or 6-MAM. 6-MAM is an active metabolite of heroin that can rapidly cross the blood-brain barrier and bind strongly to mu opioid receptors in the brain; the consequent activation of these receptors produces a characteristic sense of euphoria.[27,28] 6-MAM is further deacetylated back to morphine, which also strongly binds to and activates these same receptors to yield euphoric feelings.

Globally, heroin is produced in the following regions: Southeast Asia, Southwest Asia, Latin America, and South America.[29] Most heroin found in the United States comes from Mexico and Colombia. To produce the purest product, heroin "laboratories" aim to use acetic anhydride for the conversion of morphine to heroin.[17] However, due to increased regulation of acetic anhydride, this agent is not easily obtainable for these operations.[30,31] In acetic anhydride's place, such laboratories use glacial acetic acid or acetic chloride. When these replacement reactants are used, the conversion of morphine to heroin is much less efficient; the end product of such reactions contains large amounts of 3-MAM and 6-MAM and is commonly referred to as black tar heroin (more information on this form of the drug is provided below under "Routes and Risks of Heroin Administration").

Morphine, like acetic anhydride, is also highly regulated.[30,32] Because of this, morphine is sometimes produced from other drugs first. For example, codeine can be converted into morphine using pyridine hydrochloride. The entire process of producing heroin from codeine can be performed in a matter of hours.[30] As well, it should be noted that the opium plant itself contains not only codeine and morphine but also many other opiates.[33] While heroin can be produced directly from such opium extracts, this can result in more unwanted byproducts and impurities.[31]

Figure 2. Heroin Formation and Metabolism [17-19, 21-25, 27, 28, 30-33]



ROUTES AND RISKS OF HEROIN ADMINISTRATION

Heroin can be used via a variety of methods, including injection, inhalation, sniffing/snorting (insufflation), and smoking.[34] Each route of administration presents a myriad of risks and associated adverse effects. The various routes of administration also differ in their respective pharmacokinetic profiles as a consequence of the unique physiologic traits of each route.

The injection route of administration is a particularly prevalent and especially troubling method of using heroin for a number of reasons.[35] To start, "street" heroin can include all manner of impurities and additives that are not readily soluble in body fluids; as a result, these undissolved materials accumulate in users' bodies and can contribute to the obstruction of blood vessels servicing various organs, including the brain, liver, lungs, and kidneys. A particularly egregious example of this adulteration is the aforementioned black tar heroin, which is cheaper to manufacture than the typical white or brown powder variety. Black tar heroin is generally injected and can contain such additives as burned cornstarch, dirt, sugar, powdered milk, instant coffee, quinine, and dextrose.[34,35,36] Furthermore, the incorporation of these substances during the manufacturing process can lead to contamination of the product with bacterial spores.[35] As well, heroin laced with fentanyl, itself an opioid agonist that is 30 to 50 times more potent than the illicit heroin and up to 100 times more potent than morphine,

has become increasingly common across the United States; a significant rise in adverse incidents and overdose deaths related to fentanyl-laced heroin prompted the Drug Enforcement Administration to issue a nationwide alert in March 2015.[37]

Chronic injection, particularly of black tar heroin, can lead to issues such as abscesses, cellulitis, collapsed veins, and vascular sclerosis.[35] As users lose access to the intravenous (IV) route as a result of vein collapse and sclerosis, they often opt for the intramuscular (IM) or subcutaneous route instead, either of which can facilitate the development of potentially lethal necrotizing fasciitis.

The injection route also predisposes users to a variety of infectious diseases.[35] For example, users are vulnerable to endocarditis, usually on the right side of the heart, which can also involve the lungs. As well, intravenous use of heroin puts users at elevated risk for hepatitis A, B, and C. Hepatitis A is generally spread via the fecal-oral route, and is more prevalent in these individuals as a result of poor sanitation practices during the preparation process. In contrast, hepatitis B and C are transmitted among the injection drug user population mainly via the sharing of contaminated needles and other devices used to inject the illicit drug. Perhaps most worrisome of all is the transmission of Human Immunodeficiency Virus (HIV) in this population; as with hepatitis B and C, this virus is spread via sharing of contaminated needles and other related devices used for injection, but a related rise in unsafe sexual practices (including prostitution) also contributes to the elevated HIV risk in this group of individuals.

On February 25, 2015, state health officials announced the presence of an HIV outbreak in southeastern Indiana largely stemming from injection-based abuse of the powerful opioid analgesic oxymorphone.[38] On March 26, 2015, Governor Mike Pence declared a public health emergency in Scott County via executive order 15-05, which granted the county's local health officials additional much-needed resources to combat the virus's spread, as a result of the outbreak reaching epidemic levels; included as a part of this executive order was authorization for a temporary needle exchange program within Scott County only.[39] Similarly, Marion County has experienced a marked rise in new cases of both HIV (a 51% increase among people aged 20-24, and a 32% increase among the 25-34-year-old population) and hepatitis C (a 120% increase in the 20-24-year-old age group, and a 100% increase among 25-34-year-olds); this significant increase can be attributed to a heroin epidemic plaguing central Indiana, according to Marion County Health Department Chief Medical Officer Dr. Virginia Caine.[40] Of particular importance in light of this information, data from the Substance Abuse and Mental Health Services Administration (SAMHSA) indicate that injection was the preferred route of administration for 60-65% of national admissions to substance abuse treatment services for heroin use[41]; in combination with the aforementioned risks of IV drug use, this statistic is especially troubling for both Indiana pharmacists and pharmacists nationwide.

Intravenous injection of heroin provides users with an instantaneous, intensely pleasant, warm feeling termed the "flash"; this sensation is thought to be caused by the metabolite 6-MAM.[26] The intensity of the "flash" is believed to be related to the maximum concentrations of both this metabolite and the precursor heroin as well as to the rate of absorption of heroin into the circulation, hence its pronounced nature when the illicit opioid is administered intravenously. Notably, 6-MAM achieves its peak concentration in as little as 0.7-2.7 minutes following IV heroin administration. Compared to the IV route, IM heroin use yields notably smaller peak plasma concentrations but an extended period of circulation of heroin throughout the body; this is due to a sustained release of heroin into the bloodstream made possible by the fact that heroin is not metabolized quickly in muscle.

Relative to injection-based routes, the inhalation and smoking routes of administration represent a

smaller but still significant portion of the heroin-using population; according to SAMHSA data, inhalation was the preferred route of administration for 30-34% of heroin-related admissions to substance abuse treatment centers across the United States, while smoking and routes other than injection and inhalation accounted for 4-5% of these cases.[41] Whether heroin can be injected or smoked depends on its chemical state; heroin hydrochloride and black tar can be dissolved and injected. However, 'free base' heroin, is much harder to dissolve but has a lower boiling point, allowing this formulation to be smoked. This is similar to the difference between cocaine powder (hydrochloride salt that is injected) and crack cocaine (freebase that is smoked). Smoking heroin is also referred to as "chasing the dragon," a process in which the user places a lighter beneath a piece of aluminum foil containing heroin base and inhales the resulting vapors via a straw in his or her mouth.[26] While this technique yields plasma heroin peaks two to four times smaller than those of the IV route, it still provides the "flash" effect of marked euphoria found in IV users.

The inhalation and smoking routes of administration have their own associated risks and morbidities.[35] These can include shortness of breath, leukoencephalopathy, a reduction in pulmonary function, and the development of status asthmaticus. Users are also vulnerable to pneumonia as a consequence of heroin's adverse impact on proper lung function and their own overall poor health that results from significant substance use disorders.

Intranasal administration and inhalation into the lungs most closely approximate the pharmacokinetic profile of the IV route of administration, including the characteristic "flash".[26] Both of these routes yield high peak plasma concentrations of heroin and allow for rapid absorption rates owing to the high degree of perfusion of the nasal mucosa and the lungs. Furthermore, the lungs' alveolar-capillary beds provide a sizable surface area for absorption. These characteristics in combination with heroin's inherent lipophilicity and significant unionized fraction at physiological pH provide a pharmacokinetic basis for the use of the intranasal and inhalation routes for the self-administration of heroin. In addition, note that these routes of administration also bypass the liver's first-pass effect, allowing a greater percentage of intact heroin (and thus of its active metabolites) to exert their effects. The time to peak plasma concentration varies from 2-15 minutes when heroin is snorted or inhaled, with a half-life on par with the IV route.

SIGNS AND SYMPTOMS OF HEROIN USE DISORDER

The main active metabolites of the prodrug heroin (6-MAM and morphine) are mu opioid receptor agonists; as such, they mimic endogenous neurotransmitters that bind to these receptors and that are responsible for such effects as analgesia, sedation, euphoria, constipation, and respiratory depression.[42] The results of activating these receptors with exogenous compounds vary based on a number of factors, such as the amount used, the location of the bound receptors, and how quickly the compound reaches the receptors.

Heroin is converted to morphine once it enters the brain, where it then binds quickly to opioid receptors, thus yielding immediate effects, including the aforementioned "flash."[43] Along with the characteristic "high," users may also experience flushing of the skin, dry mouth, nausea, vomiting, and itching; all of these are similar to the effects observed upon administration of IV morphine. The user will also typically experience drowsiness along with slowing of mental function, heart function, and breathing; this respiratory depression can be life threatening[42], as discussed later.

As mentioned previously, the chronic use of heroin can impact the body in a variety of ways across multiple organ systems[42] (see Table 1 under "Reference Tables" for a broad summary of these physiological effects). In addition, changes in the physical structure and function of the brain itself are observed with repeated use of heroin; evidence of these changes is seen in possibly-irreversible abnormalities of neuronal

and hormonal systems and in deterioration of the brain's white matter. These changes may alter one's decision-making capabilities and ability to regulate behavior over the long term.

As well, tolerance and physical dependence are observed and expected in people who use heroin repeatedly. Tolerance occurs when "it takes a higher dose of the drug to achieve the same level of response achieved initially" [42,44]; this relative resistance to response can develop to not only heroin's beneficial effects but also to its adverse effects. Examples include analgesia, respiratory depression, euphoria, and mental slowing. Tolerance to constipation or miosis, however, is not observed for heroin users, similar to that seen with patients taking opioids for chronic pain. It should be further emphasized that mu opioid receptor tolerance as a result of chronic heroin use inherently also reduces the efficacy of therapeutic opioid analgesics in these individuals.[45,46]

Physical dependence develops as the neurons become accustomed to exposure to the drug and consequently function normally only in the substance's presence; in such a situation, if the drug is then withdrawn, physiological reactions occur.[42] Such withdrawal symptoms peak one to two days after the last dose of heroin and may last for a week or even months. See Table 1 in the "Reference Tables" section for a list comparing the immediate effects, risks of chronic use, and withdrawal symptoms associated with heroin use.

Tolerance and dependence are not synonymous with addiction, though continued use of heroin does frequently result in addiction.[42] Addiction is defined as "a chronic relapsing disease that goes beyond physical dependence and is characterized by uncontrollable drug-seeking no matter the consequences." In the updated fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) released in May 2013, substance abuse and substance dependence were combined into a diagnosis of substance use disorder.[44] Each substance is listed separately within the grouping, but most are evaluated by the same overall criteria. Mild substance abuse is defined as patients meeting two to three criteria; moderate substance abuse, four to five criteria; and severe substance abuse, six to seven criteria. See Table 2 under "Reference Tables" for a listing of the DSM-5 diagnostic criteria for opioid substance use disorder.

While the substances may be listed as separate diagnoses in DSM-5, many patients suffer use disorders of multiple substances.[47] Ninety-six percent of past-year heroin users report using at least one other drug, while 61% report using three different drugs.[48] Indeed, individuals addicted to alcohol, marijuana, cocaine, and prescription opioid analgesics are 2, 3, 15, and 40 times more likely to be addicted to heroin, respectively.[47] It is also critical to note that concomitant utilization of multiple drugs also increases the risk of overdose[48], which will be discussed in a later section.

TREATMENT OPTIONS FOR HEROIN USE DISORDER

Treatment for heroin use disorder includes behavioral therapies and pharmacological interventions; these treatments are more effective when administered in conjunction but may also be used alone.[49,50] Goals of therapy for use disorder treatment programs are as follows: to normalize brain function and behavior as much as possible, to minimize long term risks such as HIV and criminal behavior, and to maintain abstinence from heroin and/or other drugs of abuse. Heroin/opioid use disorder is a chronic relapsing condition and pharmacists should be understanding of this concept, and realize many patients will go through several rounds of relapse before reaching a prolonged period of abstinence. In the interim, pharmacists should consistently aim to reduce harm and risky behaviors and avoid judgement for those patients who have relapsed. Abstinence is a life-long struggle, and requires persistent awareness, treatment and management.

There are many effective behavioral therapies for heroin use disorder that may be administered in an outpatient setting. Two approaches that

have demonstrated efficacy in the treatment of heroin use disorder are contingency management and cognitive behavioral therapy.

Contingency management (CM) involves the administration of tangible rewards for abstinence; this makes use of the idea that behavior is molded by the consequences of one's actions.[51] For example, voucher-based reinforcement therapy (VBRT), a commonly used type of CM, utilizes the administration of vouchers for every drug-free sample provided; these vouchers have value and can be exchanged for goods or services that are consistent with a drug-free lifestyle, such as a movie ticket. The value of these vouchers is low at the beginning of therapy but increases as the number of drug-free samples increases.

A meta-analysis from 1970 through 2002 was performed to evaluate the use of CM for the treatment of substance disorders.[50] Seventy-five evaluations were included in this meta-analysis, the primary objective of which was to measure drug use. The study found that contingency management was an effective approach in promoting abstinence and is most effective in treating opiate and cocaine use. Of note, it was observed that the effect of CM declined over time; therefore, it may be more efficacious when used for shorter durations.

Prize incentive CM is another type of behavioral therapy similar to voucher-based reinforcement therapy.[51] Patients who supply negative drug samples are eligible to draw from a prize bowl and win cash rather than vouchers. As with VBRT, the prizes or number of chances to draw are smaller in the beginning and increase with the number of negative samples provided and counseling sessions attended. However, due to the comorbid nature of substance abuse and gambling, there was concern from practitioners that prize incentive CM would promote gambling in these patients. To that end, Petry and colleagues evaluated gambling behaviors before, during, and after participation in the study. [52] Stimulant users received 12 weeks of standard care with and without prize-based CM. No differences in gambling were observed between the groups, demonstrating that prize incentive CM does not worsen gambling behaviors.

Cognitive behavioral therapy (CBT), another option for the management of heroin use disorder, was initially utilized in patients with alcohol use disorder but was then expanded to include the use of cocaine and other drugs.[53] CBT focuses on learning processes, that is, patients learn to anticipate problems and to develop effective coping strategies. The primary features of this form of therapy are "an emphasis on the functional analysis of drug use" and "skills training"; examples include assessment of the pros and cons of continued drug use, early recognition of cravings, development of strategies for handling cravings, and avoidance of high-risk situations.[51,53]

There are two phases of treatment in patients with heroin use disorder – detoxification and maintenance. Detoxification may be done as an outpatient with medical supervision. Opioids and supportive medications, such as clonidine, nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, anti- emetics, and anti-diarrheals, may be used to control and reduce the severity of withdrawal. This is usually done when the patient is otherwise medically stable. It is timely to note here that loperamide, a mu opioid antagonist, is safe to use (at recommended doses) for heroin withdrawal induced diarrhea.[54] Recent reports to the FDA however, indicate that some individuals are abusing loperamide or using loperamide "extra-medically"[55] (i.e. more than the recommended dose) to alleviate withdrawal symptoms which has resulted in "serious cardiac adverse events" and death.[56] Therefore, on June 7, 2016, the FDA released a warning (safety announcement) about the adverse events (e.g., QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest) associated with higher than recommended doses of loperamide. Following this, on November 3, 2016, this warning was also incorporated into the product labeling.

Detoxification alone is not enough to maintain abstinence and should be combined with maintenance pharmacotherapy, which utilizes a prescribed opioid agonist or antagonist to replace the agent of abuse (such as heroin).[57,58] Options for such an intervention include buprenorphine, methadone, and naltrexone, which act to reduce cravings and block the effect of other illicit opioids.

Unlike opioids, such as morphine or oxycodone, buprenorphine is a partial agonist of the mu opioid receptors and a weak antagonist at kappa opioid receptors.[57,58] Thus, buprenorphine is a mixed opioid agonist-antagonist. Both mu and kappa receptors produce analgesia but are located in different areas of the central nervous system. As a partial mu agonist, buprenorphine does not activate mu receptors to the fullest extent as is the case for morphine or methadone. As such, buprenorphine does not have the same analgesic strength as morphine, and at the same time produces less euphoria. A patient abstaining from heroin use may find that buprenorphine reduce cravings for heroin and lessens withdrawal symptoms. It should be mentioned that withdrawal symptoms are still observed if buprenorphine is discontinued, but their onset is delayed due to the drug's prolonged duration of action; buprenorphine has an extended duration of action of up to 24 hours with multiple doses. Importantly though, as a potent partial agonist, buprenorphine acts as a functional antagonist in the presence of full agonists, that is, it will compete with full agonists such as morphine for the mu opioid receptor, particularly as it has a 25-40 higher preference to bind to mu opioid receptors. Thus, if buprenorphine is administered to or used by a person under the influence of heroin or other opioids, the drug will force this person into a relative state of opioid withdrawal. Of note, buprenorphine also causes the characteristic central nervous system (CNS) and respiratory depression common to the opioid analgesics, but the maximal extent of these effects is capped by its partial agonistic nature. Buprenorphine is available as a single agent and can still be abused as such; however, it is commonly prescribed as a combination product with naloxone called Suboxone®.[59,60] Naloxone is an opioid antagonist with the greatest affinity for the mu opioid receptor that is incorporated in this combination to serve as an abuse deterrent. Naloxone has poor oral bioavailability and thus will not be able to antagonize buprenorphine's effect when taken sublingually, as prescribed; however, if the combination of naloxone and buprenorphine is crushed and injected, naloxone will block mu opioid receptors and prevent buprenorphine from producing euphoria.

Methadone, another option for maintenance pharmacotherapy, is a mu receptor agonist and an opioid analgesic.[61,62] Its prolonged duration of action with repeated doses decreases the chances of abrupt withdrawal symptoms if methadone is stopped suddenly. However, methadone possesses rather complex kinetics, and it may cause QT interval prolongation and consequent arrhythmias. These are among the main reasons that have led some health care providers to prefer buprenorphine over methadone in treating substance use disorders.

Naltrexone is an opioid antagonist with approximately twice the potency of naloxone, a longer half-life, and excellent oral bioavailability.[63,64] It does not exert any opioid agonist activity and blocks the euphoric effects of opioids. Naltrexone, similar to naloxone, can also precipitate withdrawal symptoms if administered to patients actively taking or abusing opioid analgesics. To assist in management of heroin/opioid use disorders both naltrexone and buprenorphine are now available in long acting formulations (injectable implants).[65]

While there are a number of options for maintenance pharmacotherapy for heroin use disorder, access to buprenorphine, buprenorphine/naloxone, naltrexone, and methadone is significantly limited and highly regulated, making actually obtaining treatment a seemingly insurmountable obstacle for patients and health care providers seeking to refer their patients for such services. To that end, a presidential memorandum addressing heroin/opioid use disorder was released in

October 2015; among the strategies listed to help fight the epidemic was to double the number of physicians certified to prescribe buprenorphine over the next three years, thus increasing access to medication-assisted treatment of opioid substance use disorders.[66]

The treatment of substance use disorder with heroin or opioids is complex; it requires close monitoring, frequent follow-up, and the expertise of health care providers who are intimately familiar with the nuances of treatment. Comprehensive management programs include drug therapy in conjunction with behavioral therapy and offer the best chance at abstinence. For more detailed information regarding drug treatment options, the role of each drug in opioid use disorder, and legislation related to these issues, please see the Indiana Pharmacists Alliance online continuing education article titled "Opioid Addiction: Review of Current Legislation and Treatment Options," published in early 2015.[67]

CLINICAL PRESENTATION AND ACUTE MANAGEMENT OF HEROIN OVERDOSE

The clinical presentation of general opioid overdose often involves the "classic toxidrome of apnea, stupor, and miosis", although all three of these do not consistently appear in such cases.[68] Rather, the key indicator of opioid overdose is respiratory depression. In particular, a respiratory rate of ≤ 12 breaths/minute in an individual who is not in physiologic sleep is a powerful indicator of opioid overdose (especially when accompanied by stupor or miosis).

Patients presenting with an opioid overdose can also exhibit the following signs and symptoms (note that this is not an all-inclusive list):[68,69,70]

- Non-cardiogenic pulmonary edema
- Rhabdomyolysis, compartment syndrome, myoglobinuric renal failure (due to prolonged immobility associated with stupor)
- Hypoactive or absent bowel sounds
- Hypothermia (generally due to environmental exposure)
- Degrees of CNS depression ranging from drowsiness to coma
- Respiratory failure
- Aspiration pneumonitis
- Cyanosis
- Hypotension
- Bradycardia
- Seizures

Acute management of overdoses with opioids includes the use of the pure opioid antagonist naloxone (Narcan®, and the auto-injector form, Evzio®) and supportive care, particularly some form of airway and respiratory support.[59,68]

Naloxone, the aforementioned competitive mu opioid receptor antagonist, is the antidote utilized in cases of opioid overdose.[68] As a pure antagonist, naloxone does not impart any pharmacological effects of its own if opioids are not present in the body.[71] It is indicated for opioid overdose in combination with standard advanced cardiac life support protocols under the IV (preferred), IM, and subcutaneous routes of administration.[59] Naloxone can also be administered via the nebulized inhalation (adults only), intranasal (adults only), and intraosseous routes, although these are off-label. Evidence exists that the inhalation route is a viable alternative to parenteral routes should needleless administration be desired. Of all possible routes of administration, the endotracheal route is the least supported and desirable, backed only by anecdotal evidence. Evzio® is the single-dose auto-injector form of naloxone indicated for emergency treatment that is to be administered only via the IM or subcutaneous routes into the thigh's anterolateral aspect. Evzio® can be injected through clothing and is meant for "buddy administration," as reflected in the instructions printed directly on the device itself; the device's electronic voice instructions; and the red indicator light that confirms correct administration.

When given for opioid overdose, naloxone is dosed at an initial 0.4 – 2 mg IV, IM, or subcutaneously, with a repeat dose given every 2 – 3 minutes, as needed.[72] Because naloxone has a relatively short half-life and duration of action

(see Table 3 under the "Reference Tables" section for a summary of naloxone's pharmacokinetic parameters), administration of additional doses at a later time (e.g., 20 – 60 minutes) may be required to prevent new episodes of respiratory depression caused by opioid still present in the body. Naloxone's half-life is shorter than that of heroin, raising the possibility of recurrence of respiratory depression; however, experience in such cases reveals that while moderate sedation can arise within 20 – 30 minutes, a dangerous degree of hypoventilation is rare. Note that other sources of respiratory depression should be considered if the patient does not respond after the cumulative administration of 10 mg of naloxone.[59] However, it is important to keep in mind that higher doses may be required for successful reversal in overdose patients who were also using alcohol.[70] This point is particularly relevant within the context of heroin overdose as alcohol is the most common drug combined with heroin.[71] Indeed, many heroin overdoses (nonfatal and fatal alike) involve the simultaneous use of the illicit opioid with other drugs; chief among these are alcohol, benzodiazepines, and tricyclic antidepressants, all of which are associated with a higher risk for both nonfatal and fatal heroin overdose.

Adverse reactions to treatment with naloxone are the result of the immediate induction (precipitation) of withdrawal.[59] Symptoms of withdrawal are due to sympathetic excess secondary to catecholamine release, manifested as unmasked pain, irritability, diaphoresis, agitation, and hypertension, among others; while such reactions are uncomfortable, opioid withdrawal itself is not life-threatening. As well, opioid-tolerant patients often respond to low naloxone doses that successfully restore respiration without inciting withdrawal.[68] Importantly, as it is an antagonist, the medication does not have any intrinsic abuse potential.[71]

Naloxone has proven to be an indispensable tool in the acute management of heroin overdose in both the hospital and community settings. Between the years of 1996 and 2010, community-based overdose education with naloxone distribution (OEND) programs across the United States trained more than 50,000 individuals likely to be a bystander at a heroin overdose, which led to over 10,000 opioid overdose reversals as a result of naloxone administration.[73] The Chicago Recovery Alliance (CRA), one of the largest naloxone distribution programs, reported 319 heroin overdose reversals as of 2006, an effort that reversed an upwards trend in heroin overdoses since 1991.[74] A similar program in Baltimore, begun in April 2004, reported 131 overdose reversals as of March 2006. Other naloxone-based programs include a partnership of Project DOPE and the San Francisco Department of Public Health that reported 170 reversals as of 2006 and an initiative in New York City that reported 104 reversals as of 2006.

In Indiana, the use of naloxone in the setting of overdose prevention has been markedly expanded in recent years. Senate Enrolled Act 227 (termed the "lifeline law"), which became effective in March 2014, is an example of such a change.[75,76] This act allows the administration of "an overdose intervention drug to an individual who is suffering from an overdose" by advanced emergency medical technicians, an emergency medical responder, an emergency medical technician, a firefighter or volunteer firefighter, a law enforcement officer, or a paramedic; it also provides immunity against civil liability for these individuals for such an action (with the exception of "an act of gross negligence or willful misconduct"). This act also allows Indiana-licensed health care providers with prescriptive authority within their scope of practice to "write a prescription, drug order, or protocol for an overdose intervention drug" for the aforementioned parties (although this applies to fire departments, volunteer fire departments, and law enforcement agencies instead of firefighters, volunteer firefighters, and law enforcement officers, according to the language of the law). Likewise, Act 227 permits licensed pharmacists to "dispense a valid prescription, drug order, or protocol for an overdose intervention drug issued in the name of" the aforementioned individuals and entities. Records

indicate that law enforcement-administered naloxone saved at least 138 lives in the state as of June 1, 2015. A later bill, Senate Enrolled Act 406, expanded upon Act 227 in a number of ways, including allowing prescribers to write a standing order for an overdose intervention drug and pharmacists to dispense pursuant to that standing order.[77] This bill was signed into law on April 17, 2015.

In addition to the use of naloxone in its various forms, breathing assistance is a key facet of the acute management of a heroin overdose.[68] Stuporous patients presenting with a respiratory rate of ≤ 12 breaths/minute can be assisted with the chin-lift and jaw-thrust techniques as well as with a bag-valve mask. Orotracheal intubation is a potential option to restore ventilation while guarding against aspiration and is an alternative to naloxone administration as well as an option (in combination with positive-pressure ventilation) for patients with severe hypoxemia that does not respond to naloxone.

If rhabdomyolysis is present (shown by a creatine kinase concentration five times the upper limit of normal), fluid resuscitation should be initiated; this serves to avert the precipitation of myoglobin in the kidney tubules.[68] Hypothermia may necessitate rewarming as soon as possible, and patients presenting with the compartment syndrome (due to the unresponsive patient resting on a certain muscle compartment for an extended period of time) may require a fasciotomy.

Other approaches to combatting the scourge of heroin overdose have surfaced in recent years thanks to advances in pharmaceutics. For instance, the field of immunopharmacotherapy, which focuses on the production of antibodies against drugs of abuse, has given rise to the concept of a "dynamic" vaccine.[78] By allowing the immune system to recognize the metabolically-active portion of the so-called "opioid scaffold," this single vaccine component, in combination with an alum adjuvant, spurs the production of antibodies against not only heroin itself but also its active metabolites, morphine and 6-acetylmorphine; once bound by antibodies, these compounds can no longer cross the blood-brain barrier and thus can no longer exert their characteristic pharmacologic effects. Yet another approach to the problem of heroin overdose involves the use of Vivitrol®; this is an extended-release intramuscular form of the μ opioid receptor antagonist naltrexone, a relative of naloxone with a comparatively longer half-life.[79] By enclosing naltrexone in microspheres composed of a biodegradable polymer, this formulation of naltrexone can exert its effects over a longer period of time such that it need only be given once every 4 weeks; this is an important advancement as typical oral naltrexone therapy is plagued with low adherence rates. Furthermore, naltrexone itself is not metabolized via the cytochrome P450 (CYP) system, nor does it induce or inhibit major CYP isoenzymes, easing concerns of drug interactions.

CONCLUSION

In conclusion, there is much to learn and to know about the growing scourge of heroin and how to combat its short- and long-term effects. The problem of heroin use disorder is complex and multifaceted, and no single approach can address the issue in its entirety; only a combination of behavioral and pharmacotherapeutic interventions can effectively address the illicit opioid's effects on individual patients, with additional effort needed to remedy the substance's effects on communities across the nation. The authors of this work hope that its readers are now better equipped with the knowledge needed to grasp the problem of heroin use disorder and how it may best be treated. For completeness and future reference, a listing of heroin-related resources for the pharmacist is presented in Table 4.

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REFERENCE TABLES

Table 1. SUMMARY OF HEROIN'S PHYSIOLOGICAL IMPACT[34,35,36,42,44]

Immediate Effects	Risks of Chronic Use	Withdrawal Symptoms
Analgesia	Related to additives in heroin formulations – immune reactions causing arthritis or rheumatologic diseases, clogging of blood vessels leading to infarctions	Cold flashes, piloerection, sweating
Euphoria	Depression, antisocial behavior	Fever
Mental fog or clouded mental functioning	Liver and/or kidney disease	Insomnia, yawning, dysphoric mood
Slowed breathing, decreased heart rate	Lung – pneumonia, tuberculosis	Leg movements
Slurred speech	Related to route of administration – perforation of nasal septum, damage to nasal mucosa	Muscle or bone pain
Miosis	Reproductive changes – alterations in menstrual cycles, sexual dysfunction	Nausea or vomiting
Itching (pruritus)	Related to injections – abscesses, endocarditis, soft tissue infections, cellulitis, collapsed or scarred veins, bacteremia	Pupil dilation, lacrimation, rhinorrhea
	Sharing of injection paraphernalia – Hepatitis B and/or C, HIV, other blood borne infections	Restlessness
	Physical and psychological dependence	
	Opioid tolerance	
	Constipation	Diarrhea

Table 2. DIAGNOSTIC CRITERIA FOR OPIOID SUBSTANCE USE DISORDER[44]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    b. A markedly diminished effect with continued use of the same amount of an opioid
    c. **Note:** This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms
    c. **Note:** This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Mild substance use disorder: 2-3 criteria
Moderate substance use disorder: 4-5 criteria
Severe substance use disorder: 6-7 criteria

Table 3. NALOXONE PHARMACOKINETICS[59]

Onset of Action	IV: ~2 minutes IM, subcutaneous, endotracheal: 2 – 5 minutes Inhalation (nebulization): ~ 5 minutes Intranasal: ~8 – 13 minutes
Duration of Action	~30 – 120 minutes, depending on route IV duration is shorter than IM duration. Repeat doses are usually required.
Time to Peak	IM, subcutaneous (Evzio®): 15 minutes
Elimination Half-Life	Adults: 0.5 – 1.5 hours Neonates: 3 – 4 hours
Excretion Route	Urine (metabolites)

Table 4. HEROIN-RELATED RESOURCES FOR THE PHARMACIST	
Resource	**Notes**
National Institute on Drug Abuse (NIDA) (http://www.drugabuse.gov/drugs-abuse/heroin)	NIDA offers a number of resources related to various facets of the heroin epidemic, including information on statistics, trends, effects on users' bodies, and heroin's relation to the rise in prescription drug abuse.
Substance Abuse and Mental Health Services Administration (SAMHSA) (http://www.samhsa.gov/atod/opioids)	SAMHSA provides a compilation of data regarding substance use and abuse in the United States, including statistics on heroin use by age group and in association with comorbid mental health issues.
Indiana Family and Social Services Administration Division of Mental Health and Addiction (http://www.in.gov/fssa/dmha/index.htm)	This page is an excellent resource for pharmacists to recommend to heroin users who are seeking assistance with addiction and its numerous related issues. Answers to numerous common questions are also provided.
Behavioral Health Treatment Services Locator (https://findtreatment.samhsa.gov/)	SAMHSA's behavioral health treatment services locator allows pharmacists to suggest to heroin users nearby facilities dedicated to the treatment of addiction and other disorders.
Indiana Pharmacist Recovery Network (PRN) (http://www.prnindiana.com/)	PRN is an advocacy group for pharmacists who are currently impaired by or recovering from the use of alcohol or drugs. The organization collaborates with the Indiana Board of Pharmacy to oversee these pharmacists' recovery process and monitoring.
Indiana Region of Narcotics Anonymous (NA) (http://www.naindiana.org/home.php)	Indiana pharmacists can use the information on this site to direct heroin users to local meetings of Narcotics Anonymous, an organization that focuses on managing the disease of addiction in general.
Nar-Anon (http://www.nar-anon.org/)	Pharmacists can refer those affected by a heroin user's addiction (for example, friends or family members) to Nar-Anon; this organization seeks to empower these individuals to confront and overcome the unique challenges they face as a result of knowing an addicted individual.

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