

# Opioid Use Disorders



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## KEYWORDS

- Opioids • Opioid use disorder • Heroin • Injection • Prescription opioids
- Withdrawal • Overdose

## KEY POINTS

- The current epidemic of opioid use and addiction in adolescents and young adults is worsening, including heroin and nonmedical use of prescription opioids.
- Opioid use has devastating consequences for youth and their families, including: progression to full addiction, severe psychosocial impairment, hepatitis C virus and human immunodeficiency virus transmission with injection use, exacerbation of co-occurring psychiatric disorders, overdose, and death.
- Progression of opioid use disorders (OUDs) in youth often follows a characteristic pattern from use of diverted prescription opioid analgesics to sniffed or smoked heroin to injection heroin.
- Opioid overdose is a life-threatening emergency. Respiratory depression should be treated with naloxone, and respiratory support if necessary. Overdose should always be utilized as an opportunity to initiate addiction treatment.
- Opioid withdrawal management (detoxification) is often a necessary, but never sufficient, component of treatment for OUDs. Medications used in the treatment of withdrawal may include buprenorphine, clonidine, and others for relief of symptoms.
- Treatment for OUDs is effective, but treatment capacity is alarmingly limited and underdeveloped.
- Although there is a limited evidence base for youth-specific treatment, emerging consensus supports the incorporation of relapse prevention medications such as buprenorphine and extended-release naltrexone into comprehensive psychosocial treatment including counseling and family involvement.

## INTRODUCTION/BACKGROUND

The current epidemic of opioid use disorders (both diverted prescription opioids and heroin) in adolescents and young adults is a growing problem with devastating consequences for youth and their families. Progression from initiation to full addiction is

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common, and often accelerated compared with other substances. Severe psychosocial impairment includes criminal justice involvement, school dropout, unemployment, and co-occurring psychiatric disorders. Medical morbidity includes the well-known sequelae of injection drug use including hepatitis C virus (HCV), human immunodeficiency virus (HIV), injection site infections, and others. Worst of all is the catastrophic mortality associated with overdose, and nearly every community in the country has now unfortunately experienced this tragic loss of life in a young person with an opioid use disorder (OUD).

The term opioids encompasses a class of a large number of drugs, both natural alkaloid compounds derived directly from the resin of the opium poppy (termed opiates, including morphine and heroin), as well as related synthetic compounds (including oxycodone and hydromorphone.) All members of the opioid drug class share common pharmacologic features as agonists of the *mu* opioid receptor. Opioids are highly addictive, with rapid progression to physiologic dependence with tolerance and withdrawal. There is growing evidence to suggest a relationship between increased nonmedical use of prescription opioids and heroin use in the United States,<sup>1</sup> and a significant proportion of adolescents who start with prescription opioids go on to injection heroin use.<sup>2</sup> The progression of use often follows a pattern that maximizes drug bioavailability and effect: oral prescription opioids to inhaled prescription opioids to inhaled heroin to injection heroin. Inhalation can encompass either smoking (heating heroin in foil and inhaling the smoke) and nasal snorting (of the powdered heroin); whether a patient smokes or snorts appears to be mostly influenced by peers and regional variations, but neither method is as potent or efficient as injection, which maximizes bioavailability. This phenomenon is more prominent in adolescent than adult opioid users,<sup>3</sup> and accelerates more quickly with an earlier age of first opioid use. This progression is also related to heroin's lower cost and higher potency, because tolerance to opioids builds up rapidly in adolescents, and prescription opiates become prohibitively expensive with increased requirements for amounts of opioids as addiction advances.<sup>4</sup>

### ***Etiologic Factors***

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Though understanding remains limited, there is increasing knowledge of the multiple factors involved in the etiology of opioid use disorders as a particular class of substance use disorders (SUDs). OUDs share many features in common with addiction as a general process and with other SUDs, but there are several features that are specific to OUDs that may interact to influence vulnerability, progression, and course. These factors range over several domains, including pharmacology, genetics, environmental influences, developmental influences, and comorbidities.

Opioids are all enormously reinforcing, 1 feature of their specific pharmacologic properties. Positive reinforcement is largely mediated by the indirect downstream activation of dopamine receptors, one of the main final common pathways of reward. Although opioids produce somewhat less immediate dopamine release than stimulants, they rank high in the hierarchy of rewarding substances and produce higher levels of positive reinforcement in animal and human self-administration models than almost all substances other than stimulants, as a feature of the intrinsic properties of the opioid receptor. Also prominent and perhaps even more clinically significant in chronic OUDs is the typical negative reinforcement produced by opioid withdrawal once physiologic dependence has occurred. Although the onset of withdrawal following opioid discontinuation varies with the half-life of the particular opioid, it produces a characteristic physiologic syndrome with even brief abstinence or even delay of dosing. Steady exposure to opioids can produce this process of neuroadaptation

leading to physiologic dependence and withdrawal within as little as 4 to 8 weeks in opioid-naïve individuals, and much faster with reinstatement after relapse in those with prior dependence. Opioid withdrawal includes activation of the locus ceruleus region of the brain with increased systemic sympathetic tone, leading to its characteristic features (including chills, diarrhea, nausea, cramps, and anxiety), accompanied by high intensity cravings.

Approximately 40% to 60% of the vulnerability to any addiction is attributable to genetic factors.<sup>5-7</sup> Broad population twin studies<sup>8</sup> generally suggest that genetic factors have the strongest influence as a common vulnerability to SUDs in general rather than to phenotypic expression of vulnerability to or preference for any specific individual substance. On the other hand, with more advanced genetic techniques, several specific loci have been associated specifically with opioid use and OUDs, with moderate opioid-specific heritable vulnerability. Specific allelic variants have been identified that seem to confer risk, in various genes including those coding for dopamine receptors and the dopamine transporter, opioid receptors, opioid neuropeptides, serotonin receptors and the serotonin transporter, and cannabinoid receptors.<sup>9,10</sup> For example, polymorphisms in the gene for the *mu*-opioid receptor (OPRM1) have been variably linked to differences in binding affinity and signaling efficiency, increased basal cortisol levels and opioid-mediated dynamic cortisol response, and differential analgesic effects of morphine; additionally, some studies have found associations between these allelic variations and rates of opioid dependence, although others have not.<sup>10</sup>

As with genetic factors, environmental factors have strong influence as common factors increasing vulnerability broadly to SUDs. Typical risk factors such as stress, adversity, and exposure to substance use in family and peers tend to increase risk for all substances rather than to opioid use or preference specifically. But, in addition, there are certainly unique environmental influences that differentially increase the risk of OUDs specifically. Such influences include: exposure to opioids as a specific class of substance, most importantly nonmedical use; exposure to medical opioid analgesics; use of opioids by family, peers, and other influential role models; permissive attitudes toward opioid use by influential role models; and access to opioids as a specific substance class.

Access is a particularly important environmental risk factor. The issue of ease of access, both for prescription opioids and for heroin, has been important in the genesis of the current epidemic. With increasing trends in medical prescribing of opioid analgesics over the past 2 decades, the overall US supply of prescription opioids has expanded greatly, with nonmedical diversion an unintended (but perhaps predictable) consequence. From 1999 to 2010, the per capita kilogram sales of prescribed opioid analgesics quadrupled. This trend parallels the concurrent curves of increasing per capita opioid treatment admissions and per capita opioid overdose deaths.<sup>11</sup> And while large increases in prescribing of opioid analgesics have mostly been a phenomenon of adult medical practice, the trend has emerged to a lesser extent in pediatric practice as well.<sup>12</sup> Heroin access has been promoted by increasingly plentiful and cheaper supplies. As with all substances, youth are particularly price-sensitive in their substance use behaviors, often more so than adults.<sup>13,14</sup>

Although prescription opioid use has a 10-fold greater prevalence than heroin among youth, it also fuels heroin use as a gateway of entry. Although the cost of prescription opioids on the street remains high,<sup>15</sup> the cost of heroin has declined,<sup>16</sup> and its purity has increased dramatically in recent years.<sup>17</sup> This makes heroin a more economical alternative to prescription opioids, based both on price and potency (cheaper and better), once opioid addiction has become established.

Increasing purity has also promoted heroin use among youth in another way. Four decades ago, the low purity of available heroin meant that injection use was required to produce meaningful intoxication, and the need for injection has always been a major barrier to initiation of heroin use for youth. But over the past 2 to 3 decades, as heroin purity in street supplies has increased, often exceeding 60% purity, nasal use or smoking is now an efficient route of administration, and a young person can initiate and become addicted to heroin without injection use. Once heroin addiction is established, presumably, the hurdle to injection is less of a barrier.<sup>18</sup>

More recently, efforts to limit the supply of prescription opioids have started to succeed, through various means, including medical education about opioid analgesic prescribing, law enforcement interdiction of pill mills, use of prescription drug monitoring plans, and others. But as the availability of prescription opioids decreases and the street price of pills goes up, there is concern that there may be a corresponding shift toward heroin use. It is hoped that the trend toward less prescription opioid availability will help bring down both initial use of opioids and therefore overall rates of opioid use disorder, but it is also possible that more adolescents may start using heroin earlier after having initiated opioids through prescription opioids, or even using heroin as their first opioid.<sup>19</sup>

Developmental vulnerabilities and comorbid psychiatric disorders are additional factors that confer considerable risk for all SUDs. Examples include problems with affective regulation, depression, anxiety, excitement seeking, extreme extroversion, impulsivity, cognitive impairment, and problems with executive control. As far as anyone knows, like the common environmental and genetic vulnerability factors shared by all SUDs, these tend mostly to increase risk for all substances rather than for opioid use or preference specifically. Both co-occurring psychiatric disorders and deviation from normal developmental trajectory seem to worsen with increasing severity and chronicity of overall SUDs, and vice versa, with reciprocal worsening of course. For some, if unchecked, this progression may lead to opioid addiction. In this context, OUDs may be seen as a more advanced stage of a general progression of SUDs along a continuum. Some have hypothesized that there may be an inexact dose–response relationship for some of these shared factors, making OUDs more likely with increased cumulative risk burden as a more severe form of the more general disorder.

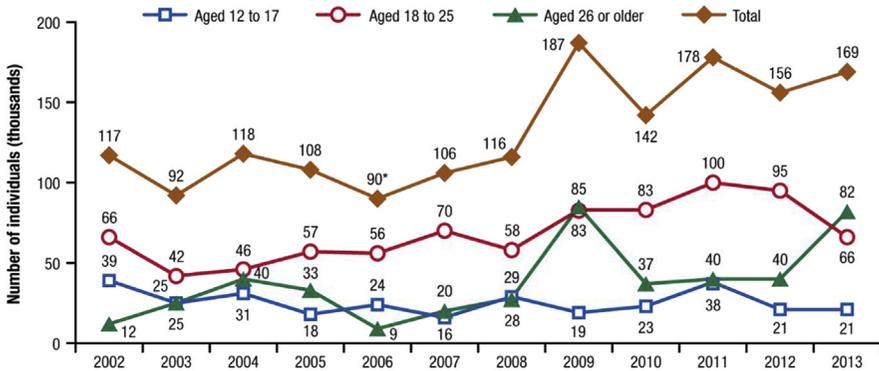
## EPIDEMIOLOGY

The nonmedical use of opioids in the general population is a growing public health and social concern across the entire lifespan.<sup>1</sup> In the United States, the number of people age 12 and older using prescription opioids more than doubled between 1975 and 2008, from 3.5% to over 9%,<sup>2</sup> while the prevalence of marijuana and alcohol abuse decreased or plateaued.<sup>3</sup> In 2009, 2.2 million Americans aged 12 years or older used prescription opioids as their first illicit drug, second only to marijuana.<sup>20</sup> In 2013, there were 169,000 persons aged 12 or older who used heroin for the first time (Fig. 1).<sup>21</sup>

### Age

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The involvement of youth in the current opioid epidemic is increasing, with alarming impact. In 2011, 8.7% of 12th graders used prescription opioids illegally during the previous year.<sup>22</sup> Another study estimated 13% of high school seniors have a lifetime prevalence of nonmedical use of prescription opioids.<sup>23</sup> In 2009, approximately 250,000 US high school students (1.2%) reported having used heroin at least once,



**Fig. 1.** Past-year initiation of heroin among individuals aged 12 or older, by age group: 2002 to 2013. (From Lipari RN, Hughes A. The NSDUH report: trends in heroin use in the United States: 2002 to 2013. The CBHSQ Report. Rockville (MD): Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality; 2015.)

and 77,000 Americans aged 18 to 20 years reported using heroin in the previous year, up from 56,000 in 2008.<sup>20</sup> Across the lifespan, the group with the highest prevalence of both prescription opioid and heroin use, as well as the greatest increases in heroin use, is young adults ages 18 to 25. While the number of users is increasing, the age of first use is decreasing.<sup>24</sup> In 2013, 12.5% of new illegal drug users began with prescription opioids.<sup>25</sup> Although the most recent SAMHSA (Substance Abuse and Mental Health Services Administration) report (2014–2015) shows some encouraging evidence that the rate of prescription opioid use among youths may be declining,<sup>26</sup> other studies have found that more adolescents are starting heroin use at a much younger age.<sup>27</sup>

Age of onset of opioid use is an important clinical epidemiologic indicator and a robust marker of risk and clinical severity. Age of first use is correlated with the lifetime risk of OUDs,<sup>28,29</sup> and earlier age of onset of opioid use is associated with a higher prevalence of dependence, increasing clinical severity, and worsening consequences. Adolescents who are primarily abusing opioids have an earlier age of onset of any substance use compared with those who are currently using marijuana or alcohol (average age 11.7 vs 12.6).<sup>30</sup> The age of onset of opioid use for those who have opioids as their first illicit drug is much earlier compared with those who switch from other substances to opioids.<sup>25,31,32</sup> Heroin users have first substance use much earlier than those who use nonheroin opioids.<sup>33</sup> Adolescents with earlier onset of prescription opioid or heroin use also have a more rapid progression from noninjection to injection heroin use.<sup>15,30,34,35</sup> The strongest predictor for progression to regular heroin use is earlier initial heroin use, while age of initial use of any opioid, and age of regular use of other substances drugs (alcohol, marijuana) are also strong risk factors.<sup>36</sup>

### Gender and Race

Contrary to the popular historic misconception of America's heroin problem being restricted to minorities and the disadvantaged inner city, youth opioid dependence, especially prescription opioid dependence, is a problem of a much broader demographic, including suburbia and higher socioeconomic groups. The prevalence of opioid addiction is highest in white males.<sup>37</sup> The socioeconomic status of youth initiating opioid use has increased over time. More male than female adolescents enter

treatment for heroin use, but compared with other SUDs, the representation of females among treatment-seeking youth is much closer to even with males.<sup>15,28,33</sup> Among females seeking treatment for SUDs, there is a higher rate of heroin as their primary substance of use compared with boys.<sup>38</sup> Girls with heroin addiction are more likely to prefer injection use than boys<sup>39</sup> and are also more likely to initiate injection heroin use at a relatively younger age compared with boys. In fact, girls often initiate injection heroin use within a year from their first illicit drug use, a faster rate of progression to injection use than boys.<sup>40</sup> Possible explanations include influence of a romantic partner (often an older male intravenous drug user), having a history of victimization/ongoing victimization, gender-specific personality traits, and a rapid development of tolerance to opioids.

### ***Injection Use***

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Injection heroin use is the more advanced and usually later stage of OUDs. Typically, inhaled (smoked or snorted) heroin is a precursor to injection heroin use.<sup>41</sup> There are varying estimates of the proportion of adolescents with any form of opioid addiction who transition to injection heroin use, ranging from 40% to 90%.<sup>2,32</sup> Almost 70% of young heroin users (aged 18–25 years) eventually transition from nasal to injection heroin,<sup>42</sup> and almost half of adolescents with current heroin addiction are injection heroin users.<sup>17,43</sup> Among patients seeking treatment for heroin addiction, the percentage of injection heroin use is even higher (62%–83%).<sup>15,30,33</sup> Sociodemographic factors associated with injection heroin use include poverty or unemployment, homelessness,<sup>37</sup> and history of childhood adversities.<sup>44–47</sup>

### ***Morbidity and Mortality***

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Morbidity and mortality related to opioid use have also escalated; in 2013 there were 16,000 deaths from prescription opioids, a 2.5-fold increase since 2001, and there were 8000 deaths from heroin, a 5-fold increase over that same period.<sup>48</sup> One hundred people die from a drug overdose every day in the United States; approximately one half of these are from prescription opioids and approximately one-fifth from heroin. Additionally, drug overdoses have surpassed motor vehicle crashes as the country's leading accidental cause of death.<sup>49</sup> Prescription opioids account for nearly 75% of prescription drug overdoses, and the mortality as a result of opioid overdose has surpassed all other forms of drug poisoning death in the United States.<sup>50,51</sup> From 2004 to 2008, more than half of all drug-related medical emergencies and emergency department (ED) visits were due to heroin and opiates, and during the same period, ED visits involving the nonmedical use of opioids more than doubled.<sup>52</sup> Opioids have been among the most common drugs used in suicide attempts in recent years.<sup>53</sup> The prevalence of HCV in young opioid users is particularly worrisome: in an opioid treatment trial of 16- to 21-year olds, 18% were HCV positive at baseline despite only 1.5 years of opioid dependence, with an additional 5% seroconverted at 12 weeks.<sup>54</sup>

## **CLINICAL PRESENTATION AND COURSE**

Opioid use disorder in an adolescent presents in many ways: from falling grades and breaking curfew, to legal involvement, to the worst case scenario—near fatal or even fatal overdose. Death does not require dependence: too many families only learn of their child's opioid use when the coroner reports the cause of their child's death, and an adolescent can overdose the very first time he or she tries opioids. One unusual feature of opioids is their ready availability; an adolescent does not need to know a drug dealer. Prescription opiates are easily found in medicine cabinets, on kitchen

counters, and in handbags. An adolescent's opioid use may become known after some crisis like arrest, job loss or school expulsion. Most adolescents know about dependence and withdrawal but many falsely believe that prescription opiates are not addictive, often reasoning that a doctor would never prescribe an addictive drug. And among heroin users, there is the myth that only intravenous heroin is addictive, and nasal/smoked heroin is safe. Adolescents who think they are using opioids recreationally are surprised when they experience withdrawal symptoms, and may attribute their opiate withdrawal symptoms to stress, viral illness, or food poisoning. Families may discover their adolescent is opioid dependent when he or she loses access to opioids (being broke, being locked up, or even going on vacation) and goes into withdrawal.

Adolescents can progress from first use to full-blown dependence in months with a course of use that is often shorter than in adults. In general, the development of opioid dependence mirrors other drug dependencies, and possible warning signs may include changes in peer group; decreasing involvement in social/leisure activities; isolation from family/old friends; mood changes such as irritability, depression, anger, and increased frequency of negative behaviors like truancy, lying, running away, stealing, and trouble with the police. As with other SUDs, tolerance develops, and the adolescent needs escalating opioid doses, which increases the risk of overdose and death because of reduced tolerance to respiratory depression.

Addiction to opioids can be conceptualized as the most complex and advanced stage of SUD,<sup>28,34</sup> with the most severe health and social consequences. Adolescents with OUDs generally have higher severity of impairment than those with nonopioid SUDs, including larger amount of substances used, greater number of days of substance use, greater extent of polysubstance use, greater psychopathology and higher rates of co-occurring psychiatric disorders, higher rates of lifetime victimization, and higher rates of criminality.<sup>4,18,27,32,35,40,55,56</sup> And as with adults, youth with heroin use have higher severity than those with prescription opioid use only, including higher rates of high school dropout; more severe psychiatric symptoms including higher rates of depression, suicide attempts, and more history of psychiatric treatment/hospitalizations; more concurrent cocaine use, and more risky sexual behaviors, prostitution, and indiscriminate sex with strangers.<sup>2</sup> Mirroring their rapid development of dependence, adolescents and young adults with opioid addiction often have a more rapid deterioration in life circumstances, which in turn presents extreme barriers to treatment engagement and recovery, entrapping them in a vicious spiral of worsening addiction severity.<sup>39</sup>

## ASSESSMENT AND DIAGNOSIS

A complete assessment for an opioid use disorder requires a thorough medical and social history, in particular gathering information on: education, vocation, family, mental health, living arrangements/family structure and support, social service agency or legal involvement, peers, sex, and use of other drugs. As with other SUDs, opioid use disorder in the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) is a diagnosis across a continuum from mild to severe according to the number of diagnostic criteria met. For opioids, withdrawal and cravings are more prominent compared with other substances. Family history of SUDs should look both for family members' past use and how any current use reflects family attitudes and the availability of opioids. The youth's living situation needs careful review of supervision (or the lack of it) and access to opioids (eg, does the adolescent stay on weekends with grandmother who is prescribed pain medications.) There are also high rates of

co-occurring mental health disorders, and patients should have a psychiatric assessment, with mood disorders, attention deficit–hyperactivity disorder (ADHD), and conduct disorder commonly seen. Patients with psychiatric illness and addiction are sometimes refused medications until they “get clean,” but concurrent treatment of substance abuse and mental health disorders is more effective than trying to treat these conditions serially.<sup>57</sup> High-risk sexual behaviors with sexually transmitted infections (STIs) and pregnancy are common, as is amenorrhea due to the dopaminergic effects of opioids.

Urine drug screens are an essential component of assessment. Most street opioids (heroin, short-acting prescription opioids, crushed long-acting prescription opioid formulations, which then are transformed to short-acting) are detectable in urine for 2 to 3 days after use. Although urine drug screenings are important, they are not sufficient to diagnose OUDs. Patients can time their use, adulterate the specimen, or substitute someone else’s urine. It is important to note that certain specific opioids, such as buprenorphine, methadone, or oxycodone, are not detected on many routine drug screens.

Patients describe euphoria, and feeling relaxed and mellow with mild-to-moderate intoxication, while on examination they can be substantially sedated. With higher doses, patients become even drowsier (nodding) and have increasing cognitive impairment. Pupillary constriction is a hallmark sign of opioid intoxication. Itching (from mast-cell histamine release), nausea, constipation, depression, urinary hesitancy, and sexual dysfunction are all common features of opioid use. Signs of injection use may include thrombosed veins (track marks), injection site erythema, bruises, abscesses or cellulitis, or scarring. An adolescent may try to hide visible injection sites with clothing (such as long sleeve shirts.)

### ***Overdose***

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Coma, pinpoint pupils, and respiratory depression are the classic triad for opiate overdose. Eventually respiratory depression can lead to full respiratory arrest and death. Youth with OUDs are especially vulnerable to overdose in the context of loss of tolerance following an interruption of opioid use. When they resume use with either a brief lapse or a full relapse, it is easy to miscalculate and use doses that were previously tolerated and seem familiar, but produce overdose due to loss of tolerance. Unfortunately one such vulnerable time is after detoxification, treatment, or other periods of abstinence or partial abstinence, unless patients are protected by relapse prevention medications. It may be that youth are even more vulnerable to this phenomenon than adults, because they are less experienced with drugs and developmentally they are more impulsive and have poor judgment.

Opioid intoxication/overdose should be considered in any emergency in which a young person presents with decreased level of consciousness or obtundation. Many adolescents use multiple drugs, and in an acute/emergent setting blood/urine toxicology screenings for other substances including blood alcohol concentration or breathalyzer should be obtained. In addition, drug use including opioids should be considered in any adolescent involved in a motor vehicle crash or other trauma.

### ***Withdrawal***

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Opiate withdrawal is biphasic: an acute phase with marked somatic symptoms and then protracted abstinence with persistent but less severe somatic symptoms accompanied by prominent cravings. Acute withdrawal is not life-threatening but it is extremely uncomfortable, and adolescents who try to quit on their own usually resume use, because they cannot tolerate withdrawal. The half-life of the drug used (for

example 4–6 hours for heroin or 1–2 days for methadone) determines the timing of symptom onset. Without the usual exogenous opioids, the opiate receptor is not activated, which causes a rebound increase in central nervous system (CNS) activity. Signs and symptoms of opiate withdrawal include tachycardia, hypertension, mild fever, sweats, rhinorrhea, sneezing, pupillary dilation, anorexia, nausea, vomiting, diarrhea, piloerection, restlessness, irritability, yawning, and insomnia. Patients report severe cravings during acute withdrawal. There are a variety of standardized withdrawal assessment tools such as the Clinical Opioid Withdrawal Scale (COWS) to quantify and track withdrawal severity.<sup>58</sup> Even after acute withdrawal, patients can have ongoing or recurrent complaints (such as malaise, restlessness, insomnia, sweats, anxiety, and irritability). In addition, cravings can persist, and the intensity/frequency of the cravings fluctuates, often elicited or intensified by exposure to triggering cues, either external (“people, places, and things”), or internal (“HALT: being hungry, angry, lonely or tired”).

## TREATMENT

There are multiple challenges facing youth with OUDs and their families. Patient engagement is difficult; treatment has to be developmentally appropriate, youth-friendly, and ideally have family involvement. Nationwide, treatment resources for adolescents are scarce, and insurance coverage and other funding varies widely. Outside of major metropolitan areas, there is often limited treatment availability, and what treatment is available may not be affordable. From 2010 to 2013 only 10.9% of those aged 12 or older who needed SUD treatment received treatment at a specialty facility. Unfortunately less than half of patients who felt that they needed help actually made an effort to get treatment.<sup>21</sup> Among adolescent opioid users, from 1998 to 2008 there was a 10-fold increase in admissions to publically funded drug treatment centers for prescription OUDs,<sup>59</sup> but despite this increase, treatment capacity is woefully limited. Detoxification alone is insufficient. The ASAM (American Society of Addiction Medicine) Criteria for adolescents recommends medically monitored inpatient/residential treatment for adolescents needing pharmacologic management for detoxification, followed by intensive outpatient services that slowly taper in frequency and intensity, followed by longitudinal outpatient maintenance and monitoring. There is an increasing treatment role for the medical community given the frequency of comorbid psychiatric disorders, and the increasing knowledge of the benefits of relapse prevention medications. These highly specialized resources are even more limited.

Many people with OUDs are convinced they do not need help and can quit on their own. Youth are even more vulnerable to this idea; developmentally they may believe they are invincible and therefore do not need treatment or medications or any help at all. The first step in treatment is just showing up, and in order to engage youth, treatment programs have to be interesting, relevant, and friendly. The involvement of caring and supportive family/adults is important, and treatment programs need to help families understand what and how much leverage they have and how to best use their influence.

### ***Detoxification (Withdrawal Management)***

Acute opiate withdrawal can be successfully managed with opioid agonists, alpha-2 agonists, nonsteroidal anti-inflammatories, anticholinergics, and antacids. Insomnia and agitation/anxiety should be aggressively managed with agents such as hydroxyzine, diphenhydramine, trazodone, clonidine, or benzodiazepines. Care should be taken when using benzodiazepines in that many patients have often abused them, and benzodiazepines are very reinforcing. Although the alpha-agonist clonidine was

long used as the primary detox medication, newer opioid agonists (such as buprenorphine) are now more routinely used, because they are physiologically directed toward the opiate receptor and therefore more effective in alleviating symptoms of acute withdrawal. Buprenorphine, a high affinity partial mu agonist, can be tapered over a period of days or transitioned to a maintenance dose for relapse prevention for medication assisted recovery. Buprenorphine can be used alone but more preferably in combination with naloxone which has poor oral bioavailability; when the combination product is given sublingually, there is minimal absorption of naloxone, but if diverted and used intravenously, the naloxone is bioeffective. Because buprenorphine will displace other opioids, the first dose should not be given until the adolescent has moderate withdrawal symptoms to avoid the possibility of precipitated withdrawal.

### ***Emergency Treatment of Overdose***

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In an acute overdose setting, patients may need emergency resuscitation including respiratory support. If opiate intoxication/overdose is suspected, the best immediate response is administration of the opiate antagonist naloxone. Naloxone can be administered by multiple routes: intramuscular, intravenous, nasal, subcutaneous, or endotracheal. Naloxone displaces bound opioids from opiate receptors, which reverses the overdose but may precipitate opiate withdrawal. Multiple and/or ongoing naloxone doses may be needed depending on the dose and half-life of the opioid. In response to the national epidemic of opiate abuse, many communities are providing/prescribing naloxone overdose kits to first responders, addicts, and addicts' families, along with appropriate training in an attempt to decrease the number of opiate overdoses and deaths.

### ***Relapse Prevention Medications***

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Although there is relatively little information about the use and effectiveness of pharmacotherapies for opioid dependence in adolescents (as opposed to adults in whom they are the clear standard of care), relapse prevention medications are nevertheless gaining more widespread adoption. Without relapse prevention medications, dropout and relapse among youth with OUDs have been the rule, with worse treatment outcomes than nonopioid youth SUDs.<sup>36</sup> Methadone is not easily available for patients under the age of 18, but can be considered when planning aftercare for young adults. Buprenorphine/Naloxone (Bup/Nal) maintenance as a relapse prevention medication has shown promising results in maintaining longer periods of abstinence from opioids, reducing treatment dropout and reducing overdose.<sup>60,61</sup> Another relapse prevention medication for opioid dependence is extended release naltrexone (XR-NTX), which can reduce opioid relapse, improve treatment adherence (including therapy/counseling), and decrease overdose in opioid users,<sup>62</sup> and shows initial promising results in opioid dependent adolescents and young adults.<sup>55</sup> Many adolescents on extended Bup/Nal or XR-NTX treatment still continue to use other nonopioid drugs, relapse on opioids when they discontinue medications, have higher attrition rates compared with older patients, and remain at high risk for overdose, particularly when they drop out of treatment.<sup>63,64</sup> Which of these medications is best for which patient is not yet well understood, but emerging evidence suggests that outcomes are better with medications integrated into comprehensive psychosocial treatment.

## **CLINICAL CASES**

### ***Case 1***

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SM is a 17-year-old white boy who lives with his parents and 2 younger siblings in a rural town. He was an A/B student in high school, where he played on the varsity

team. He began binge drinking and smoking cannabis at parties at age 15, and by 17 was using substances most weekends. During his junior year he broke his ankle, requiring surgery and internal fixation. He was prescribed opioid analgesics perioperatively, continued to have pain and was given repeated prescriptions. Two months postoperatively, he started escalating his use, taking higher doses at shorter frequencies. He started crushing the pills and snorting them. As he ran out of his prescriptions, he took opioids he found at home in the medicine cabinet and then started stealing supplies from friends and neighbors. He progressed to sniffing or smoking heroin when it was difficult to get pills, stealing money from his parents. He became irritable and reclusive, and was failing 2 classes. He tried to stop on multiple occasions, but would get sick, and was afraid to tell anyone. When confronted by his parents about the missing money, he broke down and asked for their help. His parents were devastated; they had never known a drug addict, and brought him to a substance abuse treatment center. During a 3-week inpatient stay, he underwent detoxification and received injectable extended release naltrexone (XR-NTX). He subsequently attended an intensive outpatient program (IOP), where he initially did well but briefly relapsed 6 weeks later after he declined a second dose of XR-NTX and missed sessions of treatment, thinking he could do it on his own. He came back for a brief inpatient treatment episode to restart XR-NTX. He continued in IOP, then stepped down to less intensive outpatient treatment, including monthly doses of XR-NTX with parental monitoring. He has remained abstinent from opioids for 13 months.

### Case 2

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KB is a 16-year-old white girl from a suburban area. She was raised by her grandmother after her mother died of a heroin overdose. Her 21-year-old brother is in a methadone treatment program. At age 11, she started using marijuana and cutting school; she has failed seventh grade twice. She smokes 1 pack of cigarettes per day, smokes marijuana daily, and has abused cough syrup, stimulant medications, benzodiazepines, and prescription opiates. Last year she started seeing a 23-year-old man who introduced her to heroin, first nasal then injection. She is absent from her grandmother's house regularly, from overnight to days at a time. She has been on probation for controlled dangerous substances charges, but did not follow through with court-mandated treatment. Her grandmother has had her emergently psychiatrically hospitalized for out-of-control behaviors. Emergency Medical Services were called to her school, because she was unresponsive; she was resuscitated with naloxone. She spent the night in an emergency room and was transferred to inpatient substance treatment. She reported daily injection heroin use. Her laboratory tests showed UDS positive for marijuana and opiates, mildly elevated liver function tests and HCV positivity. She underwent initial detoxification with buprenorphine and then transitioned to ongoing buprenorphine/naloxone as a relapse prevention medication. She was also started on an antidepressant. At grandmother's request, juvenile services placed her in a group home with a GPS electronic monitor. She attends intensive outpatient treatment at a dual diagnosis program where her buprenorphine/naloxone is provided through observed administration several days per week.

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