



Evidence-based Treatment of Opioid Use Disorder in child and adolescent

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Introduction

A growing concern regarding illicit drug use among vulnerable youth has emerged in Iran.

Opium is the most common opioid of use, followed by heroin, crack heroin, and prescription opioids. In a national survey among students of 6 to 12th grades in 10 provinces of the country, the prevalence of the life- time, last year, and last month opium use was 2.5%, 1.5%, and 0.9%, respectively.

Especially vulnerable children, who live or work in streets, are expected to be particularly at risk of drug use disorders. The prevalence of current opioid use is reported in the range of **1.3% to 9% among street children** in Iran.

(Amin-Esmaili, et al., 2016; Mohammadkhani, et al., 2011; Ahmadkhaniha, et al., 2014)



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دبیرخانه شورای راهبردی تدوین راهنماهای سلامت

پروکل تشخیصی و درمانی

وابستگی به مواد افیونی در کودکان و نوجوانان

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Child Neglect and Substance Abuse

Introduction

Initiation of opioid misuse commonly occurs through the use of prescription opioids. Within the current opioid epidemic, among those with a history of heroin use, most report their first opioid exposure being a **prescription opioid**.

The 2017 National Survey on Drug Use and Health reports that, daily, an average of 886 youth aged 12-17 years and an average of 1273 youth aged 18-25 years initiate use of prescription medications. For heroin use, the average number of youth who initiated use each day was 25 and 126 persons ages 12-17 years and 18-25 years, respectively.

In response to the growing impact of the current opioid public health crisis in whole the world on adolescents and young adults, psychiatrists and pediatricians have an expanding role in identifying opioid use early, preventing escalation of risky use, reducing opioid-related harms, and delivering effective therapies.

IDENTIFYING OPIOID USE IN PRIMARY CARE SETTINGS

- Research, expert consensus, and clinical guidelines, including a position statement from the American Academy of Pediatrics, recommend **screening, brief intervention, and referral to treatment (SBIRT)** as a general strategy and framework for identifying and managing substance use in pediatric primary care during routine health supervision visits.
- There are numerous validated structured tools that have been used to screen youth for substance use as part of the SBIRT model.
- Young Adults Should Have Access to a Comprehensive Set of Assessment, Psychosocial and Pharmacologic Treatment, Harm Reduction, and Recovery Services Supported by Evidence.
- All young adults with SUD (regardless of readiness for treatment) can benefit from harm reduction services. Overdose education should include **naloxone provision** to all patients who use opioids and their family members.



Decision making in treatment of OUD in Adolescents

- Overall, vast evidence demonstrates that the risks of untreated OUD far outweigh the risks of any of the medications that treat OUD;
- ✓ untreated OUD greatly **increases** the likelihood of unintentional overdose, a portion of which can result in death. (National Academies of Sciences, Engineering, and Medicine, 2019)
- An alternative to medications for the treatment of OUD is the treatment of opioid withdrawal without subsequent medication treatment (detoxification).
- ✓ Data suggest that this is **the most common treatment option** utilized by adolescents.

(DEEPA, et al., 2019)

Decision making in treatment of OUD in Adolescents

- A retrospective cohort study of adolescents in a Medicaid database found that **76%** of adolescents with a diagnosis of OUD received any treatment within 3 months of a diagnosis of OUD and **only 4.7%** of adolescents who received treatment were prescribed buprenorphine, naltrexone, or methadone.
- Detoxification carries a subsequent risk of **overdose** and **decreased** rates of retention in care, thus maintenance treatment must be considered as an option whenever necessary in this population.

(Hadland et al., 2018)

Comparing MAT with non-medical approaches to OUD

- Early introduction of any medication was associated with better retention than drug-free approaches; median retention was 123 days in buprenorphine, 150 days in naltrexone, 324 days in methadone, and 67 days among youths who received only behavioral health services.
- Medications reduce substance use and cravings, enhance retention in care, and, in some cases, reduce mortality.

(Deepa, et al., 2019)

The Effect of MAT



As part of a comprehensive treatment program, medication-assisted treatment has been shown to:

- Increase retention in treatment
- Decrease illicit opioid use
- Decrease criminal activities, re-arrest, and re-incarceration
- Decrease drug-related HIV risk behavior
- Decrease pregnancy-related complications
- Reduce maternal craving and fetal exposure to illicit drugs

It is important to remember that medication is just one part of medication-assisted treatment.

Current research on young adults (18-24) and adolescents (under 18)

Despite this expert recommendation, a review of a database of publicly funded treatment programs (n=139,092) found that In total, 761 adolescents had a first treatment admission for heroin use and 2,325 for other opioid use. 26.3% of adults and 2.4% of adolescents in treatment for heroin received treatment medications, and that 12.0% of adults and 0.4% of adolescents in treatment for prescription opioid abuse received treatment medications.

In an observational study (n=552) of youth aged 20-26 who inject drugs, use of opioid agonist therapies (methadone or buprenorphine) was associated with a reduction in HCV acquisition among young adults. Youth who had received non-medication based treatments or detoxification did not show the same reduction.

(Feder, et al., 2017; Tsuie, et al., 2014)

Medication Accessibility for Adolescents with an Opioid Use Disorder

- Washington State data show that those ages 18-19 have the **shortest time** on buprenorphine of all age groups measured, and that those 20-24 also have significantly shorter time on buprenorphine than those ages 25-29. Most of the treatment that adolescents are routed to does not include medication.
- ❖ **Why is access to evidence-based opioid treatment so difficult for adolescents?**
 - ✓ There is a **dearth of providers** that serve youth with OUD.
 - ✓ The beliefs and attitudes towards medication for adolescents with OUD stand in the way.
- Medication stigma on the part of providers, the criminal legal system, loved ones, and adolescents themselves may prevent adolescents from connecting with the treatment.

Treatment Retention and Engagement

- A retrospective chart review of individuals aged 14-25 enrolled in an outpatient treatment setting providing buprenorphine, **retention** was **45%** at 60 days and **9%** at one year.
- A systematic review of literature on medication retention in adolescents and young adults with OUD revealed that **younger age** was associated with **shorter retention** periods.
- A retrospective chart review indicated a buprenorphine retention rate of 56% at 6 months for people 18–25 years, compared to 78% among older adults.

REDUCING OPIOID-RELATED RISKS IN PRIMARY CARE SETTINGS

- Harm reduction in the primary care setting incorporates practical and evidence-based strategies that are intended to reduce negative consequences associated with drug use, while also promoting health and well-being.
- Harm reduction education is particularly important for youth misusing opioids because they tend to have riskier use and/or injection practices compared with older populations.
- They are often less aware of the dangers associated with injection and less knowledgeable about how to reduce risk for infectious complications.

Medication Assisted Treatment

There are currently 3 medications used in the treatment of OUD in youth:

- ✓ **extended-release naltrexone**
- ✓ **Buprenorphine**
- ✓ **rarely methadone**



small youth-focused studies and evidence extrapolated from adult data support the use of medications in the treatment of an OUD for youth as the **gold standard**.

Treatment for Adolescents with an Opioid Use Disorder

Medication	Research findings	Clinical considerations for adolescents
Buprenorphine	<ul style="list-style-type: none"> Two randomized controlled trials with people 15-21 (Woody et al., 2008) and 16-24 (Marsch et al., 2016) show that longer buprenorphine treatment episodes result in lower opioid use compared to shorter episodes. A randomized controlled trial with people 16-18 compared buprenorphine and clonidine detoxification. Higher opioid abstinence was shown in the buprenorphine group (Marsch et al., 2005). 	<ul style="list-style-type: none"> Buprenorphine is the only medication approved by the US Food and Drug Administration (FDA) to treat opioid use disorder in people 16 years and older. Despite FDA approval and explicit recommendation by the American Academy of Pediatrics to improve access for adolescents (Committee on Substance Use and Prevention, 2016), buprenorphine remains under prescribed.
Methadone	<ul style="list-style-type: none"> No randomized controlled trials examine methadone in adolescents. A retrospective chart review indicated that adolescents on methadone had longer treatment retention than adolescents on buprenorphine (Bell & Mutch, 2006), which parallels findings in adults. Two studies showed that adolescents enrolled in methadone treatment had less heroin use than those who dropped out of treatment (Kellogg et al., 2006; Smyth, Elmusharaf & Cullen, 2018). 	<ul style="list-style-type: none"> Methadone is not FDA-approved to treat people under 18. Methadone can only be administered in an Opioid Treatment Program (OTP), which requires written, parental consent for people under 18. OTPs are typically set up to serve high volumes of adults with opioid use disorder; such environments may not be therapeutic for adolescents. Because methadone is used infrequently with adolescents, there is less information to inform dosing decisions.
Naltrexone	<ul style="list-style-type: none"> Mitchell et al. (2021) attempted a randomized controlled trial with youth (15-21) comparing extended-release naltrexone (XR-NTX) with "treatment as usual". Numerous randomizing challenges meant that results are difficult to interpret. Those who received naltrexone XR-NTX had an average of 1.3 injections, indicating very low retention. A retrospective chart review of an Australian Emergency Department examined 8 adolescents (aged 15-19) before and after a naltrexone implant. Results indicated reduction in overdose associated with naltrexone implants (Hulse & Tait, 2003). 	<ul style="list-style-type: none"> Naltrexone is not FDA-approved to treat people under 18. <u>Overdose risk is increased when people miss doses or discontinue naltrexone.</u> Adolescents tend to have poor treatment retention; therefore, this consideration is especially important. Developmentally, adolescents are prone to test limits. In the case of naltrexone, they may try to "challenge" the medication's blocking effect. That is, take large amounts of opioids to see if they can feel the effect on top of naltrexone. <u>This behavior increases risk for overdose.</u> As with adults, naltrexone: 1) <u>does not have established efficacy in preventing return to opioid use</u>; and 2) induction onto naltrexone can be a barrier because full opioid withdrawal is required prior to induction.

Evidence for treatment of OUD in Adolescents

TABLE 3 Evidence for Treatment With Medication for OUD

Study	Study Population	Study Description	Follow-up	Main Outcomes
Buprenorphine Marsch et al ⁷⁰	Adolescents ages 13–18 y (<i>n</i> = 36)	A double-blind, double-dummy, parallel-groups randomized controlled trial; assigned to a 28-d outpatient detox with buprenorphine or clonidine. Buprenorphine taper: <ul style="list-style-type: none"> • If ≥ 70 kg and/or self-reported use >3 bags of heroin or equivalent in opiates, given daily starting dose of 8 mg of buprenorphine; otherwise started on 6 mg • Then tapered down by 2 mg every 7 d 	28-d detox only	72% of those in buprenorphine group were retained in treatment versus 39% of those in the clonidine group ($P < .05$). For those in the buprenorphine group, a significantly higher percentage of scheduled urine test results were opiate negative (64% vs 32%; $P = .01$).
Woody et al ⁷¹	Youth ages 15–21 y (<i>n</i> = 152)	Randomized clinical trial at 6 US community programs; assigned to 12 wk of buprenorphine or 14-d taper (detox). Buprenorphine dosing: <ul style="list-style-type: none"> • 12-wk group: titrated up to max of 24 mg/day with taper starting at week 9 • 14-d detox group: titrated up to max of 14 mg/day and tapered off by day 14. 	12 wk	Those in the detox group had significantly higher proportions of opioid-positive urine test results at weeks 4 and 8 but not at week 12. Those in buprenorphine group had less injection drug use and more remained in treatment versus youth in detox group.
Matson et al ⁵²	Youth ages 14–25 y (<i>n</i> = 103)	Retrospective chart review of clinic patients seen at an adolescent medicine specialty addiction medicine clinic. Buprenorphine dosing: <ul style="list-style-type: none"> • Home induction based on protocol; majority were on 8 mg twice daily maintenance. 	1 y	Opioid abstinence was high at 85.2% with high adherence at 86.6% during clinic visits; 75% of patients returned for a second visit. Low retention of 45% at 60 d and 9% at 1 y.
Marsch et al ⁷²	Youth ages 16–24 y (<i>n</i> = 53 in total; <i>n</i> = 11 under age 18)	Double-blind, placebo, randomized controlled trial (2 sites); assigned to 28-d taper versus 56-d taper of buprenorphine. Buprenorphine taper: <ul style="list-style-type: none"> • Titrated up to max of 16 mg/day. 	63 d	Those in longer taper group had a significantly higher percentage of opioid-negative urine test results (35% vs 17%, $P = .039$).
Extended-release naltrexone Fishman et al ³³	Youth ages 16–20 y (<i>n</i> = 16)	Case series in a community-based adolescent substance abuse treatment program in Baltimore, Maryland, offering monthly injection of extended-release naltrexone.	4 mo	85% (12 out of 14 who came back for a second visit) received at least 2 doses. 63% were retained in treatment of at least 4 mo. 56% had either substantially decreased opioid use, improvement in at least 1 psychosocial domain, or no new problems due to substance use.
Vo et al ⁷³	Youth ages 17–25 y (<i>n</i> = 14 in home-based delivery group; <i>n</i> = 21 in treatment as usual group receiving naltrexone in clinic)	2-y pilot clinical quality improvement initiative offering home-based delivery of extended-release naltrexone with a convenience sample of youth attending a community-based adolescent substance abuse treatment program in Baltimore, Maryland. Intervention: Naltrexone initially delivered to the treatment center from a pharmacy and then brought to patient's home by a team consisting of a nurse practitioner and a counselor every 3–4 wk.	16 wk	64% (9 out of 14) received at least 1 dose of extended-release naltrexone at home. Home delivery group had an average of 3.3 doses of the potential 5 monthly doses (including first inpatient dose) versus 2.0 doses for treatment as usual group. 50% of the home delivery group received all 5 doses versus 9% in the treatment-as-usual group.

Evidence for treatment of OUD in Adolescents

TABLE 3 Continued

Study	Study Population	Study Description	Follow-up	Main Outcomes
Methadone	DeAngelis and Lehmann ⁷⁴	Community-based opioid treatment center in Connecticut. Intervention: "low-dose" methadone maintenance regimen based on individual needs for 2–13 wk, followed by a taper off methadone lasting 3–14 wk.	18 mo	Average methadone dose was 20 mg/day with a range of 10–60 mg/day. Average maintenance phase lasted 7 wk, and average taper phase lasted 7 wk. 35% of youth remained opioid-free and were retained in treatment or were working or in school.
	Guarino et al ⁷⁵	Qualitative study with focus groups consisting of patients ($n = 7$), staff ($n = 6$), and parents ($n = 3$) to better understand components of effective treatment with methadone in a young adult methadone program in New York. Treatment model: outpatient intensive weekly counseling in individual and group settings plus the option of family therapy; patients encouraged to taper off methadone once status is "stabilized."	n/a	The following themes emerged: (1) youth themselves must be motivated for treatment; (2) engagement in treatment is often challenging given youth's limited lifetime history with significant negative consequences due to use; (3) youth-centered treatment is desired with variable treatment options; (4) duration of treatment should be dictated by individual youth's need, goals, and outcomes; (5) effective treatment involves the family of youth; and (6) youth remain hopeful that they will be tapered off methadone.
Comparative effectiveness trials	Bell and Mutch ⁷⁶	Retrospective chart review of all youth at first presentation for treatment of opioid dependence in an Australian treatment center: 20 youth received methadone, 25 youth received buprenorphine, and 15 youth received symptomatic medication for withdrawal; 1 received no medication.	Variable	Youth receiving methadone had significantly longer retention in the first treatment episode versus those receiving buprenorphine (mean: 354 vs 58 d; $P < .01$) and missed fewer days in the first month (mean: 3 vs 8 d; $P < .05$). However, time to re-entry after first episode of buprenorphine was significantly shorter than after methadone.
	Mattick et al ⁶¹	Cochrane Systematic Review comparing buprenorphine to placebo and buprenorphine to methadone for opioid dependence. Quality of evidence varied from high to moderate quality.	Interventions ranged in duration from 2 to 52 wk	High quality of evidence (14 studies) that buprenorphine was superior to placebo in retention of participants at all doses examined (2–16 mg/day). Moderate quality of evidence (3 studies) that high-dose buprenorphine (≥ 16 mg/day) was more effective than placebo in suppressing illicit opioid use. High quality of evidence (5 studies) that buprenorphine in flexible doses was less effective than methadone in retention; however, no difference was observed in suppression of illicit opioid use with moderate quality of evidence (12 studies).
	Lee et al ⁷⁷	Open-label, randomized controlled, comparative effectiveness trial at 8 US community-based inpatient programs with follow-up in outpatient program. 283 randomly assigned to extended-release naltrexone versus 287 randomly assigned to buprenorphine.	24 wk	Extended-release naltrexone had a substantial induction challenge with only 72% of participants successfully initiated versus 94% of participants successfully initiated onto buprenorphine ($P < .0001$). Among those with successful induction, there was no significant difference in 24-wk relapse between the 2 groups ($P = .44$). Among those with successful induction, there was no significant difference in opioid-negative urine test results or opioid-abstinent days between the 2 groups.

n/a, not applicable.

Evidence for treatment of OUD in Adolescents

Notably, in 2015 the Vancouver Health Authority issued new clinical practice guidelines that recommend buprenorphine as a first line treatment for opioid use disorder (OUD), including among youth;

Compared to methadone, buprenorphine has been associated with **improved educational and employment outcomes, lower relapse rates, higher therapy retention rates, lower likelihood of misuse, and lower likelihood of overdose.**

a 2017 meta-analysis that included 19 studies of adults with OUD found that overdose **deaths decreased** by 70% when individuals were stabilized on buprenorphine/ naloxone and 80% when stabilized on methadone.

(BC Centre on Substance Use and BC Ministry of Health, 2017; Vancouver Coastal Health, 2017; Amass, et al., 2004; Bell, et al., 2009; Sordo, et al., 2017)

Buprenorphine

When buprenorphine is offered, it is commonly framed as a detox medication with short stints on buprenorphine focused on tapering off the medication.

Youth prescribed buprenorphine for OUD are **more likely to be retained** in treatment and have **lower rates of illicit opioid** use while taking buprenorphine.

Short-term buprenorphine tapers contradict research findings, which show that **longer** buprenorphine treatments yield better results, that is, better treatment retention and less opioid use.

One randomized trial demonstrated that buprenorphine-naloxone **maintenance** was **more effective** than buprenorphine- naloxone **tapering** for opioid-dependent adolescents.

(Pecoraro, et al., 2013; Matson, et al., 2014; Marsch, et al., 2016, Borodovsky, et al., 2018)

Buprenorphine

There has been one study in which researchers assessed efficacy of a 28- day buprenorphine taper when compared with a 28-day clonidine taper (used to treat opioid withdrawal symptoms) in a purely adolescent group (13–18 years of age), which showed that buprenorphine **was superior** to clonidine in **retention** and **reduction of opioid use**.

In addition, the receipt of buprenorphine after an opioid overdose was associated with decreased all-cause mortality and opioid-related mortality.

(Marsch, et al., 2005;)

Buprenorphine

Woody et al, compared 2 different regimens among 152 youth 15 to 21 years of age with opioid dependence and found that:

Those youth receiving buprenorphine for 12 weeks (8 weeks of maintenance dosing with a 4-week taper off) reported **less opioid use** at 4 and 8 weeks, **less injection** drug use, and demonstrated **retention** in treatment compared with youth receiving a 14-day taper of buprenorphine.

In a smaller study, researchers found similar results with youth receiving a 56-day buprenorphine taper, demonstrating **greater treatment retention** and a significantly **higher percentage** of opioid-negative urine test results compared with youth who only received a 28-day taper (35% vs 17%). These authors also found that a 2- to 3-times-weekly attendance requirement was associated with better short-term outcomes when compared with a daily attendance requirement.

Buprenorphine

However, Borodovsky et al found overall sufficient evidence for using buprenorphine as a long-term strategy to treat OUD in youth, Importantly, detoxification with buprenorphine or methadone **has not** been shown to be effective in adults or youth in promoting abstinence beyond initial stabilization; thus, **maintenance with medications** is the recommended approach.

Additionally, there is a promising new formulation of buprenorphine for the treatment of OUD that may benefit youth because it may overcome adherence issues found with sublingual daily dosing: buprenorphine extended-release injection for subcutaneous use.

(Bell, et al., 2006; Matson, et al., 2014; Lafwall, et al., 2018; Haight, et al., 2019)

Comparison of Buprenorphine and Clonidine

In a study by Motamed et al., 36 adolescents (aged 13 - 18) with opioid dependence received a 28 day, outpatient, medication-assisted withdrawal with buprenorphine or clonidine. Patients in this study also took behavioral counseling. Both heroin dependence and prescription opioid-dependence adolescents who received buprenorphine experienced notably **better treatment outcomes** than those who received clonidine.

In another study , buprenorphine treatment was found to be more effective than clonidine in **controlling opioid withdrawal**. However, it **lost its superiority** towards the end of the follow-up. It seems that clonidine could be a good alternative to buprenorphine in detoxification. In the era of individualized medicine, there is no debate against having multiple evidence-based treatment options where individual planning can be tailored to patient risks and needs, instead of using only one of the treatments, it is **better to develop a combination** protocol of both methods.

Inpatient Opioid Withdrawal Management of Street Children and Adolescents in Iran

Clinical chart abstractions were performed on a sample of 40 serial opioid-dependent street children and adolescents (mean age: 11.14 ± 3.6 years)

Clonidine, ibuprofen, and hydroxyzine were used for the symptomatic treatment of opioid withdrawal. In this study, clonidine was initiated at 0.1 mg/per day in two divided doses, and then the dose was increased to 0.4 mg/day given in 2 - 3 divided doses based on the severity of the withdrawal symptoms on days 2 - 4 following admission. All clonidine doses were delivered after blood pressure had been controlled, which was indicated by a systolic blood pressure > 90 mmHg.

The study suggests that inpatient withdrawal management with clonidine, antihistamines, and non-steroidal anti-inflammatory drugs could be **feasible** for and **well tolerated** by children and adolescents with opioid dependence during the inpatient period.

(Firouzkouhi, et al., 2016)

Naltrexone

In a small case series of 16 youth who received **extended-release naltrexone** at an outpatient addiction specialty treatment center, **63%** were retained in treatment of at **least 4 months**, and 56% had a “good” outcome (defined as having decreased opioid use, improvement in at least 1 psychosocial domain, or no new problems due to use).

Monthly naltrexone may be useful for youth **without a long history** of opioid use and those who are **able to abstain** from opioids to initiate therapy. Additionally, for youth who have **difficulty with daily adherence** to oral medication, such as buprenorphine, extended-release naltrexone may be preferred.

(Mattick, et al., 2014; Camil, et al., 2020)

The Use of Naltrexone Among Young Adults with Opioid Use Disorder

One study examined the use of Naltrexone among young adults and also relationships between retention in treatment and 1) family engagement, 2) assertive community outreach and 3) use of other substances in a sample of youth being treated for opioid use disorders

Family sessions contributed to increased retention in treatment, evidenced by the increase in number of injections. More frequent communication resulted in a higher number of received injections. There is a **positive correlation** between number of **family sessions** and **number of doses**.

The study showed that most young adults seeking treatment for opioid use disorder are also using other substances and that **the longer** they stay in treatment, the **greater** the chance of **decreasing use of other drugs**. The review of 13 studies with 462 young adults found that Naltrexone is effective in **improving treatment retention, extending abstinence, and preventing relapses** in adolescents and young adults with OUD.

The Use of Naltrexone Among Young Adults with Opioid Use Disorder

Seven articles that included 242 adolescents or young adults being treated with naltrexone for OUD were identified from the literature.

In summary, naltrexone has shown to be **effective in improving treatment retention, extending abstinence, and preventing relapses** in adolescents and young adults with OUD. As with the studies involving alcohol, naltrexone appeared to be well-tolerated in participants with opioid use disorders.



(Rozenberg, et al., 2020)

Summary of studies of naltrexone use in adolescent and young adults with opioid use disorders

Opioid Abuse					
Study	Total N	Design and setting	Intervention	Treatment outcomes	Tolerability of treatment
Hulse & Tait, 2003	N=8 Adolescents with median age 18	Retrospective case series review of the hospital medical records across four teaching hospitals	Naltrexone implant treatment	Opioid overdose in post-implant treatment Two opiate and four non-opiates overdoses post implantation	Well-tolerated treatment
March et al., 2005	N=36 adolescent and young adults (mean age 17.3)	A double-blind, double-dummy, parallel group randomized controlled trial	Random assignment to 28 days MAT assistant w/d treatment with clonidine and buprenorphine, than offered treatment with naltrexone	Treatment retention, opioid abstinence 61% of participants detoxified from buprenorphine and 5% from clonidine initiated naltrexone treatment	Well-tolerated treatment
Fishman et al., 2010	N = 16 adolescent and young adults (mean age 18.5 years)	Clinical chart abstractions by convenience sample	Treated for opioid dependence with XR-NTX who attended at least 1 out-patient clinical follow-up visit	With 63% retained in treatment and 56% with “good” outcome	Well-tolerated treatment
Dhawan, et al., 2014	N=2 Ages 15 and 17	Case studies	Oral naltrexone and buprenorphine for treatment of opioid dependence	Ongoing abstinence from opioid for over two years with buprenorphine and over a year with naltrexone	Occasional body aches and discomfort
Vo et al., 2016	N = 56 young adults 19-26 years old (mean age 23.1)	Naturalistic study using retrospective chart review over 24 weeks outpatient program	Community treatment program using XR-NTX (23%) and buprenorphine (77%)	Mean number of XR-NTX doses was 4.1 Retention in treatment 65% at 12 weeks and 40% at 24 weeks Opioid negative screen	Well-tolerated treatment

Summary of studies of naltrexone use in adolescent and young adults with opioid use disorders

				50% at 12 weeks and 39% at 24 weeks. No statistically significant difference between groups	
Hadland et al., 2018	N=3,654 Ages 13-22	Retrospective cohort study using environmental data and health insurance claims from 11 states enrolled in Medicaid Jan. 2014 – 2015	Treatment for opioid use within 3 month of diagnosis with naltrexone, buprenorphine, naltrexone, or methadone, compared with behavior treatment only	Retention in treatment among youth receiving naltrexone was longer than recipients of behavioral services only and slightly longer than buprenorphine group	Well-tolerated treatment
Vo et al., 2018	N = 14 young adults (mean age 20.5)	Naturalistic case series based on retrospective chart review. Outpatient treatment	16 weeks of treatment of home-based administration XR-NTX with assertive outreach	50% of home-based treatment group versus 9% treatment as usual received 5 doses	Well tolerated with mild side effects possibly associated with XR-NTX administration, such as abdominal discomfort, headaches, and dizziness

Methadone

Methadone is rarely used as a second- line treatment of an OUD in youth. Methadone access is restricted to **licensed opioid treatment programs** and is further restricted for **youth 16 and 17 years** of age. Typically, youth, **18** years of age must be **pregnant** or demonstrate **2 treatment failures** of detoxification or **psychosocial interventions** without pharmacotherapy to be eligible for treatment with methadone.

Individual patient **characteristics** and **preferences** should be taken into consideration when choosing a first line opioid agonist treatment. For patients at high risk of dropout (such as adolescents and socially unstable patients), treatment retention should take precedence over other clinical considerations.

(Feder, et al., 2017; Hammond, et al., 2016)

Primary care management of opioid use disorders

Box 2. Clinical factors in prescribing methadone versus buprenorphine–naloxone

Factors favouring methadone include the following:

- Injection opioid use
- Pregnant or adolescent injection opioid users
- Other risk factors for treatment dropout (eg, unstable housing, lack of social support, concurrent mental illness)
- Previous treatment dropout with buprenorphine or adverse effects

Factors favouring buprenorphine–naloxone include the following:

- Oral prescription opioid use
- At risk of methadone toxicity (eg, elderly; heavy alcohol users; those with cardiac or respiratory compromise, at risk of QT prolongation, or taking benzodiazepines or atypical antipsychotics)
- In a rural community without methadone access
- Previous treatment dropout with methadone or adverse effects
- Job requiring alertness (eg, driving or operating machinery)
- Sexually active men at low risk of treatment dropout
- Requiring regular primary care for screening, health maintenance, or a chronic medical or psychiatric illness

(Anita Srivastava, et al., 2017)

Methadone

In a small retrospective study of 61 youth, methadone was shown to have better retention rates compared with buprenorphine. This is a similar pattern seen in studies of adult patients; although, at **higher doses**, both medications performed equally well in suppressing illicit opioid use among adults.



(Bell, et al., 2006; Mattick, et al., 2140)

Treatment Gap

There are also a number of gaps in the delivery of the mentioned medications to youth with OUD;

- ❖ only 1 in 4 commercially insured youth with an OUD received any pharmacotherapy to treat their addiction. Specialty treatment programs reported 2.6% of youth 15 to 17 years of age received medications to treat heroin use disorder, compared with 26% of adults, and only 0.4% of youth received medications to treat prescription OUD compared with 12% of adults.
- ❖ Similarly, ,5% of youth ,18 years of age and approximately one-quarter of young adults 18 to 22 years of age with Medicaid received medications for OUD within 3 months of diagnosis. Timely receipt of pharmacotherapy to treat OUD has been associated with greater retention in care, compared with youth receiving only behavioral services.
- ❖ Less than 2% of youth between 13 to 22 years of age received medications for OUD within 30 days of a nonfatal opioid-related overdose, whereas 30% received behavioral services. In contrast, 30% of adults received medications for OUD after an overdose.

Treatment Gap

Among young adults seeking to enroll in substance use treatment, **only 35%** successfully linked to treatment because of **stigma** and/or **discrimination**, **insurance barriers**, **wait lists**, and **inability to pay**. There are also significant **racial and sex** disparities, with fewer African American and Hispanic youth as well as females receiving pharmacotherapy compared with white males.



Summary of Selected Studies Reviewed by Expert Panel

TABLE 1 Summary of Selected Studies Reviewed by Expert Panel (Studies Listed Alphabetically)

Author and y	Sample	Setting	Study Period	Design	Outcome	Main Findings	Contribution to Summit Principles
Chadi et al ⁴ 2019	N = 81 144 youth ages 10–22 y continuously enrolled in Medicaid for at least 6 mo diagnosed with NUD	Insurance claims data from 11 states enrolled in Medicaid	January 2014 to June 2015	Retrospective cohort study to compare youth who received treatment with those who did not	Receipt of treatment (counseling for NUD, varenicline, or sustained-release bupropion) within 6 mo of NUD diagnosis	There was low receipt (5.5%) of treatment of NUD among youth enrolled in Medicaid. Among youth with NUD receiving treatment, older age and co-occurring mental health and SUD were associated with receipt of pharmacotherapy.	Identifies gaps in the provision of any treatment of NUD among young adults, and, in particular, gaps in the provision of pharmacotherapy for NUD. Suggests substantial area for improvement in the treatment of NUD among young adults.
Hadland et al ⁵ 2017	N = 20 822 youth ages 13–25 y diagnosed with OUD	Health insurance claims data from all 50 states enrolled in a large US commercial health insurer	January 2001 to December 2014	Retrospective cohort study to compare youth who received medications for OUD with those who did not	Dispensing of medication (buprenorphine or naltrexone) within 6 mo of first OUD diagnosis	Medication receipt increased over the study period, but only 1 in 4 individuals (26.8%) received pharmacotherapy. Younger individuals ($P < .001$), female patients ($P < .001$), and Black and Hispanic youth ($P < .001$) were less likely to receive a medication than older, male, and non-Hispanic white youth, respectively.	Identifies gaps in the provision of pharmacotherapy for young adults with OUD. Also, identifies likely disparities in the receipt of treatment by age, sex, and race and ethnicity that should be prioritized, as access to and use of medications for OUD are expanded.
Hadland et al ³ 2018	N = 4837 youth ages 13–22 y diagnosed with OUD	Health insurance claims data from 11 states enrolled in Medicaid	January 2014 to December 2015	Retrospective cohort study to compare youth who received any treatment (including medications for OUD and/or behavioral therapy)	Retention in care, with attrition defined as ≥ 60 d without any treatment-related claims	Youth who received buprenorphine, naltrexone, or methadone within 3 mo of diagnosis of OUD were 42%, 46%, or 68% less likely to discontinue treatment, compared with youth who received behavioral treatment only.	Reveals the likely role of pharmacotherapy for OUD in supporting retention in care among young adults. Data suggest that retention in care may be improved with the use of medications.
Marsch et al ⁶ 2016	N = 53 youth ages 16–24 y who met DSM-IV criteria for opioid dependence	New York City, New York	2005–2010	Multicenter randomized controlled trial, double-blind and placebo controlled to compare duration of taper off buprenorphine (56 vs 28 d) after withdrawal treatment	Opioid abstinence and treatment retention	Individuals with a 56-d buprenorphine taper had a significantly higher percentage of opioid-negative urine test results (35% vs 17%; $P = .039$) and were retained in treatment significantly longer (37.5 vs 26.4 d; $P = .027$) than individuals with a 28-d buprenorphine taper.	One of the only youth-focused trials to date. The sample was composed mostly of young adults and revealed superiority of maintenance buprenorphine given over 4 wk, compared to 2 wk, suggesting better outcomes with longer buprenorphine treatment. Additionally, a higher frequency of visits was associated with poorer treatment outcomes.
Rafful et al ⁷ 2018	N = 671 individuals who inject drugs	Tijuana, Mexico	March 2011 to July 2017	Longitudinal cohort study comparing individuals who received IDT to those who did not	Reported nonfatal overdose event in the past 6 mo	IDT significantly increased the odds of reporting a nonfatal overdose event (aOR: 1.76; 95% CI: 1.04–2.96).	Similar to the findings of the systematic review by Werb et al, ⁸ suggests that compulsory treatment may be associated with harm.
Sordo et al ⁹ 2017	N = 138 716 individuals with OUD	19 prospective or retrospective cohort studies that	Studies published until	Systematic review and meta-analysis comparing individuals who received	Risk for all cause and overdose mortality during and after	Retention in methadone and buprenorphine treatment was associated with substantial	Compiling data across numerous studies, highlights that maintaining young adults in

TABLE 1 Continued

Author and y	Sample	Setting	Study Period	Design	Outcome	Main Findings	Contribution to Summit Principles
		reported deaths from all causes or overdose	September 2016	opioid agonist treatment to those who did not	substitution treatment. Trends in mortality risk after initiation and cessation of treatment	reductions in the risk for all cause and overdose mortality. Mortality risk increased during the induction phase and time immediately after leaving treatment.	treatment with an opioid agonist is likely highly protective.
Wakeman et al ¹⁰ 2019	N = 2706 adult primary care patients (1353 matched pairs from practices with and without integrated addiction treatment)	Boston, Massachusetts	November 2014 to December 2015	Retrospective cohort study comparing individuals who received integrated primary care-based addiction treatment (medications for OUD and recovery coaching) to those who did not	Inpatient admissions, hospital bed days, ED visits, primary care visits	The intervention group had fewer inpatient days (997 vs 1096 d, with a mean difference of 7.3 d per 100 patients; $P = .03$) and a lower number of ED visits (36.2 vs 42.9 visits per 100 patients; $P = .005$) than matched patients without pharmacotherapy and recovery coaching.	Describes the experience of a hospital system that has been able to provide comprehensive outpatient care to individuals with SUDs and some of the associated benefits, including shorter hospitalization and fewer ED visits.
Werb et al ⁸ 2016	N = 10 699 individuals with SUDs	9 peer-reviewed scientific studies presenting original data assessing outcomes of compulsory treatment	Studies published until July 2015	Systematic review comparing those who received compulsory drug treatment to those who did not	Posttreatment drug use, criminal recidivism	In the majority of studies (78%), researchers did not detect any significant positive impacts of compulsory treatment on drug use or criminal recidivism, with the authors of some studies suggesting potential harms.	Highlights that compulsory treatment, although commonly pursued, is not associated with improved treatment outcomes and, in fact, may be harmful.
Woody et al ¹¹ 2008	N = 152 youth ages 15–21 y who met DSM-IV criteria for opioid dependence and sought outpatient treatment	6 community program sites in New Mexico (2), Delaware, Maine, Maryland, and North Carolina	July 2003 to December 2006	Randomized controlled clinical trial comparing 12 wk of buprenorphine treatment to detoxification with buprenorphine over 14 d	Opioid-positive urine test results at weeks 4, 8, and 12	Individuals in the detox group (14-d taper) had higher proportions of opioid-positive urine test results compared with individuals in the 12 wk buprenorphine-naloxone group at weeks 4 ($P < .001$) and 8 ($P = .001$), but not at week 12 ($P = .18$).	One of the only youth-focused trials to date. The sample is composed mostly of young adults and revealed the superiority of maintenance buprenorphine over detox only over 2 mo.

aOR, adjusted odds ratio; CI, confidence interval; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ED, emergency department; IDT, involuntary drug treatment; NUD, nicotine use disorder.

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