Current Pediatrics Reports (2018) 6:99–106
https://doi.org/10.1007/s40124-018-0161-z

ADOLESCENT MEDICINE (M GOLDSTEIN AND L JOHNSON, SECTION EDITORS)

Opioid Use Disorders in Adolescents—Updates in Assessment and Management

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Published online: 25 April 2018

Abstract

Purpose of Review To review information specific to adolescents regarding trends in opioid use, risk factors for opioid misuse, medical co-morbidity, and treatment updates.

Recent Findings Although opioid misuse in adolescents is uncommon, it is associated with morbidity and mortality such as hepatitis C and overdose. Adolescents commonly start with prescription opioid misuse before transitioning to heroin use. The existing literature supports the use of buprenorphine/naloxone for the treatment of adolescent opioid use disorders. Safe medication storage and disposal is important to decrease adolescent prescription opioid misuse.

Summary Opioid misuse occurs in adolescents, and pediatric providers need to remain up to date.

Keywords Adolescent · Opioid use disorder · Prescription opioid misuse · Heroin · Medication

Introduction

Over the past 15 years, there has been a marked and steady increase in drug overdose deaths in the USA. In 2016, an estimated 64,000 individuals died of a drug overdose [1]. The rise in overdose deaths has been attributed to an increase in the use of prescription opioids for the management of chronic non-cancer pain [2]. In 2015, over 63% of fatal overdoses involved opioids [3•]. In parallel to sales of prescription opioids and drug overdose deaths, there has been an increase in admissions for the treatment of opioid use disorders [3•]. While the majority of overdoses occur in adults, 772 adolescents between the ages of 15 and 19 years died from a drug overdose in 2015 [4••]. Additionally, drug use disorders begin in adolescence with symptom onset by 18 years of age in 50% of individuals and by 24 years of age in 80% of individuals with a lifetime history of a drug use disorder [5]. Pediatricians need to remain up to date in the midst of this public health emergency that is related to an adolescent onset disorder. We review new information specific to youth regarding the prevalence of opioid use, risk factors associated with opioid misuse, risks associated with opioid use, treatment of opioid use disorders, and strategies for prevention and harm reduction.

Prevalence

In 2016, 3.6% of adolescents aged 12 to 17 years and 7.3% of emerging adults aged 18 to 25 years misused an opioid in the USA [6]. Prescription opioids, including oxycodone, codeine, hydromorphone, and morphine, are the most commonly misused opioids [6]. In 2016, 3.5% of adolescents and 7.1% of emerging adults reported past-year prescription opioid misuse, while 0.1% of adolescents and 3.5% of emerging adults reported past year heroin misuse. Though the prevalence of past year prescription opioid misuse in youth has been declining since it peaked in 2008, an opposite trend has been observed with past year heroin use which has been increasing since 2012 [7]. In accordance with changing patterns of use among young people, the primary type of opioid misused by adolescents seeking treatment for an opioid use disorder

This article is part of the Topical Collection on *Adolescent Medicine*

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between 2010 and 2015 changed from predominantly prescription opioids to heroin [8]. A total of 153,000 adolescents (0.6%) and 392,000 emerging adults (1.1%) met criteria for an opioid use disorder in 2016 [6].

Risks Factors Associated with Opioid Misuse

History of medical use of a prescription opioid, i.e., an opioid was prescribed and the individual took the medication as prescribed, is a risk factor for later prescription opioid misuse that has been replicated in studies [9–11, 12•]. It is estimated that youth who are prescribed an opioid for any reason before high school graduation are at 33% increased risk for prescription opioid misuse before the age of 23 years relative to youth with no history of an opioid prescription [12•]. Many youth with a history of medical use and prescription opioid misuse, 80% in one study, misuse prescription opioids that were prescribed to them [11]. Among adolescents with prescription opioid misuse generally, e.g., individuals with and without a history of medical use of a prescription opioid, prescription opioids were most commonly accessed for free from a friend (49%), from their own prescription (35%), or bought from a friend (32%) [13]. It is not surprising that youth are able to access prescription opioids for free since one study of 8th and 9th graders found that 74% of adolescents prescribed a medication with potential for misuse had unsupervised access to the medication [14].

Several psychosocial risk factors were recently found to be associated with prescription opioid misuse. Adolescents with a history of a depressive episode when compared to those without a depressive episode had a 1.5 times increased risk for prescription opioid misuse and a 2.2 times increased risk for an opioid use disorder among adolescents with a history of prescription opioid misuse [15]. Another study also found adolescents who endorsed prescription opioid misuse with the goal to get high had increased symptoms of an affective disorder in addition to increased symptoms of anxiety, somatic, attention, and conduct disorders when compared to adolescents with no opioid use [16]. Furthermore, a history of childhood emotional or physical abuse has been associated with recent prescription opioid misuse in early adulthood [17]. An association between abuse and prescription opioid misuse is supported by research by Stein and colleagues who found that higher scores on the Adverse Childhood Experience questionnaire were associated with a younger age of first opioid misuse among adults entering an inpatient opioid detoxification unit [18].

Opioids—Prescription Opioids Versus Heroin

New research on opioid misuse in youth has primarily focused on prescription opioid misuse relative to heroin use. This likely reflects the recently documented pattern of progression from prescription opioid misuse to heroin use among individuals with opioid use disorders. When Cicero and colleagues examined the first opioid misused by adults entering treatment for a heroin use disorder between 1960 and 2010, they found a clear change from heroin to prescription opioids as the first opioid misused beginning in the early 1990s onwards [19]. Identified reasons for transitioning from prescription opioid misuse to heroin use in this study included easier access to heroin and the cheaper cost of heroin relative to prescription opioids [19]. A similar pattern of a progression from prescription opioid misuse to heroin use has been documented in adolescents [20, 21]. Specifically, in a national sample of adolescents collected between 2002 and 2011 in the USA, youth with a history of prescription opioid misuse were 13 times more likely to initiate heroin use [20]. The highest risk for initiation of heroin use was associated with prescription opioid misuse that started in early adolescence between the ages of 10 and 12 years [20]. The majority of youth with a history of prescription opioid misuse started misusing prescription opioids between the ages of 16 to 18 years (45%), followed by 33% between the ages of 13 and 15 years, and 11% between the ages of 10 and 12 years. This literature highlights the importance of targeted interventions to prevent prescription opioid misuse and earlier identification of youth with prescription opioid misuse in order to decrease the prevalence of opioid use disorders in youth.

Although research on opioid misuse patterns between 1990 and 2010 clearly documented individuals with new opioid misuse began with prescription opioids and later transitioned to heroin, a newer opioid misuse pattern has been documented in adults that is important for adolescent providers to be aware of. Among adults entering treatment for an opioid use disorder who began using opioids between 2005 and 2015, the percentage of individuals who used heroin as the first opioid misused sharply increased from 8.7% of individuals in 2005 to 33% of individuals in 2015 [22••]. Correspondingly, the percentage of these individuals who used oxycodone as the first opioid misused declined from 42% in 2005 to 24% in 2015. The authors speculate that the change in the first type of opioid misused was due to the decreased supply of prescription opioids on the black market. With decreased availability, prescription opioids for misuse increased in cost at roughly the same time that heroin decreased in cost [23]. It is unclear if there has also been a change in the type of opioid first misused by adolescents. Since trends in adolescent opioid misuse generally mirror adult opioid misuse trends, providers should be prepared to assess for heroin use in youth. If adolescents are now beginning to misuse opioids with heroin it is unclear what the clinical implications of this change will be.

Clinically, it is very important to identify what type of opioid a patient is using since opioids vary in potency and subsequent risk for overdose. Frequently, unbeknownst to

the individual misusing opioids, illicit opioids such as heroin have been adulterated with more potent synthetic opioids such as illicitly manufactured fentanyl and carfentanil [24]. Illicitly manufactured fentanyl is approximately 50 to 100 times as potent as morphine, and carfentanil is estimated to be 10,000 times as potent as morphine [25]. These more potent synthetic opioids are thought to be the key factor driving recent drug overdose deaths [26]. One challenge for clinicians and public safety officials in the identification of synthetic opioids is that routine toxicology testing does not commonly test for these substances. Common qualitative urine toxicology screens only test for opiates including heroin, morphine, and codeine [27•]. An additional opioid-specific panel is needed to detect synthetic opioids including oxycodone, hydrocodone, buprenorphine, and methadone [27•]. Fentanyl is not routinely tested for in opioid-specific panels but with the rise in use it is increasingly being included. Clinically, it is important to know what substances are included in a test when using toxicology testing to guide assessment and treatment recommendations. Furthermore, there is a role for toxicology testing even when opioid misuse is disclosed since adolescents may be unaware that the opioid they are using has been mixed with more potent opioids such as fentanyl.

Risks Associated with Opioid Use

Much of the medical morbidity and mortality associated with opioid misuse is related to infectious diseases such as hepatitis C and overdose. After a decline in the number of cases of acute hepatitis C in the USA in the early 2000s, the incidence has been steadily increasing since 2011 [28]. The largest increase in rate of hepatitis C occurred among individuals 20 to 29 years of age who also have the highest rate of acute hepatitis C relative to other age groups. In contrast, individuals aged 0 to 19 years of age have the lowest rate of acute hepatitis C. The most common risk behavior reported among individuals with acute hepatitis C was injection drug use [28]. A recent study using national surveillance data found increases in opioid injection mirrored increases in reported cases of acute hepatitis C infection among demographic subgroups suggesting that the increases in acute hepatitis C infection were related to opioid injection drug use [29•]. It is important to note that hepatitis C is spread not only through shared syringes, but also through the sharing of other injection paraphernalia such as "cookers" and cotton filters [30]. Since the incidence of acute hepatitis C increases from the lowest rate among children and adolescents to the highest rate among emerging adults, prevention efforts could target youth who are misusing opioids and are not yet injecting drugs. Regardless, since intranasal and injection drug uses are not uncommon among youth misusing opioids, all should be tested for hepatitis C [31].

Overdose risk factors specific to youth with substance use disorders have been less well characterized relative to risk factors identified in adult populations. In adults, opioid misuse has been identified as a risk factor for overdose [32–35] in addition to history of overdose, use of benzodiazepines [33, 35], binge drinking [36, 37], cocaine use [38], amphetamine use [39, 40], depression [41], and increased impulsivity [42]. In youth, among an urban sample with a history of prescription opioid or tranquilizer (benzodiazepines, clonidine, quetiapine) misuse, history of intranasal drug use, injection drug use, and psychiatric hospitalization increased risk for overdose [43]. We recently evaluated risk factors associated with a history of overdose among treatment-seeking youth with substance use disorders [44] and found an association between overdose history and greater lifetime substance use disorder diagnoses, intravenous drug use, and increased psychopathology. These youth-specific findings suggest that providers need to thoroughly assess for psychopathology in addition to risk factors associated with substance use when evaluating overdose risk in young people.

Adolescent Opioid Use Disorder Treatment

Adolescent substance use disorder treatment can involve several components including medication, therapy, family involvement, and community supports (Table 1). Despite a limited literature, medication is strongly recommended for the treatment of adolescent opioid use disorders [47••, 48••] due to the chronic course of the illness and the increased risk for overdose and death associated with continued opioid use. Three medications have FDA approval for the treatment of opioid use disorders in adults: buprenorphine/naloxone, naltrexone-extended release, and methadone [49]. Randomized controlled trials for medication in adolescents with opioid use disorders have only been conducted for buprenorphine/naloxone [50–52]. Research on naltrexone-extended release in adolescents has been limited to case series reports [53, 54]. Methadone is very difficult for adolescents to access in the USA, and no recent research exists on the use of this medication in adolescents.

Buprenorphine/naloxone is a partial μ-opiate receptor agonist that can be prescribed in the outpatient setting by providers who completed additional training to receive a waiver from the DEA. Buprenorphine has been shown to be more effective compared to clonidine, an alpha2 adrenergic agonist, for detoxification off of opioids for 35 adolescents with an opioid use disorder [50]. Adolescents randomized to buprenorphine were more likely to have negative urine toxicology tests and more likely to transition to naltrexone for maintenance treatment of their opioid use disorder compared to those randomized to clonidine. A large subsequent study of 152 youth ages 15 to 21 years with opioid dependence found

Table 1 Possible components of treatment for adolescents with opioid use disorders

Medication	• Buprenorphine/naloxone (office based, DEA waiver required)
	• Naltrexone extended release (intramuscular injection)
	• Methadone (clinic based, requires special consent)
	• Naloxone (for overdose reversal)
	• Medication for co-occurring psychiatric disorders (e.g., fluoxetine for depression
Behavioral therapy	• Motivational enhancement therapy (increase engagement and retention in treatment)
	• Cognitive behavioral therapy (build coping skills, increase understanding of cues/cravings)
	• Adolescent Community Reinforcement Approach (increase engagement in prosocial substance free activities)
	• Contingency management (positive feedback/rewards for treatment attendance/abstinence)
Monitor drug use	• Toxicology testing—urine or saliva
Medical treatment	• Assess and treat infectious diseases—hepatitis C, human immunodeficiency virus, sexually transmitted diseases
Family involvement	• Caregiver only—community reinforcement and family training
	• Family therapy (e.g., brief strategic family therapy, family behavior therapy, functional family therapy, multidimensional family therapy, multisystemic therapy)
Community recovery support	• Mutual help organizations—alcoholics anonymous, narcotics anonymous, SMART recovery
	• Educational support—recovery high schools, collegiate recovery programs
	• Vocational support

Source: [45, 46]

that longer treatment with buprenorphine/naloxone was associated with improved outcomes [51]. Specifically, youth randomized to buprenorphine/naloxone stabilization and maintenance for 8 weeks with a taper over 4 weeks compared to those who were detoxified from opioids with buprenorphine/naloxone over 2 weeks had less opioid use, less injection drug use, and less need for additional substance use disorder treatment outside of the once weekly therapy and medication visits that were part of the study. A recently published study reported on outcomes associated with the duration of the buprenorphine/naloxone taper for youth aged 16 to 24 years with opioid dependence [52]. Youth tapered off buprenorphine/naloxone over 56 days were more likely to have opioid negative toxicology tests and remain engaged in treatment for a longer period of time compared to those tapered off buprenorphine/naloxone over 28 days.

The literature on the use of naltrexone-extended release in youth with opioid use disorders has been limited to case series reports [53]. Naltrexone-extended release is an opioid receptor antagonist that has no DEA restrictions around prescribing and is administered once monthly with an intragluteal injection. A descriptive study of 16 youth, mean age 18.5 years, who received naltrexone-extended release showed that the majority of the sample (56%) substantially reduced their opioid use or were abstinent from opioids at 4-month follow-up [53]. A more recent case series reported on the feasibility of home-based administration of naltrexone-extended release [54]. Fourteen youth, mean age 20.5 years, who initially receive extended release of naltrexone in residential treatment were enrolled in a pilot program offering home-based injections. Nine subjects received a home-based injection, one received a clinic-based injection, and four dropped out of care or were admitted to a higher level of care before receiving an injection as an outpatient. Compared to a historical sample treated in this same program that received naltrexone extended release in residential treatment followed by injections in a clinic, subjects in the home-based program received more doses of medication (mean 4.4 doses versus 2.4 doses) and were more likely to be retained in outpatient treatment over 4 months (64% versus 19%). The drop-off in patient retention after the initial dose of naltrexone-extended release in residential treatment reflects an initial challenge with once monthly medication for high-risk patients. Once monthly medication ensures adherence but the decreased frequency of medication visits relative to buprenorphine/naloxone, which may initially be weekly, can make it difficult to retain high-risk patients in outpatient treatment. More frequent clinical interactions during initial treatment engagement may help increase retention in treatment. Another challenge in the use of an opioid antagonist medication for patients with opioid use disorders is the need for a period of abstinence (e.g., 7 to 10 days) from opioids prior to starting naltrexone to decrease the risk for precipitated opioid withdrawal. In summary, the existing data support the use of medication for adolescents with opioid use disorders until

at a minimum the adolescent has stabilized in treatment, has strong relapse prevention skills, and is working on longer term goals such as school or work.

Although the use of medications to treat opioid use disorders has increased over the past 10 years in all age groups, adolescents relative to adults are less likely to receive medication. Only 18% of adolescents admitted for treatment due to heroin use in 2015 had a treatment plan that included treatment with buprenorphine/naloxone or methadone compared to 42% of adults aged 45 years and older [8]. A large retrospective cohort study from a national commercial insurance database had similar findings [55]. They found that 28% of youth ages 13 to 25 years with an opioid use disorder were started on buprenorphine or naltrexone in 2014 [55]. Within the age range of 13 to 25 years, younger individuals were less likely to receive medication. For example, only 9.7% of individuals aged 16 to 17 years received medication compared to 31% of those ages 21 to 25 years. Differences in medication receipt based on sex and race also existed. Females relative to males were significantly less likely to receive medication. Non-Hispanic black and Hispanic youth were significantly less likely to receive medication relative to non-Hispanic white youth.

It is important that medication be discussed as part of the treatment plan for youth with opioid use disorders since these medications save lives. A recent meta-analysis in adults with opioid use disorders showed overdose deaths decreased by 70% when individuals were stabilized on buprenorphine/naloxone and 80% when stabilized on methadone [56]. More research is needed to help providers, patients, and families determine which medication is best indicated for the treatment of opioid use disorders in youth, duration of treatment, and barriers to the use of these medications specific to youth.

Behavioral therapy should also be part of the treatment plan for an adolescent with an opioid use disorder. Several behavioral therapies have been shown to be efficacious for adolescents with substance use disorders including motivational enhancement therapy, cognitive behavioral therapy, the adolescent community reinforcement approach, and contingency management [57]. To our knowledge, there has been one study to date that focused on the efficacy of behavioral therapy specifically for adolescents with opioid use disorders. In a large community sample of adolescents receiving the adolescent community reinforcement approach, individuals with primary opioid problem use were compared to those to those with primarily marijuana or alcohol problem use [58•]. There were equal rates of treatment initiation, engagement, retention, and satisfaction with treatment between the two groups, and both groups also had decreases in most substance use outcomes. At 1-year follow-up, however, the adolescents with primary opioid problem use reported higher frequency of substance use and more days of emotional problems and residential treatment, compared to those with primary marijuana or alcohol problem use. This likely reflects the higher severity of illness in the primary opioid problem use group at baseline. It is helpful to know that the adolescent community reinforcement approach is an intervention that can be implemented with young people who have opioid use disorders and is effective for this population. If providers trained in the adolescent community reinforcement approach are available, this may be the best type of therapy to use with adolescents with opioid use disorders. Given the limited number of providers trained to work with adolescents with substance use disorders, providers should not feel limited to only refer patients to the adolescent community reinforcement approach until there is greater evidence on the relative efficacy of the different behavioral treatments specific to adolescents with opioid use disorders.

Adolescent caregivers are also an important part of an adolescent's treatment. Youth with opioid use disorders often struggle earlier in their course of illness with low insight into the risks associated with opioid misuse and are subsequently reluctant to change their use and/or engage in treatment. Caregiver involvement is key to facilitate youth engagement in care, provide collateral on the adolescent's functioning at home and school, and monitor medication adherence. The adolescent community reinforcement approach formally includes caregivers in the manualized protocol with two sessions with caregivers only and two sessions with the adolescent and caregiver together to work on positive and effective communication [59]. When adolescents are not ready to engage in treatment, caregivers can learn skills to increase an adolescent's motivation to engage in care through a caregiver focused intervention, the Community Reinforcement and Family Training approach [60]. Community Reinforcement and Family Training has been shown to be effective in motivating youth to engage in care, decreasing their substance use regardless of engagement in care, and improving the lives of caregivers by strengthening their self-care skills [61]. When an adolescent is willing to engage in care, family therapy can be a very effective intervention to decrease adolescent substance use by addressing family risk factors that may be contributing to an adolescent's substance use [45].

Prevention and Harm Reduction

Given the scope of the opioid epidemic, there is a need for prevention programs to decrease the risk of opioid use, particularly in adolescence when substance use begins. Promising results were found in a recent randomized controlled trial of universal prevention interventions implemented during middle school [62]. A significant association was observed between the universal prevention interventions and the decreased prescription opioid misuse in late adolescence and young adults.

Providers can help caregivers decrease risk for prescription opioid misuse by discussing safe medication storage and disposal with all families. It is also important for providers to educate patients and families on the importance of taking medication as prescribed, provide clear clinical parameters for when to use a medication "as needed," and discuss risks associated with diversion. Options for safe medication disposal have been increasing since 2014 when the DEA authorized registrants such as retail pharmacies and hospitals and clinics with on-site pharmacies to become authorized collectors of controlled substances and other prescription drugs [62]. If medication collection sites are not easily accessible, the FDA provides guidance on their website on how to safely dispose of medications at home.

Providers can also reduce harm associated with opioids by encouraging patients and families to access naloxone if anyone in the home is prescribed a prescription opioid or anyone has a history of opioid misuse. Naloxone is a short-acting opioid antagonist that can be administered intramuscularly, intranasally, or intravenously to reverse an opioid overdose. Most health insurances cover naloxone and, in some states, naloxone can be accessed over the counter in retail pharmacies [63].

Conclusions

Opioid misuse begins in adolescence, and the opioid epidemic has not spared youth. Adolescent opioid misuse commonly begins with prescription opioid misuse and can progress to heroin use. It is important to identify what type of opioid an adolescent is using since heroin use relative to prescription opioid misuse can be associated with increased morbidity due to adulterants such as fentanyl. Medication is an important part of the treatment plan for adolescents with opioid use disorders since medications for opioid use disorders decrease overdose mortality. All providers should discuss the importance of safe medication storage and disposal with patients and families to decrease prescription opioid diversion and subsequently decrease the prevalence of prescription opioid misuse in the youth.

Compliance with Ethical Standards

Conflict of Interest Amy M. Yule received grant support from the Massachusetts General Hospital Louis V. Gerstner III Research Scholar Award from 2014 to 2016. Dr. Yule is currently receiving funding through the AACAP Physician Scientist Program in Substance Abuse 5K12DA000357-17. She was a consultant to Phoenix House from 2015 to 2017 and is currently a consultant to the Gavin Foundation (clinical services).

Timothy E. Wilens receives or has received grant support from the following sources: NIH(NIDA). Dr. Timothy Wilens is or has been a consultant for the following: Alcobra, Neurovance/Otsuka, and Ironshore. Dr. Timothy Wilens has a published book *Straight Talk About Psychiatric Medications for Kids* (Guilford Press) and co/edited books *ADHD in Adults and Children* (Cambridge University Press), *the Massachusetts General Hospital Comprehensive Clinical Psychiatry* (Elsevier), and *Massachusetts General Hospital Psychopharmacology and Neurotherapeutics* (Elsevier). Dr. Wilens is co/owner of a copyrighted diagnostic questionnaire (Before School Functioning Questionnaire), and he has a licensing agreement with Iron shore (BSFQ Questionnaire). Dr. Wilens is Chief, Division of Child and Adolescent Psychiatry and (Co) Director of the Center for Addiction Medicine at Massachusetts General Hospital. He serves as a consultant to the US National Football League (ERM Associates), U.S. Minor/Major League Baseball, Bay Cove Human Services (Clinical Services), Phoenix/Gavin House and Bay Cove Human Services.

Rachael M. Lyons declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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