

Treatment of Opioid-Dependent Adolescents and Young Adults With Buprenorphine

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Rising rates of opioid use among teenagers and young adults are a public health concern. Despite short durations of opioid use compared with those of adults, youth with opioid dependence have a host of co-occurring conditions, including polysubstance abuse, psychiatric disorders, hepatitis C infection, HIV risk, and high-risk sexual and criminal behaviors. Opioid-dependent youth typically are offered outpatient/residential treatment with brief detoxification, but one study showed that heroin users fare worse following residential treatment. Although abundant research supports the use of medication-assisted treatment for opioid-dependent adults, research is only recently emerging for youth. Buprenorphine, a partial opioid agonist, was proven safe and effective in improving abstinence from opioids in two controlled clinical trials. More research is needed to determine several clinically relevant areas: appropriate duration of agonist treatment, ways to enhance medication adherence, the value of integrated treatments for co-occurring conditions, and the role of opioid antagonists in opioid-dependent youth.

Introduction

Whereas the use of marijuana and most other substances has decreased or remained stable among teenagers during the past decade, use of opioids, particularly nonheroin opioids, has more than doubled, from 4% to 9% [1]. The risks associated with escalating opioid use are evidenced by a 43% increase in emergency department visits in the United States related to nonmedical use of opioids from

2004 to 2006 [2]. Also, between 1995 and 2004, the percentage of treatment admissions for individuals 29 years of age and younger with heroin use as their primary problem and injection as their usual route of administration increased from 53% to 72% [3]. These statistics are alarming because injection drug use (IDU) is a major risk factor for hepatitis C virus, hepatitis B virus, and HIV infections [4], and youth with IDU histories are at high risk of drug overdose [5].

Corresponding to the overall rise in opioid use, admissions for intravenous heroin-using youth 12 to 20 years of age increased almost 300% (from 1705 to 5112) from 1995 to 2005 [6]. Reflecting this increase in treatment demand, research has started to emerge describing the characteristics and treatment needs of clinical samples of opioid users and abusers [7–10,11•]. Many of the findings from these single-site reports are consistent: treatment-seeking opioid-using/abusing youth are predominantly white, in their later teenage years, have poor school attendance or performance, report high levels of legal problems or criminal justice system involvement, and are using multiple substances. Moreover, 45% to 70% reported injecting heroin, with many reporting having shared needles and injection equipment.

In addition, Subramaniam et al. [11•] found that teenagers with an opioid use disorder tended to be from suburban areas outside city limits and developed opioid dependence in less than 1 year of regular opioid use. A total of 83% met criteria for a *DSM-IV* Axis I psychiatric disorder, and the onset of psychiatric disorders preceded the onset of substance use disorders, supporting the theory that psychiatric disorders are a risk factor for the development of substance use disorders. In addition to repeated findings of high HIV-risk behaviors (ie, both IDU and high-risk sexual behaviors), Woody et al. [12••] found that 18% of 152 opioid-dependent adolescents and young adults who were opioid dependent for an average of 1.5 years were infected with hepatitis C at baseline evaluation for a randomized trial of buprenorphine–naloxone. These characteristics emphasize the complexity and severity of the clinical presentations of opioid-dependent youth and

highlight the need for empiric data on effective treatments in this younger population.

Currently, usual care for opioid-addicted youth consists of brief detoxification followed by individual and group therapy, commonly in outpatient and sometimes in residential settings [13], but the outcome of either approach has not been well studied. A recent study comparing post-residential treatment outcomes of 56 heroin users and 94 non-heroin-using teens found that both groups showed reductions in the number of days of substance use across the 1-year period and at 12 months, but the rates of relapse and the amounts of use were significantly higher for the heroin group [8]. Despite the rising rates of treatment admissions, this study is one of the few to evaluate the short- and long-term outcomes of residential treatment for opioid-addicted youth. Other than two recent randomized trials of medication-assisted therapy, the treatment literature consists of small, uncontrolled studies published in the 1970s [14].

Medication-Assisted Treatments for Opioid Dependence

Many studies of adults with opioid dependence have shown that medication-assisted therapy using methadone, a full μ -opioid agonist, or buprenorphine, a partial μ -opioid agonist, is effective in reducing opioid use when used as maintenance therapy over an extended period of time (see Cochrane reviews by Mattick et al. [15,16]). These data helped to establish medication-assisted treatments as the standard of care. Patients maintained on higher methadone doses (80–120 mg) generally have better treatment retention and outcomes than those on lower doses (40–60 mg), and those on methadone or buprenorphine do significantly better than those receiving psychosocial treatment alone [17].

Despite strong evidence for the effectiveness of methadone in adults, it is not a viable treatment option for most opioid-dependent youth because it is available only in licensed methadone maintenance treatment programs that are often not easily accessed by young people. Patients younger than 18 years of age must verify that they have been opioid dependent for at least 2 years, have failed two prior treatments, and obtain the consent of a parent or legal guardian if they are to enroll in methadone maintenance treatment [18]. Furthermore, there is stigma associated with use of opioid agonists such as methadone for youth, who typically have a short duration of opioid addiction (generally < 2 years), and data are not available on the impact of methadone or other opioid agonist substitution therapies on the developing brain, musculoskeletal development, or other aspects of growth and development.

On the other hand, sublingual buprenorphine, a Schedule III narcotic under the Controlled Substances Act, received US Food and Drug Administration approval in 2003 for the treatment of opioid dependence in individuals 16 years of age and older, and the Drug Addiction

Treatment Act of 2000 allowed qualified physicians (with addiction certification or 8 hours of specific continuing medical education training on the use of buprenorphine) to receive a waiver from the special registration requirements of the Controlled Substances Act to dispense or prescribe buprenorphine in their medical offices [19]. The use of buprenorphine in office-based settings that developed as a result of these events is safe and effective [20] and greatly increased access to medication-assisted treatments for opioid-dependent individuals. Buprenorphine also holds promise for the treatment of opioid-dependent youth because of its pharmacologic profile. As it is a partial μ -opioid agonist, there is a ceiling on the opioid effect that is protective against accidental or intentional overdose, which is a serious risk associated with the use of full agonists such as methadone [21]. Another safety feature is that buprenorphine is predominantly marketed in the US as Suboxone (Reckitt Benckiser, Parsippany, NJ), which combines buprenorphine and naloxone in a 4:1 ratio in an effort to reduce diversion and intravenous use [22]. If Suboxone is used sublingually as directed, the naloxone is not absorbed, but if injected, the naloxone precipitates an acute opioid withdrawal that typically discourages this route of administration. The impact of this combination on diversion and abuse will only be known after several years of postmarketing surveillance, but preliminary data indicate that it is having some effect. Alho et al. [23] found that the price opioid addicts were willing to pay for Suboxone was significantly lower than the price they would pay for buprenorphine in Finland.

Evidence for Buprenorphine in the Treatment of Opioid-Dependent Youth

Two recently published controlled trials showed evidence for the efficacy of buprenorphine in the treatment of opioid-dependent youth. The first, by Marsch et al. [10], was a double-blind, double-dummy, parallel-group, randomized controlled trial that recruited 36 adolescents (age 13–18 years) who met the *DSM-IV* criteria for opioid dependence between October 2001 and December 2003 at a research clinic in Vermont. In this study, participants were randomly assigned to a 28-day, outpatient, medication-assisted withdrawal treatment with sublingual buprenorphine or oral clonidine. Both medications were provided along with three-times-weekly behavioral counseling and incentives contingent on opiate abstinence. A significantly greater percentage of adolescents who received buprenorphine were retained in treatment relative to those who received clonidine (72% vs 39%; $P = 0.05$). A significantly higher percentage in the buprenorphine condition had opiate-negative urines (64% vs 32%; $P = 0.01$), and 61% in the buprenorphine condition, compared with 5% of those in the clonidine group, initiated after-care treatment with oral naltrexone.

The most recent trial was conducted by Woody et al. [12••] as part of the National Institute on Drug Abuse Clini-

cal Trials Network. This large, multisite study randomly assigned 152 treatment-seeking, opioid-dependent patients 15 to 21 years of age to buprenorphine–naloxone (BUP condition) for 12 weeks or a 14-day buprenorphine–naloxone taper (DETOX condition), with each arm being offered weekly group and individual drug counseling. Patients in this trial were recruited from six community-based treatment programs in different parts of the United States, and outcomes were assessed at weeks 4, 8, and 12 and months 6, 9, and 12. Patients were excluded if they were abusing sedatives or alcohol, had liver enzymes that were five or more times greater than normal upper limits, or if they were on any psychotropic medication other than a selective serotonin reuptake inhibitor. Patients assigned to the BUP condition were dispensed buprenorphine–naloxone 5 to 7 days per week under direct observation (with take home over the weekend), with a maximum dose of 24 mg/d for 9 weeks followed by a 3-week taper. Those in the DETOX group were dispensed a maximum of 14 mg/d and ended the dose taper by day 14. During weeks 1 to 12, those in the BUP condition, as compared with the DETOX condition, had fewer opioid-positive urines ($P < 0.001$), better retention ($P < 0.001$), less self-reported opioid use ($P < 0.001$), less injecting ($P = 0.02$), and received less nonstudy addiction treatment ($P < 0.004$). DETOX patients provided higher percentages of positive urines than those in the BUP condition when missing values were not imputed (odds ratio, 2.65; 95% CI, 1.28–5.50; chi-square test = 6.64 [1]; $P = 0.01$), although high rates were seen in both groups (BUP, 41% to 56%; mean, 48%; DETOX, 65% to 76%; mean, 72%). Similar results were observed when missing values were imputed positive.

In both studies, buprenorphine was found safe and effective in treating opioid-dependent youth 15 to 21 years of age. However, several pertinent study design limitations should be considered. The mean ages were 17.3 [10] and 19.2 years [12••], and only 13% were less than 18 years of age, which did not allow for sufficient evidence to assess the treatment of younger teens (ie, those < 18 years of age). Both studies dispensed medications under direct observation 5 to 7 days per week to ensure compliance. Thus, it is difficult to assess whether similarly positive results would result in usual care settings in which patients are typically given prescriptions for 7 days or more and medications are taken—often unsupervised—at home. Finally, both studies excluded participants who had severe medical or psychiatric illnesses and females who were pregnant, thereby limiting the generalizability of these study results. Nevertheless, despite these limitations, the results of these two studies provided new and important evidence supporting the use of sublingual buprenorphine (with or without naloxone) for 4 or 12 weeks in combination with psychosocial treatments for the treatment of opioid-dependent youth.

Conclusions and Future Directions

Data from many adult studies and those from the two recent randomized trials of medication-assisted treatment in opioid-

addicted youth provide strong evidence that the traditional opposition to use of medication-assisted treatment in this young age group should be reconsidered, and that additional studies are needed to confirm and extend these results. It is conceivable that changes in practice may be affected through planned education/dissemination efforts that target substance abuse counselors with training sessions/workshops to increase and update their knowledge on the efficacy of medications in this population. They could play a key role in referring patients for medication management in conjunction with counseling. These efforts could also target physicians, particularly those in training and early in their professional careers, via formal workshops conducted online, locally, and/or at national association meetings. In addition, some of their apprehension and unfamiliarity with the medication or these patient populations could be addressed by increasing their membership in the national mentorship networking program, the Substance Abuse and Mental Health Services Administration–funded Physician Clinician Support System [24], through which these physicians can receive individualized guidance on including buprenorphine treatments in their practice.

In addition to improving treatment adoption, several research questions remain unanswered regarding opioid treatments:

- How long should one treat an opioid-dependent youth with buprenorphine?
- What is the impact of long-term use of opioid agonist maintenance treatment on the brains of developing youth?
- How does one ensure adequate medication adherence when patients are given prescriptions for the medications to be taken at home?
- How does one intervene to address severe co-occurring conditions such as polysubstance abuse, psychiatric disorders, hepatitis C infections, and high HIV risk behaviors that, if untreated, may lead to poorer treatment outcomes?

Alternatively, because of the widespread stigma of the use of opioid agonists with youth (even if unfounded), future research is needed to evaluate the role of the opioid antagonist naltrexone, particularly the once-monthly, injectable, extended-release preparation (Vivitrol; Alkermes, Cambridge, MA), which has been shown to be effective in achieving opioid abstinence in adults [25]. Such empiric evidence is bound to provide the clinician with a menu of treatment options from which to select to customize treatments for a growing population of complex and severely compromised youth with opioid dependence.

Disclosure

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