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Buprenorphine treatment for adolescents and young adults with opioid use disorders: a narrative review

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Abstract

In the past decade, a new cohort of adolescents and young adults with opioid use disorders (OUD) has emerged. While medications and psychosocial treatments are available, few adolescents and young adults with OUD can access and remain in treatment. Effective, practical, and scalable treatment paradigms for this young population are needed. Buprenorphine is a medication with unique pharmacological and regulatory characteristics that make it a promising component of adolescent and young adult OUD treatment models. Three randomized controlled trials and multiple observational studies have evaluated the use of buprenorphine to treat this population. However, data from these studies have not been consolidated into an up-to-date summary that may be useful to clinicians. The objective of this narrative review is to inform clinical practice by summarizing results of primary and secondary analyses from randomized controlled clinical trials and observational studies that have evaluated the use of buprenorphine to treat adolescents and young adults with OUD. Based on results from these studies, we encourage the conceptualization of OUD among youth as a chronic medical condition requiring a long-term management strategy. This includes treatment with buprenorphine in conjunction with medication-prescribing protocols that do not necessarily require daily clinic attendance for observed medication adherence. However, more study of treatment delivery models, addressing such issues as medication adherence and intensity requirements, is needed to determine practices that optimize outcomes for youth.

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Keywords

Young Adults; Adolescents; Opioid use disorder; Buprenorphine; Treatment

Introduction

Opioids are highly addictive (Wise, 1989) and close to half a million adolescents (age 12-17) and a million young adults (age 18-25) in the United States engaged in risky use of prescription opioids in 2014 (Center for Behavioral Health Statistics and Quality, 2015a). From 1997 to 2012, the annual incidence proportion of youth (age 15-19) hospitalizations for prescription opioid poisonings increased by over 170% (Gaither et al., 2016). Additionally, 6-9% of the youth who engage in risky opioid use, develop an opioid use disorder (OUD) (Parker et al., 2015), often within six (Subramaniam et al., 2009a) to twelve (Parker et al., 2015) months after initiation. In recent years, the incidence rate of OUD diagnoses among youth age 13-25 has more than quintupled (Hadland et al., 2017) and some estimates indicate that approximately 120 new cases of youth OUD occur per day (Parker et al., 2015).

In recent years federal and state governments have taken measures to address the prescription opioid epidemic (e.g., monitoring pharmaceutical opioids, educating healthcare providers and the public) (Kanouse et al., 2015). Parallel to these efforts, risky prescription opioid use among adolescents and young adults has declined (Center for Behavioral Health Statistics and Quality, 2015a; Johnston et al., 2015). However, many adolescents and young adults who regularly use prescription opioids are now transitioning to heroin - contributing to an increase in heroin use in the U.S (Pollini et al., 2011; Peavy et al., 2012; Jones, 2013; Mars et al., 2014; Cerda et al., 2015; Jones et al., 2015; Lipari et al., 2015; Carlson et al., 2016; Ihongbe et al., 2016; Palamar et al., 2016). These trends have created an urgent need for treatment for adolescents and young adults with prescription opioid- and heroin-based OUD.

Opioid agonist medications are a necessary and effective component of standard treatment for adults with OUD (Mattick et al., 2014; Connery, 2015). Buprenorphine (a partial mu-opioid receptor agonist medication) substantially improves opioid abstinence and treatment retention outcomes for adults with OUD (Johnson et al., 1992; Ling et al., 1998; Fudala et al., 2003), and significantly reduces mortality risk (Sordo et al., 2017). This large body of literature (Connock et al., 2007; Thomas et al., 2014) has helped support the spread of buprenorphine treatment for adults with OUD. Consequently, this population often has the option to engage in longer-term buprenorphine treatment rather than short-term buprenorphine detoxification - resulting in better treatment retention and illicit opioid abstinence outcomes (Fiellin et al., 2014). Adults are also increasingly able to access treatment in the community through programs that do not specialize in substance use disorder (SUD) treatment (e.g., primary care) (Center for Behavioral Health Statistics and Quality, 2013) thereby expanding overall treatment capacity and reducing treatment burden.

By contrast, adolescents with OUD have limited access to opioid agonist medications and standard models of opioid agonist-based care for OUD youth are lacking (Fiellin, 2008;

Pecoraro et al., 2013; Hadland et al., 2017). The vast majority of adolescents with OUD do not receive treatment (Wu et al., 2011b; Wu et al., 2016) and those who do, primarily receive abstinence-based residential treatment or outpatient psychosocial therapy – strategies that produce high rates of dropout and relapse (Pecoraro et al., 2013; Matson et al., 2014). Among adolescents who receive treatment for OUD, less than three percent receive opioid agonist treatment (Feder et al., 2017). Those who do receive opioid agonist treatment, primarily receive short-term detoxification instead of longer-term treatment (Pecoraro et al., 2013; Matson et al., 2014). While young adults (unlike adolescents) can and do access adult-oriented office-based buprenorphine treatment programs, they still have significantly higher rates of treatment dropout than adults (Schuman-Olivier et al., 2014a).

The regulatory framework for buprenorphine prescribing makes this medication a viable component of standard youth OUD treatment. Under the Drug Addiction Treatment Act of 2000, physicians working in general healthcare settings (e.g., primary care) can become qualified to prescribe buprenorphine/naloxone to treat OUD (Center for Substance Abuse Treatment, 2004). Additionally, buprenorphine/naloxone, unlike methadone, is approved for patients as young as 16 (McCormick, 2002; Substance Abuse and Mental Health Services Administration, 2015). These regulations provide a new opportunity to leverage youths' familiarity and comfort with pediatric healthcare settings to facilitate their engagement in treatment (Hadland et al., 2016). Furthermore, in contrast to the strict limitations on take-home doses of methadone, physicians can provide a prescription for buprenorphine that can be filled at a pharmacy and taken at home which may help retain youth in treatment (Pecoraro et al., 2013; Hadland et al., 2016). Given (1) these regulatory advantages, (2) youths' preference for less structured, less stigmatized, and non-judgmental treatment settings (Brands et al., 2005; Moore et al., 2014), (3) evidence linking earlier age of onset of opioids to higher risk of developing an opioid use disorder as an adult (McCabe et al., 2007; Chen et al., 2009), (4) youths' particularly rapid escalation in opioid use severity (e.g., more regular use or injection use) (Mills et al., 2004; Daniulaityte et al., 2006; Lankenau et al., 2012) and (5) high risk for overdose (Frank et al., 2015), it is prudent to begin developing new approaches that engage this population in treatment as early and for as long as possible to prevent OUD exacerbation and related consequences (Committee On Substance Use Prevention, 2016).

However, unlike the plethora of randomized controlled trial data that exist to inform treatment of adult OUD with buprenorphine, to-date, only three randomized controlled trials have generated data using buprenorphine and buprenorphine/naloxone to treat adolescents and young adults with OUD (Marsch et al., 2005; Woody et al., 2008; Marsch et al., 2016). By combining the primary outcomes data from these trials, along with secondary analyses, observational studies, and case reports, and comparing them to the adult buprenorphine treatment literature, we can glean preliminary clinical patterns that may help inform buprenorphine treatment practices for this young population and generate future research directions. The goal of this narrative review is to offer preliminary clinical practice recommendations by highlighting and synthesizing the scientific literature supporting the use of buprenorphine for treating youth with OUD. Of note, there is emerging research to suggest that naltrexone may be a promising treatment for youth with OUD (Fishman et al.,

2010b). However, given the overall lack of a comparable knowledge base for the use of naltrexone among youth, this review focuses specifically on buprenorphine.

Methods

We sought to summarize relevant randomized controlled trials and observational studies. We obtained published and unpublished scientific literature and data for this narrative review using PubMed, PsycINFO, Web of Science, Cochrane Library, the National Institute on Drug Abuse (NIDA) Clinical Trials Network Dissemination Library, and the NIDA Data Share and Substance Abuse and Mental Health Services Administration (SAMHSA) websites. We used the following search terms and phrases to obtain relevant scientific literature: “abstinence”, “abstinent”, “addiction”, “adolescent(s)”, “agonist”, “behavior(al) therapy”, “buprenorphine”, “buprenorphine/naloxone”, “buprenorphine-naloxone”, “cohort”, “contingency management”, “counseling”, “detoxification”, “dose”, “emerging adult(s)”, “heroin”, “injection”, “inpatient”, “intravenous”, “maintained”, “maintenance”, “medication-assisted”, “non-medical prescription opioid use”, “nonmedical prescription opioid use”, “observational”, “office-based”, “opiate”, “opioid abuse”, “opioid dependence”, “opioid misuse”, “opioid use”, “opioid use disorder”, “outpatient”, “overdose”, “pediatric”, “poisoning”, “psychotherapy”, “randomized controlled trial”, “residential”, “retention”, “substance abuse”, “substance dependence”, “taper”, “teenager”, “therapy”, “treatment”, “vouchers”, “withdrawal”, “young adult(s)”, “young people”, “young person(s)”, “young”, “youth”. We included studies of buprenorphine-based treatment for OUD adults that were either early foundational studies or reported buprenorphine administration schedules similar to those found in youth-specific studies. Studies that solely examined the use of other medications for OUD (e.g., methadone or naltrexone) were only included as part of the introduction and future directions sections of this review. In the following sections, unless otherwise noted, the term “adolescent” refers to individuals age 12 to 17 and the term “young adult” refers to individuals age 18 to 25. The term “youth” encompasses both adolescents and young adults.

The results of this review are presented using the following section structure: (1) demographic and clinical characteristics of youth with OUD, (2) a description of buprenorphine and buprenorphine/naloxone, (3) results from randomized controlled trials, (4) results from observational studies, (5) considerations for psychosocial treatment. At the end of the review, we provide relevant recommendations and future research directions based on the studies reviewed.

Demographic Characteristics of Youth with OUD

Gender and Race

Data from the National Treatment Episode Data Set (TEDS) (which characterizes residential treatment admissions to substance use disorder facilities across the United States), indicate that in 2013, over 3000 adolescents and over 100,000 young adults age 18-24 were admitted to treatment with either primary heroin or other opioid use disorder (Center for Behavioral Health Statistics and Quality, 2015b). Among young adults, the prevalence of lifetime, past-year, and past-month heroin use is approximately twice as high for males than females

(Ihongbe et al., 2016), and among youth, 58% of residential treatment admissions for heroin and/or prescription opioids are male (Treatment Episode Data Set, 2014). Females are more likely to report having shared equipment (e.g., needles and solutions) and having someone else inject them (Evans et al., 2003; Meade et al., 2010). Caucasian youth report higher rates of risky prescription opioid use and heroin use (Wu et al., 2011a; McCabe et al., 2012b; Young et al., 2012; Ihongbe et al., 2016) and are more likely to screen positive for OUD than other racial groups (McCabe et al., 2012a). The majority (70 - 95%) of youth that present to treatment for OUD are Caucasian (Hill et al., 2013; Matson et al., 2014; Treatment Episode Data Set, 2014), but this overrepresentation may be due in part to additional treatment barriers that racial minorities often face (Wu et al., 2011b; Hadland et al., 2017).

Co-Occurring Mental Health and Substance Use

In clinical samples of youth with OUD, the prevalence of co-occurring psychiatric disorders can range from approximately 20% (Pugatch et al., 2001) to 80% (Subramaniam et al., 2009a). Between one-fourth and one-half of youth OUD treatment admissions present with co-occurring depression and/or anxiety (Pugatch et al., 2001; Rodriguez-Llera et al., 2006; Subramaniam et al., 2009a; Branson et al., 2012; Mackesy-Amiti et al., 2012; Matson et al., 2014; Marsch et al., 2016). As with OUD adults (Darke et al., 2002), suicidality is not uncommon in this population. In clinical samples, roughly 20% of youth entering treatment for OUD report either past-year or lifetime suicide attempt or suicidal ideation (Pugatch et al., 2001; Clemmey et al., 2004; Mills et al., 2004; Subramaniam et al., 2009a; Matson et al., 2014). Histories of physical and sexual trauma are also common in this population and if not properly addressed, may contribute to an inability to complete treatment (Jaycox et al., 2004; Williams et al., 2008; Neumann et al., 2010). Clinical and epidemiological samples of youth with OUD also demonstrate high rates of co-occurring substance use and substance use disorders (Subramaniam et al., 2009a; Wu et al., 2011b; Ihongbe et al., 2016). In particular, past-month cannabis use is common (60 - 74%)(Subramaniam et al., 2009a; Hill et al., 2013) as is having a diagnosed cannabis use disorder (Subramaniam et al., 2009a; Treatment Episode Data Set, 2014).

Youth Who Use Prescription Opioids vs. Youth Who Use Heroin

There are significant clinical differences between youth who use prescription opioids and youth who use heroin. Youth who use prescription opioids report secondary preferences for a wider range of substances such as cannabis and alcohol and tend to have more past-year SUD diagnoses than youth who use heroin (mean 4.3 vs. 2.8) (Subramaniam et al., 2009a). Youth with heroin use disorders tend to be at a more severe stage of their OUD than youth who use prescription opioids. For example, in clinical samples, almost all youth who use heroin, but only 75% of youth who use prescription opioids, meet DSM-IV criteria for past-year opioid dependence (Subramaniam et al., 2009a). Epidemiological samples demonstrate that adolescents are more likely to have a prescription opioid use disorder while young adults are more likely to have both a prescription opioid and heroin use disorder (Wu et al., 2016). At treatment entry, youth who use heroin are more likely to be using on a daily basis, tend to have more severe withdrawal, and are more likely to be injecting than youth who use prescription opioids (Pugatch et al., 2001; Motamed et al., 2008; Subramaniam et al., 2009a; Treatment Episode Data Set, 2014). The increased injection use is particularly concerning

given its association with elevated risk for HIV and HCV (Sullivan et al., 2005). Additionally, in clinical samples, youth (age 14-18) who use heroin are more likely to score high on measures of depression and to have dropped out of school (Subramaniam et al., 2009a).

Buprenorphine and Buprenorphine/Naloxone

Neuropharmacology

Buprenorphine is a partial mu-opioid receptor agonist, meaning that there is a plateau "ceiling effect" for the opioid agonist effects of buprenorphine (Walsh et al., 1994; Chiang et al., 2003)., which lowers (but does not eliminate) its potential for misuse, and reduces the risk of respiratory suppression upon overdose compared to full mu receptor agonists like heroin (Center for Substance Abuse Treatment, 2004; Bell et al., 2009a; Bell et al., 2009b; Bukstein, 2015). Because buprenorphine has a higher binding affinity for mu-opioid receptors than many full mu agonists (Center for Substance Abuse Treatment, 2004), it has a blocking property that may deter illicit opioid use during treatment. Certain formulations of buprenorphine also include naloxone. Naloxone is an opioid antagonist capable of displacing opioid agonists from opioid receptors (Robinson et al., 2014). It is included as part of the combination buprenorphine/naloxone formulation to deter misuse since, when buprenorphine/naloxone is consumed as intended (i.e., sublingually), the naloxone is poorly absorbed and has a negligible clinical effect (Chiang et al., 2003) but is potently active when injected. According to the American Academy of Pediatrics, no age-specific safety concerns for buprenorphine have been identified (Committee On Substance Use Prevention, 2016). However, buprenorphine use by opioid naïve, non-tolerant youth can result in fatal respiratory depression (Kim et al., 2012).

Randomized Controlled Trials (RCT)

Overview of RCT Study Designs

We identified three RCTs that have evaluated buprenorphine for treating adolescents and young adults with OUD. The primary outcome in all three trials was opioid abstinence as measured by urine drug toxicology. The first trial was a double-dummy, double-blind, comparison of youth (ages 16-18) with OUD (n=36) randomized to either a 28-day buprenorphine or clonidine detoxification (Marsch et al., 2005). The second trial, was a multi-site comparison of youth (ages 15-21) with OUD (n=152) randomized to either a 2-week buprenorphine/naloxone detoxification or an 8-week buprenorphine/naloxone administration period combined with a 4-week taper (i.e., 12-week group) and followed over a 12 week study period (Woody et al., 2008). The third trial was a double-blind comparison of youth (ages 16-24) with OUD (n=53) randomized to either a 28-day or 56-day buprenorphine/naloxone detoxification and followed over a 63-day study period. Results from all three trials demonstrated either that buprenorphine was more effective compared to clonidine or that longer buprenorphine administration schedules were more effective than shorter "detoxification" administration schedules in achieving higher rates of abstinence and retention (detailed below and in Table 1).

Opioid Abstinence

In each of the RCTs that compared the efficacy of different buprenorphine administration lengths (Woody et al., 2008; Marsch et al., 2016), youth who received buprenorphine for longer periods of time demonstrated significantly better opioid abstinence outcomes than youth who received buprenorphine for shorter periods of time (Table 1). The relative efficacy of longer (56-day) over shorter (28-day) detoxification demonstrated by Marsch et al. 2016 (35% opioid-negative vs. 17% opioid-negative at 63 days respectively) is consistent with the pattern of results from early buprenorphine detoxification studies with OUD adults (Amass et al., 1995; Becker et al., 2001). Additionally, rates of abstinence for the 56-day taper group are comparable to abstinence rates of OUD adults who receive a 28-day buprenorphine stabilization combined with a 28-day taper (30% opioid-negative at 56 days)(Ling et al., 2009). The abstinence rate for youth who received twelve weeks of buprenorphine in Woody et al. 2008 (57% at week 12) is similar to abstinence rates in multiple RCTs of OUD adults who received buprenorphine over similar time frames (45-55% abstinent at week 12) (Johnson et al., 1992; Fudala et al., 2003; Mattick et al., 2003). Finally, relative differences in abstinence rates between the 28-day buprenorphine and clonidine detoxification strategies in Marsch et al. 2005 (64% vs. 32% respectively) are consistent with the pattern of results from adult-specific studies comparing buprenorphine and clonidine detoxification strategies (Lintzeris et al., 2002; Ling et al., 2005).

Treatment Retention

In each of the RCTs that evaluated different buprenorphine administration lengths, youth who received buprenorphine for longer periods of time were more likely to remain in treatment than you who received buprenorphine for shorter periods of time (Table 1). In Marsch et al. 2016, 18% of the 28-day buprenorphine detoxification group and 36% of the 56-day group completed the 63-day trial. Retention rates for the 12-week treatment group in Woody et al. 2008 (84%, 74%, and 70% at weeks 4, 8, and 12 respectively) were similar to or better than rates of retention in multiple RCTs evaluating similar buprenorphine administration schedules for OUD adults (70-78%, 60-61%, and 50% at weeks 4, 8, and 12 respectively) (Johnson et al., 1992; Mattick et al., 2003) as well as observational data of OUD youth (ages 15-24) treated in outpatient buprenorphine treatment settings (Matson et al., 2014; Schuman-Olivier et al., 2014a). Retention rates of the buprenorphine and clonidine groups in Marsch et al. 2005 (72% vs. 39% respectively) are consistent with the pattern of results from adult-specific studies comparing buprenorphine and clonidine detoxification strategies (Lintzeris et al., 2002; Ling et al., 2005).

Buprenorphine self-administration location

In the Marsch et al. 2016 trial, some participants were allowed to self-administer buprenorphine at home two to three times per week. Those who received this flexible prescribing protocol had a higher mean percent of opioid-negative urine toxicology results (43.2% vs. 8.6%) and higher retention rates (46.7% vs 17.3%) than those participants who were required to come to the clinic on a daily basis - regardless of detoxification schedule condition (Marsch et al., 2016). These results differ from published studies with OUD adults that found no impact of frequency of clinic visits on retention rates (Fiellin et al., 2006; Bell

et al., 2007) although the administration schedules in these adult studies were notably different.

Adverse Effects

All three RCTs of buprenorphine treatment for youth with OUD found that buprenorphine is relatively safe and well tolerated. Woody et al. 2008 reported minor side effects in a minority of participants (headache 16-21%, insomnia <10%, vomiting <10%). In particular, there was no evidence of liver toxicity (Bogenschutz et al., 2010). No trial-specific serious adverse effects were reported in any of the three trials (Marsch et al., 2005; Woody et al., 2008; Marsch et al., 2016).

High-Risk Behaviors

Youth with OUD who use buprenorphine reduce their injection drug use, and the longer they use buprenorphine, the greater the reduction (Woody et al., 2008; Meade et al., 2010). For example, in the Woody et al. 2008 study, at the end of 12 weeks of treatment, 15% of participants in the 12-week treatment group were still injecting, while 35% of the 2-week detoxification participants were still injecting (Meade et al., 2010). Furthermore, while the rates of injection declined for both groups, the decline was significantly greater for the 12-week treatment group (Meade et al., 2010). Importantly, as with OUD adults (Sullivan et al., 2008; Edelman et al., 2014), buprenorphine does not seem to affect risky sexual practices such as unprotected intercourse (Meade et al., 2010).

Predictors of Treatment Outcomes

In treatment predictors—Secondary analyses of the Woody et al. 2008 trial data indicate that the first two weeks of treatment are crucial for long-term opioid abstinence and retention. In the first two weeks, youth who submit opioid-negative urine screens each week, adhere to buprenorphine five or more days per week, and attend at least one counseling session each week, are more likely to be opioid-negative (Subramaniam et al., 2011) and less likely to have dropped out (Warden et al., 2012) at week 12 of treatment.

Past 30-day behavior (at treatment entry) predictors—Youth with past 30-day injection of opioids, amphetamines, or cocaine and/or active medical or psychiatric problems at treatment entry have lower rates of opioid use at week 12 of treatment compared to those without these characteristics (Subramaniam et al., 2011). However, analyses of the same dataset indicate that the presence of injection drug use or co-occurring psychiatric disorders at baseline is not associated with better retention (Warden et al., 2012). These data also indicate that youth with past 30-day hallucinogen use or severe past 30-day poly-substance use are more likely to drop out of treatment by week 12 (Warden et al., 2012).

RCT Buprenorphine Induction and Dosing

Table 1 provides details concerning the induction procedures used for each of the three RCTs. Across the three RCTs, maximum buprenorphine or buprenorphine/naloxone doses administered to a participant at any point during the study ranged from 2 - 32 mg/day. Thus far, the use of buprenorphine or buprenorphine/naloxone has been evaluated in combined

total of 223 OUD youth in these clinical trials (18 participants in the Marsch et al. 2005 trial were given clonidine). Figure 1 displays the percent of these 223 patients who received a particular maximum dose.

Pain at Induction—It may be important to consider untreated pain during induction as it is common among individuals with OUD (Potter et al., 2008) and potentially alters opioid use disorder treatment procedures and outcomes (Clark et al., 2008; Clark et al., 2011). Secondary analyses of 69 patients enrolled in the Woody et al. 2008 trial provide insight into the role that pain may play in buprenorphine dosing for OUD youth. At treatment entry, investigators used the EQ-5D scale (Rabin et al., 2001) to assess the degree of pain the patient experienced the week before induction (0=no pain, 1=some pain, or 2=extreme pain). Over 50% of the sample reported having some pain and close to 20% of the sample reported extreme pain. The degree of pain predicted maximum daily buprenorphine dose. Patients who reported “extreme” pain received the highest dose of buprenorphine per day (mean 19.7 mg) which was significantly greater than the dose for patients who reported “some” pain (mean of 15 mg) or no pain (mean 12.8 mg). Withdrawal severity at the end of the first dosing week as measured by the Short Opioid Withdrawal Scale (SOWS) also predicted maximum daily dose and thus past-week pain might be a byproduct of episodes of withdrawal. However, overall withdrawal severity was not correlated with baseline reports of past-week pain, which suggests (but is by no means conclusive) independent effects of withdrawal and past-week pain. Among participants who reported extreme past week pain, 22.2%, 12.5%, and 37.5% were opioid positive at weeks 4, 8, 12 respectively. Analyses comparing these outcomes to those reporting some pain or no pain indicated no significant differences (Chakrabarti et al., 2010).

Observational Studies

Overview of Observational Study Designs

Observational studies have reported on OUD youth treated with buprenorphine for up to one year in real-world outpatient treatment settings. These studies include retrospective medical record reviews that provide descriptions of clinic-specific models of care and treatment protocols. We identified nine observational studies, key points of which are summarized in Table 2. This summary includes study characteristics such as duration, induction procedures, and treatment outcomes. As the longest buprenorphine administration length youth have received in a randomized controlled trial was 12 weeks (Woody et al., 2008), these studies provide useful additional information about buprenorphine treatment models used to offer care to youth for longer periods of time.

Abstinence and Retention

Similar to youth-specific RCT data, youth-specific observational data support the notion that longer buprenorphine administration schedules produce better illicit opioid abstinence outcomes. For example, Matson et al. 2014 reported rates of illicit opioid abstinence of up to 85% for those youth who are able to remain in treatment and continue to receive buprenorphine (Matson et al., 2014). Conversely, observational data on young adults with OUD who received a short (3-day) buprenorphine detoxification in an outpatient setting,

indicate lower rates of abstinence (12% abstinent at six months)(Gandhi et al., 2003) although these rates are higher when detoxification is implemented in residential treatment settings (approximately 31-43% at six months) (Schuman-Olivier et al., 2014b). In terms of retention, published observational studies have generally reported six-month retention rates ranging from 25% (Matson et al., 2014) to 40 % (Schuman-Olivier et al., 2014a; Vo et al., 2016) and one-year retention rates between 9-17% (Smyth et al., 2012; Matson et al., 2014; Schuman-Olivier et al., 2014a; Mutlu et al.). Importantly, close to one-fourth of youth who receive an induction leave treatment within the first week (Bell et al., 2006; Matson et al., 2014) but anywhere from one-fourth to one-half of youth who drop out of treatment will come back within a year (Bell et al., 2006; Matson et al., 2014; Mutlu et al.).

Buprenorphine Treatment with Psychosocial Support (RCT and Observational Data)

Study participants in all three RCTs received behavioral therapy and were required to attend 2-3 counseling sessions per week (either one-on-one or group sessions). These therapies contained psychoeducational, cognitive-behavioral, and family or social systems components (Marsch et al., 2016). For example, study therapists helped participants learn how to foster positive social relationships, avoid triggering situations, and develop healthy coping skills (Woody et al., 2008). Importantly, study participants who received longer buprenorphine treatment attended more counseling sessions than participants who received shorter buprenorphine treatment (Woody et al., 2008). Participants in Marsch et al., 2005 and 2016 also received contingency management using the community reinforcement approach (Budney et al., 1998) to reinforce components of treatment. For example, participants earned vouchers for submitting opioid-negative urine screens, attending scheduled clinic appointments, and completing study assessments. Participants could submit their vouchers to receive prizes to help them engage in non-drug use related activities (e.g., movie tickets, ski or gym passes, CDs, and clothing) and develop non-drug-using social networks. The original study reports contain more details on the structure of the contingency management programs (Marsch et al., 2005; Marsch et al., 2016).

The literature concerning the effect of psychosocial treatment in conjunction with buprenorphine treatment for adults with OUD has yielded mixed findings (Amato et al., 2011a, 2011b) although contingency management may be uniquely effective (Carroll et al., 2017). In the youth buprenorphine treatment literature, no studies can point to the isolated effect of psychotherapy above and beyond the therapeutic effect of buprenorphine treatment. For example, while all three randomized controlled trials evaluating buprenorphine treatment for youth provided subjects with counseling services, it was not possible to evaluate the additive effect of counseling on retention and abstinence outcomes.

Observational studies of youth-specific residential treatment programs describe the use of psychosocial therapies and emphasize the importance of tailoring therapy to meet unique needs of youth. For example, residential treatment programs encourage patients to engage in 12-step AA or NA programs with younger age compositions – which can improve abstinence outcomes (Kelly et al., 2005; Labbe et al., 2013). Adolescents also have poorer

insight into their substance use problems than adults (Winters et al., 2014) and thus motivational interviewing strategies are often geared towards pre-contemplative patients (Grenard et al., 2006). Many programs also place heavy emphasis on addressing the multiple interrelated systems affected by substance use disorders such as school, family, and the justice system (Fishman et al., 2003; Clemmey et al., 2004; Perry et al., 2004).

Recommendations

Here we propose a series of recommendations for the treatment of youth with OUD, based on the data reviewed. We note two things. First, there will not be one single approach to treatment that works for all youth and thus treatment plans need to be tailored to the needs of each patient (Subramaniam et al., 2013). Second, it is important to note that these recommendations are not meant to be interpreted as definitive as they are based on a limited amount of data. Overall, we encourage the conceptualization of OUD in youth, as in adults, as a chronic medical condition that requires long-term management strategies that include buprenorphine as one of the first-line treatments, rather than a time-limited disorder amenable to high rates of "cure". There is no evidence to support a "fail-first" approach in which buprenorphine would be reserved for only after a trial of treatment without medication.

Buprenorphine Induction and Dose

Youth with OUD have been treated with a range of maximum buprenorphine doses (2-32 mg per day). At induction, the dose should ideally be escalated gradually until there are no longer signs of withdrawal or craving. As with adults, titration pace and total dose should be based on patient severity, amount of illicit opioid used (tolerance), and clinical response. Youth may benefit from buprenorphine dosing titrated on a case-by-case basis, as they will present with varying levels of severity of OUD and pain. We recommend clinician-observed inductions when patients are exposed to buprenorphine for the first time in order to ensure that dosing is adequate and that the patient is educated properly about medication adherence and the effects of buprenorphine (Subramaniam et al., 2013).

Buprenorphine Treatment Duration

We do not know the optimal duration of buprenorphine treatment for adolescents and young adults with OUD. However, it is becoming increasingly clear, that like adults with OUD, adolescents and young adults have better opioid abstinence and treatment retention outcomes the longer they receive buprenorphine. We underscore the comments of Pecoraro et al. 2013 who state that although we recommend longer buprenorphine administration, this does not mean that we expect youth to use buprenorphine for the rest of their lives (Pecoraro et al., 2013). It is possible that some patients with OUD can recover to a point where medication is no longer needed. However, more data are necessary in order to provide clinicians with the ability to determine when youth have reached such a point. Based on the results of the three RCTs reviewed we would recommend, at the very least, 12 weeks of buprenorphine treatment for youth as young as age 16 with a DSM-5 diagnosed opioid use disorder. However, published observational studies report treating youth with buprenorphine for up to a year and thus we see no reason why clinicians and patients should feel rushed to

discontinue buprenorphine after twelve weeks of buprenorphine treatment if discontinuation is not clinically warranted. If youth are eventually tapered off buprenorphine, it is better to use a slow taper schedule (Subramaniam et al., 2013; Matson et al., 2014; Marsch et al., 2016) during times when the patient's environment is stable rather than during stressful life transitions (e.g. entering college or starting a job). Monitoring should be continued well past the period of discontinuation, with the expectation that many patients may need to resume using the medication.

Buprenorphine self-administration location

Allowing participants to bring buprenorphine home several days per week and not requiring daily clinic attendance for observed self-administration results in better retention and opioid abstinence outcomes, independent of the length of buprenorphine detoxification (Marsch et al., 2016). Treatment structured in this way may be particularly important to youth, but more data will be required to determine how useful it is in relation to other necessary components of treatment. Additionally, permitting some at-home self-administration may give patients enough day-to-day flexibility to effectively utilize education, employment, or housing support opportunities (Smyth et al., 2012). An important dynamic to consider is that early adherence to buprenorphine improves abstinence and retention outcomes (Subramaniam et al., 2011; Warden et al., 2012; Matson et al., 2014) but youth may disengage from treatment when required to attend a clinic for daily observed dosing (Marsch et al., 2016). Thus it may be necessary to require daily observed medication adherence in the initial stages of treatment and then transition to a flexible (non-daily) buprenorphine prescribing schedule to bolster treatment retention. This approach may help strike a balance between reducing the risk of non-adherence and diversion while also leveraging the flexible prescribing regulations to enhance retention. Another possibility is to reserve daily dosing requirements for those with early markers of poor outcomes or who have difficulty managing less restrictive regimens. Although daily dosing may not be required, or even counterproductive, it is important to note that most studies have required observed, onsite, dosing at least several times per week, at least early in treatment, presumably consistent with the developmental need for increased structure in youth. Whenever possible, parents should take an active role in observed dosing at home to help youth remain adherent to their medication and should be vigilant for signs of relapse (Levy et al., 2007; Fishman et al., 2010a; Subramaniam et al., 2013). Importantly, while frequent in-person dosing and parental involvement can be helpful, such structure may not be viable for many young people seeking treatment and can represent significant barriers to treatment if required by treatment providers.

Psychosocial Treatment

Youth with OUD struggle to stay abstinent after leaving treatment (Gandhi et al., 2003) and exposure to environmental triggers and peers who use opioids portend relapse (Acri et al., 2012). Buprenorphine reduces cravings and withdrawal - creating a window of opportunity for youth to develop coping mechanisms and relapse prevention skills. The length of this window is likely proportional to the amount of time that buprenorphine is administered as the data indicate that youth who continue to receive buprenorphine, continue to attend counseling sessions (Woody et al., 2008). Currently however, from an RCT data perspective, it is unclear if there is an additive effect of psychotherapy on opioid abstinence and retention

outcomes for youth treated with buprenorphine. However, the results from all three youth-specific RCTs of buprenorphine treatment have been generated with simultaneous counseling as part of the study design, and we cannot rule out the possibility that counseling contributed to the overall effect sizes of the abstinence and retention results observed. Thus, we recommend co-administration of evidence-based counseling or behavioral therapy (e.g., MET, CBT, etc) if the treatment program can provide such services. Medical practitioners who are unable to provide such services should work to coordinate them through other available resources, but should not be deterred from prescribing buprenorphine as long as patients continue to make clinical progress with carefully monitored outcomes such as negative urine drug tests and improvements in psychosocial function. Counseling should address salient issues in the patient's life such as unstable housing, disengagement from academics or employment, legal problems, conflict at home (Subramaniam et al., 2013) as well as promote development of new non-drug-using social networks (Kelly et al., 2013).

Future Directions

The United States is in the midst of an opioid epidemic and while medications and psychosocial treatments are available, few adolescents with OUD access and remain in treatment. Additional RCT and observational data are necessary to inform the design of practical and scalable treatment paradigms that address this treatment gap. The present data indicate few age-related differences in terms of the physiological characteristics of OUD and response to buprenorphine. However, multiple studies have noted that youth are a uniquely difficult population to recruit and retain in treatment (Woody et al., 2008; Moore et al., 2014; Schuman-Olivier et al., 2014a). Thus, subsequent studies should focus on determining developmentally appropriate buprenorphine treatment engagement strategies. Particular emphasis should be placed on evaluating various medication prescribing protocols, buprenorphine administration durations, and treatment settings.

Data to-date suggest that flexible medication prescribing and attendance requirements enhance treatment engagement. Going forward, it will be important to answer questions about optimal prescribing schedules for this population. For example, if daily clinic attendance and observed dosing is required at the beginning of treatment, how long should it last? Once youth are switched over to non-daily dosing, how many doses should be given at a time? Relatedly, should the number of unobserved doses permitted increase over time or remain constant? Along these lines, future studies should aim to determine best practices for ensuring adherence when at-home self-administration doses are provided (Subramaniam et al., 2009b) and for the use of drug testing as a tool to monitor youth.

There is an additional need to evaluate buprenorphine administration durations longer than 12 weeks and to understand how these different administration durations interact with the different prescribing protocols (discussed above) and treatment settings (discussed below). However, given youth's neurodevelopmental vulnerability (Fiellin, 2008), these efforts should also consider the potential iatrogenic effects of longer durations of buprenorphine administration. Relatedly, adult data have demonstrated that relapse rates are high in the OUD adult population and opioid agonist medications are protective against the increased mortality risk associated with treatment discharge (Sordo et al., 2017). If these patterns are

true of youth as well, then the potential iatrogenic effects of extended buprenorphine use must be balanced against the risk of post-discharge mortality.

Treatment setting does matter to OUD youth and potentially impacts treatment engagement and retention (Moore et al., 2014; Schuman-Olivier et al., 2014a). Future research efforts should focus on determining how different access points and treatment settings (e.g., primary care, addiction-focused clinics) impact engagement and retention. It is likely that developmentally-specific settings and engagement strategies for youth are important. Buprenorphine-waivered pediatricians and the settings they work in may be uniquely suited for treating this population (Committee On Substance Use Prevention, 2016; Hadland et al., 2016; Saloner et al., 2017). Retrospective or prospective observational data from heterogeneous real-world treatment programs may be particularly useful in this regard.

Another potentially important future research initiative is to isolate the independent effect of different psychosocial therapies in conjunction with buprenorphine treatment. Along these lines, it will be important to refine family-based psychotherapies and youth-focused therapeutic models that keep youth engaged in care and provide them with the skills necessary for healthy functioning after leaving treatment to support recovery and relapse prevention.

As new medications such as long-acting buprenorphine implants are developed, it will also be important to evaluate their effectiveness in this population. Although outside the scope of this review, extended-release naltrexone is another relapse prevention medication that has shown promise in youth (Vo et al., 2016). It is the subject of ongoing research and could be considered as an alternative approach in standard clinical practice. Methadone is also a potential treatment for youth (Bell et al., 2006; Guarino et al., 2009; Smyth et al., 2012) but is difficult for minors to access because of stricter federal regulations (Substance Abuse and Mental Health Services Administration, 2015).

Opioid addiction and overdose remain an ongoing and growing concern in many parts of the world. Expanding our understanding of how to develop and implement engaging and effective models of care for youth with OUD is critical to providing the early intervention necessary to prevent escalation of problematic opioid use and ultimately save the lives of adolescents and young adults.

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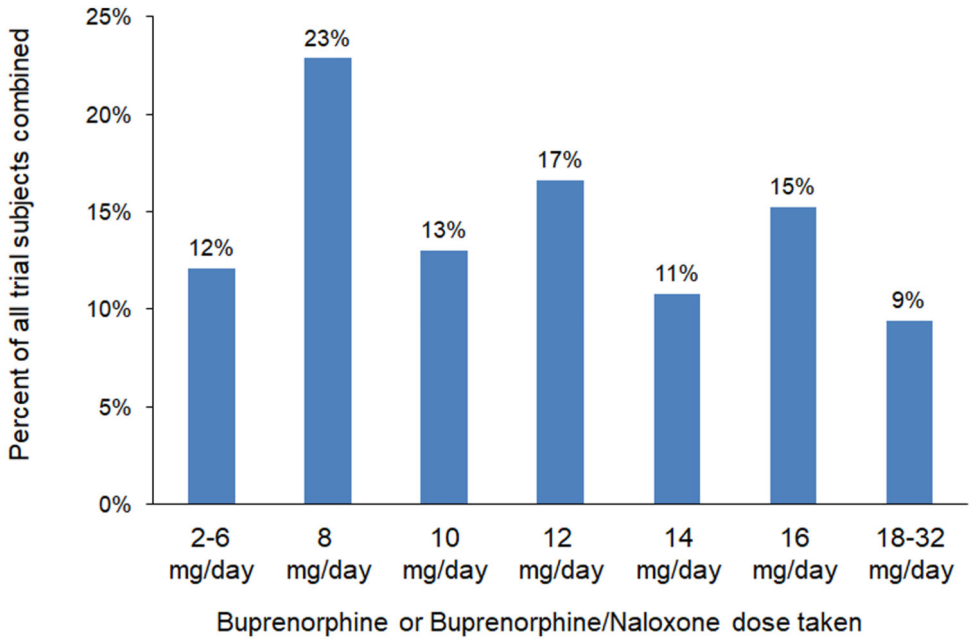

Figure 1.

Maximum daily dose of buprenorphine or buprenorphine/naloxone taken for adolescents and young adults across three randomized controlled trials (n=223)*. *Marsch et al. 2005, Woody et al. 2008, Marsch et al. 2016, Youngest age in these data is 15 years old (n = 1). Note 1: Only N=18 were used for Marsch et al. 2005 since the other 18 subjects in this trial received clonidine. Note 2: woody et al. 2008 data downloaded from https://datashare.nida.nih.gov/ To calculate maximum dose for each subject from Woody et al. 2008, we used vaiable EXSOSTOT, i.e., "*Total Amount Taken_mg Buprenorphine*" in the trial's orignal case report form (pg. 115). Note 3. Woody et al. 2008 reports N=150 out of N=152 who received a particular maximum dose of buprenorphine. Compare first paragraph of Results section and Consort diagram of original Woody et al. 2008 paper.

Table 1

Comparison of three randomized controlled trials that evaluated buprenorphine (BUP) or buprenorphine/naloxone (B/N) treatment for youth with opioid use disorders

	Marsch et al. 2005		Woody et al. 2008		Marsch et al. 2016	
	Trial Location: Burlington Vermont Duration of study participation: 28 days		Trial Location: Multiple U.S. Sites Duration of study participation: 84 days		Trial Location: New York City Duration of study participation: 63 days	
	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
STUDY CHARACTERISTICS						
Intervention	28-day clonidine detoxification	28-day BUP detoxification	2-week B/N detoxification	8-week stable B/N & 4-week BUP taper	28-day B/N detoxification	56-day B/N detoxification
Arm sample size (n)	18	18	78	74	28	25
DEMOGRAPHICS						
Average age	17.4	17.3	19.2	19.14	21	19.9
Max age	18	18	21	21	24	24
Min age	16	16	16	15	17	16
% under 18	44%	56%	18%	16%	14%	28%
Average age opioid use onset	14.7	15	-	-	17	16
% Male	28%	50%	62%	57%	54%	64%
% Caucasian	94%	100%	72%	76%	81%	70%
% with injection at study entry	39%	33%	48%	47%	57%	60%
Main Problem - Heroin	50%	55%	53%	57%	86%	76%
Main Problem - Rx Opioids	50%	45%	32%	36%	14%	24%
OTHER BASELINE SUBSTANCE USE/MENTAL ILLNESS						
Substances						
Alcohol	18% (use disorder)	17% (use disorder)	40% (past 30-day)	47% (past 30-day)	25% (use disorder)	28% (use disorder)
Nicotine	29% (use disorder)	50% (use disorder)	88% (past 30-day)	96% (past 30-day)	71% (use disorder)	32% (use disorder)
Cocaine	3% (use disorder)	17% (use disorder)	47% (past 30-day)	41% (past 30-day)	25% (use disorder)	28% (use disorder)
Amphetamine/Stimulant	6% (use disorder)	6% (use disorder)	50% (past 30-day)	43% (past 30-day)	7% (use disorder)	4% (use disorder)
Cannabis	12% (use disorder)	22% (use disorder)	69% (past 30-day)	64% (past 30-day)	21% (use disorder)	28% (use disorder)

	Marsch et al. 2005		Woody et al. 2008		Marsch et al. 2016	
	Trial Location: Burlington Vermont Duration of study participation: 28 days		Trial Location: Multiple U.S. Sites Duration of study participation: 84 days		Trial Location: New York City Duration of study participation: 63 days	
	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
Mental Illness						
ADD/ADHD	23%	18%	-	-	50%	32%
Oppositional Defiant Disorder	17%	23%	-	-	32%	42%
Major Depression	18%	18%	-	-	52%	52%
Conduct Disorder	6%	13%	-	-	29%	33%
Mixed Anxiety/Depression	-	-	-	-	71%	60%
Manic Episode Disorder	-	-	-	-	44%	36%
BUP & B/N ADMINISTRATION PROCEDURES						
Induction location	On site	On site	On site	On site	On site	On site
# hrs opioid abstinent at induction	24 hrs	24 hrs	6 hrs	6 hrs	8-10 hrs	8-10 hrs
First dose at induction	n/a	6 or 8 mg	2 mg	2 mg	6-8 mg (based on severity)	
Additional induction doses	n/a	None	2-6 mg 1.5-2 hrs after first dose		2-8 mg 1 hr after first dose	
Withdrawal measurement	CINAS†		SOWS†		CINAS†	
Take home doses permitted?						
During induction	n/a	No	No	No	No	No
After induction	n/a	No	Yes (weekends)	Yes (weekends)	Yes: 2-3 × per wk	Yes: 2-3 × per wk
MAX BUP or B/N DOSE GIVEN IN ONE DAY*						
32 mg	n/a	-	-	1%	-	-
24 mg	n/a	-	-	7%	-	-
22 mg	n/a	-	-	3%	-	-
20 mg	n/a	-	1%	11%	-	-
18 mg	n/a	-	-	5%	-	-
16 mg	n/a	-	9%	27%	18%	8%
14 mg	n/a	-	24%	7%	-	-

	Marsch et al. 2005		Woody et al. 2008		Marsch et al. 2016	
	Trial Location: Burlington Vermont Duration of study participation: 28 days		Trial Location: Multiple U.S. Sites Duration of study participation: 84 days		Trial Location: New York City Duration of study participation: 63 days	
	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
12 mg	n/a	-	24%	14%	11%	20%
10 mg	n/a	-	22%	16%	-	-
8 mg	n/a	39%	13%	8%	61%	44%
6 mg	n/a	61%	4%	1%	11%	28%
4 mg	n/a	-	1%	-	-	-
2 mg	n/a	-	1%	-	-	-
OUTCOMES **						
% Opioid abstinent	32% (-) (utox)	64% (-) (utox)	49% (-) (utox)	57% (-) (utox)	17% (-) (utox)	35% (-) (utox)
% Retained in treatment	39%	72%	21%	70%	18%	36%
Alcohol use ***	-	-	24% (+) (slf rpt)	22% (+) (slf rpt)	-	-
Cocaine use ***	87% (-) (utox) (entire sample)		26% (+) (slf rpt)	16% (+) (slf rpt)	-	-
Marijuana use ***	29% (-) (utox)	36% (-) (utox)	50% (+) (slf rpt)	50% (+) (slf rpt)	-	-
Benzodiazepine use ***	93% (-) (utox)	90% (-) (utox)	-	-	-	-
Risk behaviors (inject/sexual) ***	Reduced HIV risk behavior scores		33%	16%	-	-
Initiated naltrexone treatment	5%	61%	-	-	-	-

*Woody et al. 2008 trial dose data were downloaded from https://datashare.nida.nih.gov/

**"utox" = Urine toxicology; "(-)" indicates negative urine screen/abstinent; "(+)" indicates positive urine screen

***During treatment

†"SOWS" = Short Opiate Withdrawal Scale; "CINAS" = Clinical Institute Narcotic Assessment Scale

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Table 2

Design and results of observational studies of youth patients (pt) diagnosed with opioid use disorder (OUD) treated with buprenorphine (BUP) or buprenorphine/naloxone (B/N)[*]

	Mutlu et al. 2016	**Vo et al. 2016**	**Matson et al. 2014**	**Schuman-Olivier et al. 2014**	**Smyth et al. 2012[**]**	**Fishman et al. 2010**	**Levy et al. 2007**	**Bell et al. 2006**	**Ghandi et al. 2003**
# BUP or B/N pts	112	43	103	70	19	42	3	25	123
Mean age, (SD)	16.9 (0.96)	23.3 (No SD)	19.2 (1.6)	23.1 (1.7)	16.6 (0.9) [***]	18.3 (range: 13-20) [***]	17.6 (1.2)	16.1 (1.0)	21.8 (2.1)
% Male	90%	67%	51%	64%	46% [***]	53% [***]	66%	44%	56%
Study type [****]	RMRR	RMRR	RMRR	RMRR	RMRR	RMRR	Case reports	RMRR	Prospective
Cohort	Intakes 1/11-12/13	Intakes 1/13-4/15	Intakes 1/10-1/11	Intakes 11/07-6/10	Intakes 5/00-7/08	All pt data on file 4/08-1/10	Not reported	All pt data on file 8/00-4/03	Pts recruited over 7 months
Patient observation duration	Pt medical record data w/in 1 year post intake	Pt medical record data w/in 24 weeks post intake	Pt medical record data w/in 1 year post intake	Pt medical record data w/in 1 year post intake	Pt medical record data w/in 1 year post intake	Varies	Observations of up to 12 months	# of days from first to last dose	Follow-up data 1, 3, & 6 months post detoxification
Maintenance or detoxification	Maintenance	Maintenance	Maintenance	Maintenance	Maintenance	Maintenance	Maintenance	Maintenance	3-day detoxification
Outpatient or inpatient Tx	Both	Both	Outpatient	Outpatient	Outpatient	Both	Outpatient	Outpatient	Outpatient
Induction									
Location	Onsite - inpatient	Onsite	Pt home	Onsite & pt home	Onsite	Onsite - inpatient	Onsite & pt home	Not reported	Onsite
Required # hours opioid-free	8	Not reported	18-24	Usually 24 Methadone: 72	Heroin: 8 Methadone: 24	Not reported	24	Not reported	Not reported
First dose	2 mg	Not reported	8 mg	Clinical judgement	2 mg	Not reported	2 mg	Not reported	2-4 mg
Additional doses	6 mg max on day 1. Final day 1 dose used on day 2	Not reported	8 mg	30-60 min after 1st dose 12 mg max on day 1	2-6 mg "*later that afternoon*" 12 mg max on day 2	Not reported	Add 2 mg every 30 min until <5 on COWS	Not reported	2 mg
Withdrawal measure [†]	Clinician judgement	Not reported	Not reported	Pts need COWS >7 before induction	COWS	Not reported	Pts need COWS ≥ 5 before induction	Not reported	SOWS & ClNAS
At-home self administration									
During induction	No	No	Yes	Yes	No	No	Yes.	Not reported	No
After induction	Yes[‡]	Yes[‡]	Yes[‡]	Yes[‡]	Yes[‡]	Yes[‡]	Yes[‡]	Not reported	No
Highest reported dose per day	8 mg	Not reported	16 mg	mean 15.7 mg(SD 6.3 mg)	12 mg	Not reported	32 mg	16 mg	6 mg
Outcomes	• Month 1: 70% retention • Month 6: 26% retention	• Month 1: approx 75% OPI (-) • Month 3: approx	• 2nd clinic visit: 75% retention • Month 2: 45% retention	• Month 3: 57% retention • Month 6: 38% retention	• Month 3: 11% retention • Month 12: 5% retention	• Mean retention to 1st dropout: 9 wks (range 1-32)	• BUP/NAL is a viable Tx for OUD subtypes • Consider developmental challenges	• Mean retention, 58 days (range 1-185) • 68% re-entered Tx	• Month 1: 7% OPI (-) • Month 3: 10% OPI (-) • Month 6: 12% OPI (-)

	Mutlu et al. 2016	Vo et al. 2016	Matson et al. 2014	Schuman-Olivier et al. 2014	Smyth et al. 2012**	Fishman et al. 2010	Levy et al. 2007	Bell et al. 2006	Ghandi et al. 2003
	• Month 12: 16% retention • Month 1: 70% OPI (-) • Month 6: 20% OPI (-) • Month 12: 10% OPI (-) • 21% of drop out pts re-entered Tx	45% OPI (-) • Month 6: approx 40% OPI (-) • Month 1: approx 90% retention • Month 3: approx 60% retention • Month 6: approx 40% retention	• Month 12: 9% retention • Mean total clinic visits: 5.7 (range 1-23) • 85% OPI (-) while in Tx • 28% of drop out pts re-entered Tx w/in 1 year • THC or OPI (+) predicts dropout • BUP (-) predicts dropout	• Month 9: 21% OPI (+) • Month 12: 17% retention • Month 1: 48% OPI (+) • Month 2: 28% OPI (+) • Month 3: 29% OPI (+) • Lower BUPdose not entirely responsible for low retention	• N=8 planned discharge • N=5 drop out • N=4 switch to methadone	• Mean cumulative retention: 18 wks (range 1-43)		during study time window	• # days use heroin in past month: baseline m (SD): 27 (7) • # days use heroin in past month: month 1m (SD): 12 (12) • # days use heroin in past month: month 3m (SD): 12 (12) • # days use heroin in past month: month 6 m (SD): 11 (12) • 82.8% no aftercare engagement

*Tx = Treatment; OPI = opioid; (+) = positive urine toxicology result; (-) = negative urine toxicology result

**Heroin-dependent patients only (Prescription opioid-dependent patients excluded)

***Value applies to entire sample that includes youth not treated with BUP or B/N (value for BUP and B/N subsample was not reported)

****RMRR indicates “Retrospective Medical Record Review”

†“COWS” = Clinical Opiate Withdrawal Scale; “CINAS” = Clinical Institute Narcotic Assessment Scale

‡Based on patient's clinic attendance & urine toxicology results