Management of opioid use disorder in the USA: present status and future directions

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Opioid use disorder is characterised by the persistent use of opioids despite the adverse consequences of its use. The disorder is associated with a range of mental and general medical comorbid disorders, and with increased mortality. Although genetics are important in opioid use disorder, younger age, male sex, and lower educational attainment level and income, increase the risk of opioid use disorder, as do certain psychiatric disorders (eg, other substance use disorders and mood disorders). The medications for opioid use disorder, which include methadone, buprenorphine, and extended-release naltrexone, significantly improve opioid use disorder outcomes. However, the effectiveness of medications for opioid use disorder is limited by problems at all levels of the care cascade, including diagnosis, entry into treatment, and retention in treatment. There is an urgent need for expanding the use of medications for opioid use disorder, including training of health-care professionals in the treatment and prevention of opioid use disorder, and for development of alternative medications and new models of care to expand capabilities for personalised interventions.

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Introduction

Opioid use disorder can be defined as a pattern of opioid use associated with a range of physical, mental, social, and legal problems, and with increased mortality leading to clinically significant impairment or distress (panel 1).[1–4] Although opioid use disorder often follows a chronic course, it can respond to treatment. The correct use of medications to treat opioid use disorder markedly improves outcomes, facilitates recovery, and protects against overdoses. Despite the strength of the evidence, reluctance exists to acknowledge opioid use disorder as a medical disorder and to treat the disorder with medications among many clinicians and the lay public. By conceptualising opioid use disorder as a chronic illness, clinicians could better understand its course and treatment, how to achieve and sustain remission, and help prevent relapse.[5]

Prevalence, comorbidity, and risk factors

As with other substance use disorders, younger age, male sex, lower educational attainment level, being unemployed, and having lower income are known to increase the risk of opioid use disorder. In the USA, the prevalence of opioid use disorder is greater among Native Americans, black people, and non-Hispanic white people than among the Hispanic or Asian American populations.[6–9] Although the disorder was more prevalent in rural compared with urban communities in the USA in 2003–08, data from 2009 to 2014 suggest there is no difference in prevalence between these populations.[7] Psychiatric disorders increase the risk of opioid use disorder, although the risk varies by the type of disorder. For example, a history of anxiety disorder increases the risk of opioid use disorder by 50%, whereas a history of another substance use disorder increases the risk by 300%.[10,11] Although most overdoses are unintentional, concern is growing that some might be intentional and could be better understood as suicides.[8] Recent surgery[9] or administration of opioids in the emergency room[12] can increase the risk of long-term opioid use, although the proportion of those individuals who develop an opioid use disorder is not well known.

Individuals with opioid use disorder have increased general medical comorbidity. Individuals with a substance use disorder often do not receive regular health care, leading to undertreatment of medical conditions. Among the most important comorbid conditions to consider with opioid use disorder are HIV and hepatitis C , which are a continued risk. WHO estimates that injection drug use accounts for approximately 10% of HIV infections globally and 30% of those outside of Africa.[13] Management of HIV can be complex and challenging due to the presence of multiple comorbidities[14] as well as social, physical, economical, and legal factors that often disrupt the HIV continuum of care. Linkage and retention in care are difficult because of mutual distrust between patients and clinicians, who might see individuals with addiction as manipulative and undeserving of care.[15] However, treatment of opioid use disorder can result in reduction of HIV risk associated with sexual activity or injecting.[16] An important goal in research and in the clinic is to improve the integration of treatment for opioid use disorder and HIV. As for hepatitis C, infection can be as high as 40 per 100 person-years,[17] especially in new intravenous drug users. Effective treatments for hepatitis C exist but are

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and Embase for manuscripts published between Jan 1, 2008, and Nov 1, 2018. We searched for the term "opioid use disorder" in combination with the terms "prevalence", "comorbidity", "risk factor", "screening", "assessment", "medication assisted treatment", "overdose", "implementation", or "prevention". We mainly selected publications from the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

***Panel 1*: International Classification of Diseases 11th revision criteria for opioid use disorder[1]**

Hazardous pattern of use of opioids

A hazardous pattern of opioid use is one that has caused damage to a person's physical or mental health or has resulted in behaviour leading to harm to the health of others. The pattern of opioid use is evident across a period of at least 12 months if substance use is episodic or at least 1 month if use is continuous (ie, daily or almost daily). Harm to the health of the individual occurs due to one or more of the following: (1) behaviour related to intoxication; (2) direct or secondary toxic effects on body organs and systems; or (3) a harmful route of administration. Harm to the health of others includes any form of physical harm, including trauma, or mental disorder that is directly attributable to behaviour related to opioid intoxication on the part of the person to whom the diagnosis of harmful pattern of use of opioids applies.

Opioid dependence

Opioid dependence is a disorder in personal regulation of opioid use arising from repeated or continuous use of opioids. The characteristic feature is a strong internal drive to use opioids, which manifests as impaired ability to control use, increasing priority given to use over other activities, and persistence of use despite harm or negative consequences. These experiences are often accompanied by a subjective sensation of an urge or craving to use opioids. Physiological features of opioid dependence might also be present, including tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of opioid dependence are usually evident over a period of at least 12 months, but the diagnosis might be made if opioid use is continuous (daily or almost daily) for at least 1 month. This syndrome corresponds to opioid use disorder in the Diagnostic and Statistical Manual of Mental Disorders 5th edition and to the term opioid addiction. Note that opioid dependence is distinct from physical or physiological dependence, which connote the adaptations that ensue with repeated exposure to opioids and that lead to withdrawal symptoms on opioid discontinuation. As such, the term dependence generates confusion because sometimes it is used interchangeably with other terms. In this Review, we favour the term opioid use disorder or opioid addiction instead of dependence.

expensive and underprescribed to individuals with opioid use disorder. Because opioid use disorder medication treatment is associated with reduced hepatitis C incidence, it represents an important strategy to prevent the spread of hepatitis C among people with opioid use disorder.[18] Individuals with opioid use disorder, particularly those who inject drugs, are also at increased risk of other infections such as bacterial endocarditis, cellulitis, endophthalmitis, and brain, spleen, or myocardial abscesses and emboli, among others.[19]

Another important medical consequence of opioid use disorder is neonatal abstinence syndrome. Neonates born from mothers exposed to opioids during pregnancy can have withdrawal symptoms in the first few days after delivery.[20] Increases in the prevalence of opioid use in the general US population have led to a rise of opioid use in pregnancy[21] and in the number of infants treated for neonatal abstinence syndrome.[20] In a large, US 2017 nationally representative sample, 1·4% of pregnant women had used heroin or misused an opioid in the month before the interview.[22] Neonatal abstinence syndrome is often treated with replacement opioids that are gradually tapered over days or weeks. The evidence regarding the optimal treatment strategies is mainly derived from small or low-quality studies.[23] However, a large study published in 2018 suggested that treatment with methadone could be superior to morphine[24] whereas a smaller study showed superior effects for low-dose buprenorphine in comparison to morphine.[25] Additional research suggests that environments where stimulation is minimised, in general, yield better outcomes than treatment in standard neonatal intensive care units.[26] In parallel, protocols to treat pregnant women with opioid use disorder have resulted in significantly better outcomes for neonates whose mothers are treated with methadone or buprenorphine compared with those whose mothers do not receive medications.[27] There are currently no published randomised trials on the benefits of naltrexone treatment during pregnancy.

Screening and assessment

Although rates of treatment seeking are greater for individuals with heroin use disorder than prescription opioid use disorder,[28] overall, less than half of individuals with opioid use disorder seek help.[6,29] Individuals might be unaware of the adverse consequences of their behaviours, afraid to disclose them, or have mixed feelings about stopping opioid use.[28] Because individuals with opioid use disorder might seek treatment for other disorders or symptoms, such as infections or pain, screening for opioid misuse and opioid use disorder in psychiatric and general medical settings is likely to be an effective way to identify individuals whose disorder would otherwise be missed. When opioid misuse or opioid use disorder is identified through screening instruments, a more in-depth evaluation of the severity of the disorder is warranted.

Several screening instruments can help to identify patients who use drugs, but most do not specify the types of drug being used.[30] A useful addition is the Tobacco, Alcohol, Prescription Medications, and Other Substance Use tool, which was developed and tested in primary care.[31–34] Assessing for other medical and psychiatric comorbidities is also warranted to ensure adequate treatment or prevention interventions. Clinicians that provide pharmacotherapy should confirm the diagnosis of opioid use disorder using the International Classification of Diseases 11th revision or Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria, evaluate its severity, and determine what psychiatric and general medical comorbid conditions need to be treated. The adverse consequences of opioid use disorder—which might not be limited to mental or physical problems, but might also include interpersonal, financial, legal, or housing issues—are also important to consider.[6] Drug testing is useful to investigate the use of other substances and to help monitor progress. Substance use by other family members, particularly those living in the same

	Time after last use	Signs	Symptoms
Early withdrawal	Short-acting opioids: 8–24 h; long-acting opioids: up to 36 h	Mydriasis, piloerection, muscle twitching	Lacrimation, rhinorrhoea, diaphoresis, yawning, tremor, insomnia, restlessness, myalgia, arthralgia, abdominal pain, nausea, vomiting
Fully developed withdrawal	Short-acting opioids: 24–72 h; long-acting opioids: 72–96 h	Tachycardia, tachypnoea, hypertension or hypotension, dehydration, hyperglycaemia	Fever, anorexia, nausea, vomiting, diarrhoea

Table 1: **Withdrawal symptoms**

household, should also be carefully evaluated, as this factor has been shown to decrease the likelihood of remission and increases the risk of relapse.[35] Clinicians who are not equipped to provide treatment should refer patients for appropriate care. Reasons for referral might include insufficient expertise, licensing requirements, additional psychiatric comorbidity, or need for wrap-around services. Regardless of the level of care provided, adopting a welcoming attitude that avoids risk of embarrassment or stigmatisation is crucial to facilitate an honest discussion on or about substance use. Respecting the patient's decisions regarding their care without moral or paternalistic attitudes is paramount. Because referrals to offsite care often have low rates of follow-up, clinicians should consider participating in some of the models described later in this Review.

Although in most cases opioid use disorder does not present with acute symptoms (unless an overdose has taken place), in some cases it presents as opioid withdrawal (table 1). Opioid withdrawal, in the absence of other complications, is generally not life-threatening, however uncomfortable. The duration of the acute withdrawal period depends on the severity of the physical dependence on opioids and the specific opioid from which the patient is withdrawing. Short-acting opioids are associated with shorter periods of acute withdrawal (generally 7–10 days), whereas long-acting opioids are associated with withdrawals lasting 14 days or more. Symptoms of acute withdrawal can be assessed with standardised measures such as the Clinical Opiate Withdrawal Scale or the Subjective Opiated Withdrawal Scale.[36] After the acute withdrawal phase is complete, many patients complain of a protracted withdrawal syndrome characterised by dysphoria, craving, insomnia, and hyperalgesia. Because symptoms of acute or protracted withdrawal can be a powerful trigger for relapse, medically supervised withdrawal is generally not recommended at present, despite the existence of several withdrawal protocols.[37] When withdrawal occurs, it can be managed symptomatically (eg, with ondansetron for nausea, loperamide for diarrhoea, and lofexidine or clonidine for tachycardia, hypertension, anxiety, and sweating) and this process can be used as an opportunity to induct interested patients into opioid use disorder treatment.

Medication for opioid use disorder

Medications for the treatment of opioid use disorder are summarised in table 2. Detailed information on medications for opioid use disorder was published by the US Substance Abuse and Mental Health Administration in 2018.[44]

Withdrawal

Medically supervised withdrawal (formerly known as detoxification) is the gradual taper of methadone or buprenorphine, guided by a clinician, to alleviate withdrawal symptoms. An alternative approach is the use of α_2-adrenergic receptor agonists such as lofexidine (approved by the US Food and Drug Administration [FDA] for the treatment of opioid withdrawal in 2018) or clonidine.[45] Most patients who undergo medically supervised withdrawal without the subsequent support of opioid use disorder medications relapse shortly thereafter.[46–48] Medically supervised withdrawal is required for patients starting naltrexone. It is recommended that individuals do not use short-acting opioids for at least 7 days, or long-acting opioids for 10–14 days, before starting naltrexone.[44] Some promising data suggest that a combination of rapid taper, consisting of a single day of buprenorphine followed by ascending doses of oral naltrexone along with clonidine and other adjunctive medications (eg, clonazepam and prochlorperazine) can allow use of faster induction protocols for extended-release naltrexone.[49] Overdosing is a potential complication of medically supervised withdrawal (or withdrawal due to unavailability of treatment—eg, in some justice settings such as prisons) that is not followed by ongoing treatment because of the decrease in tolerance following medically supervised opioid withdrawal.[50]

Maintenance

Ongoing outpatient medication for opioid use disorder leads to better retention and outcomes.[51] Three medications are approved by the FDA for the treatment of opioid use disorder: methadone (a full μ-opioid receptor agonist), buprenorphine (a partial μ-opioid receptor agonist and κ-opioid receptor antagonist), and naltrexone (a μ-opioid receptor and κ-opioid receptor antagonist).[52–55] These medications also reduce the risk of death by overdose.[56–59] The efficacy of these medications makes their use, often called medication-assisted treatment, the standard of care for most patients with opioid use disorder. Patients should be informed of the efficacy, risks, benefits, and relative advantages of each of these medications. In deciding on the selection of a specific medication, the provider should ascertain the patient's

	Type	Dosage	Provider	Clinical management
Opioid use disorder				
Methadone*	Full μ-opioid receptor agonist	Daily dose 80–160 mg	Dispensed mainly by so-called methadone clinics	Discontinuation requires slow tapering to avoid withdrawal; reduces illicit opioid use and overdoses and improves other outcomes
Buprenorphine*	Partial μ-opioid receptor agonist and κ-opioid receptor antagonist	Daily sublingual dose 8–24 mg	Dispensed by physicians or nurses	As a partial μ-opioid receptor agonist, some patients might experience withdrawal when treated with buprenorphine; extended release formulations (eg, 1-month, 6-month) might facilitate adherence; reduces illicit opioid use and overdoses and improves other outcomes; κ-opioid receptor antagonist properties might improve mood
Naltrexone*	μ-opioid receptor antagonist that interferes with the binding of opioid drugs, thus inhibiting reward and analgesia	Daily oral dose of 50 mg or one monthly injection of 380 mg	Dispensed by physicians	Patients need to have medically supervised opioid withdrawal before induction to avert withdrawal symptoms; evidence still limited, but studies suggest that the drug reduces opioid use and might prevent overdoses; κ-opioid receptor antagonist properties might improve mood
Heroin (diamorphine)[38]	μ-opioid receptor agonist	Daily or twice-daily intravenous doses of 150–250 mg	Dispensed by physicians	Taken under direct medical or nurse supervision; indicated only for heroin users who have not responded to standard medications for opioid use disorder; less safe than medications for opioid use disorder; costly and requires high-intensity support; used by very few countries
Slow-release morphine[39]	μ-opioid receptor agonist	Maximum recommended daily dose is 1200 mg	Dispensed by physicians	Requires treatment by or in consultation with an addiction specialist; evidence base is more limited than for methadone; caution is required when cross-tapering from another agonist due to only partial cross-tolerance; not approved for use in the USA
Hydro-morphone[39]	μ-opioid receptor agonist	Maximum dose 200 mg; maximum daily dose 500 mg	Dispensed by physicians	Indicated only for heroin users who have not responded to standard medications for opioid use disorder; less safe than medications for opioid use disorder (eg, comparatively greater risk of infectious complications); found to be non-inferior to injectable heroin in one randomised double-blind trial;[40] requires supervised administration; not approved for use in the USA
Withdrawal				
Lofexidine* or clonidine	α_2-adrenergic receptor agonists	Oral 0·18 mg tablets every 5–6 h	Dispensed by physicians or nurses	Indicated for the treatment of withdrawal symptoms, not for maintenance treatment
Overdose				
Naloxone*	μ-opioid receptor agonist that displaces opiod drugs (eg, heroin, fentanyl, or morphine) interfering with their respiratory depressant effects	Autoinjector: 2 mg per 0·4 mL naloxone for intramuscular or subcutaneous injection;[41] nasal spray: 4 mg for intranasal dosing;[42] intravenous injection: 0·4 mg/mL[43]	Dispensed by physicians; in many jurisdictions, naloxone can be dispensed through a so-called standing order signed by a health official; the order covers the whole population and negates the need for prescriptions for individuals	Indicated for overdose reversal, not for maintenance treatment; triggers an acute withdrawal syndrome in individuals who have recently taken (prescribed or illicit) full or partial μ-opioid receptor agonists; can be administered by non-professionals (eg, bystanders or first responders)

*Approved by the US Food and Drug Administration for opioid use disorder management, opioid withdrawal, or overdose reversal.

Table 2: **Medications for opioid use disorder, withdrawal, and overdose**

responses to past treatment with opioid use disorder medications if available, the level of physical dependence and tolerance to opioids, and the patient's preference.

Methadone has been available much longer than buprenorphine or extended-release naltrexone, and has the most comprehensive evidence of efficacy, including decreased risk for overdoses and HIV infection.[55,60,61] Higher methadone doses are associated with better outcomes.[62,63] A Cochrane review concluded that the relative risk of abstinence of opioid use was 1·59 (95% CI 1·16–2·18) for high (60–100 mg/day) versus low (less than 60 mg/day) doses of methadone.[64] Because methadone is a μ-opioid receptor agonist, it has no ceiling effect. Methadone can lead to overdoses when it is used at doses above the patient's tolerance or when it is combined with other CNS depressants such as alcohol, benzodiazepines, heroin, or other synthetic opioids. Methadone should be started at low doses, followed by gradual increases with daily monitoring over several weeks. Methadone, with a few exceptions, has to be administered in licensed outpatient treatment programmes and cannot be prescribed by office-based clinicians even though there is evidence of its benefit. This restriction limits accessibility, increasing barriers to treatment.

Buprenorphine is also associated with increased treatment retention, decreased illicit opioid use, decreased overdose risk, and reduced HIV and hepatitis C risk behaviours.[55] Continued buprenorphine is superior to buprenorphine taper in decreasing illicit opioid use.[65,66] Because buprenorphine is a partial μ-opioid receptor agonist, to minimise the risk of diversion to injection use, it is often prescribed in a formulation that includes naloxone, a short-acting opioid antagonist that has poor bioavailability when sublingually administered but blocks buprenorphine effects if injected. As a partial agonist,

buprenorphine has lower lethality than methadone.[67] However, buprenorphine can still be lethal when combined with other CNS depressant substances.[68] The antagonistic effects of this drug at the κ-opioid receptor, which is upregulated in animal models of opioid use disorder and associated with depressive-like behaviours, are also believed to be of therapeutic benefit.[69,70]

Extended-release formulations of buprenorphine were developed to improve treatment adherence. 6-month buprenorphine implants have been shown to be as effective as low-dose, sublingual buprenorphine in patients stabilised on sublingual buprenorphine.[71] However, to date, there are few data supporting the acceptability and effectiveness of buprenorphine implants in routine clinical practice. In 2017, the FDA approved a 1 month extended-release buprenorphine injection for patients with opioid use disorder who have been treated with sublingual buprenorphine for at least 1 week. Another 1-month formulation and a 1-week extended-release formulation of buprenorphine are currently under FDA review.

Naltrexone is a μ-opioid receptor antagonist, but the utility of the immediate release formulation for opioid use disorder treatment has been limited by poor treatment adherence. The development of a monthly extended-release naltrexone formulation significantly improved treatment retention compared with injectable placebo and has been shown to reduce illicit opioid use.[52,53,72] The formulation has been particularly useful in justice system settings that are reluctant to use agonist therapies,[53] although whether it would be superior to treatment with oral or injected buprenorphine is unclear. Patients need to be abstinent for 1 week before extended-release naltrexone induction, to avoid triggering a withdrawal syndrome. Naltrexone is also a κ-opioid receptor antagonist, which could contribute to the mood improvements previously observed in opioid use disorder patients treated with naltrexone.[73] There are, at present, no reliable predictors of extended-release naltrexone outcome.[74]

Comparative effectiveness of medications

A paucity of information exists about the comparative effectiveness of medications for opioid use disorder, and no studies have identified predictors of which patients will respond better to each medication.[74] A Cochrane review concluded that flexible-dose methadone leads to greater retention than does sublingual buprenorphine.[55] Whether the same results hold when compared with extended-release buprenorphine will be important to clarify.

No published Cochrane review of extended-release naltrexone versus buprenorphine exists. However, two randomised controlled trials have compared sublingual buprenorphine with extended-release naltrexone. One study showed the rates of relapse among individuals inducted onto treatments with either buprenorphine or extended-release naltrexone did not differ significantly. However, a substantial proportion of patients were unable to complete extended-release naltrexone induction, mostly due to early relapse. As a result, in the intention-to-treat analysis, patients treated with extended-release naltrexone rather than buprenorphine were significantly more likely to relapse during the 24 weeks of treatment (hazard ratio 1·36; 95% CI 1·10–1·68).[75] The other study[76] found that among adults with opioid use disorder who were abstinent at the time of randomisation, extended-release naltrexone was as effective as buprenorphine in treatment retention and reduction of illicit opioid use and that treatment induction between the two treatment groups did not differ significantly.

Medications for opioid use disorder are associated with reduced risk of overdose deaths, infections, and criminal behaviour and are more cost-effective than treatment with no medication or no opioid use disorder treatment.[77–79] Despite this evidence, four important areas are in need of additional knowledge. The first area relates to safe discontinuation of medication for opioid use disorder, for example the identification of suitable patients and identifying when and under what circumstances the discontinuation could occur. In the first 6 months of treatment, relapse is high and associated with poor outcomes, which highlights the importance of improving long-term retention of patients on medication; although for how long is unresolved.[80] Overall, published studies suggest that longer time in treatment is associated with better outcomes and that the risk of relapse greatly increases after medication discontinuation.[51,81–84] A meta-analysis found that the rate ratio of all-cause mortality was 3·20 (95% CI 2·65–3·86) for individuals not on methadone treatment versus those on methadone treatment, and 2·20 (1·34–3·51) for individuals not on buprenorphine treatment versus those on buprenorphine treatment. Studies with extended-release naltrexone and sublingual buprenorphine seem to confirm these outcomes.[53] However, these studies did not determine whether individuals relapsed because they discontinued treatment, whether they discontinued treatment because they wanted to use opioids, or whether there was an interplay of both processes.

The second area where further research is needed concerns the effects of counselling or psychotherapy. To date, the preponderance of evidence indicates that neither intervention increases retention in buprenorphine treatment nor improves abstinence rates.[47,66,85] However, there is evidence that, similar to findings for methadone treatment,[86] interim buprenorphine (ie, without concomitant counselling) is superior to no medication.[87] Further research is needed to determine the additional benefits of concurrent psychotherapy, and whether benefits vary by type of patient (eg, by presence of comorbidity) or type of psychotherapy. Additionally, whether the benefits outweigh the barrier to treatment created by requiring provision of psychotherapy when

***Panel 2*: Risk factors for overdose**

- Male sex
- Age 35–44 years
- Substance use disorder
- Other psychiatric disorders (eg, mood disorders)
- History of suicide attempt
- History of overdose
- Recent discontinuation of treatment for substance use disorder
- Severe chronic pain
- Being on high opioid prescription doses (>90 morphine milligram equivalents)
- Long history of opioid use or misuse
- Use of a higher dose than prescribed
- Use of opioids with other central nervous depressants, such as alcohol or benzodiazepines
- Intravenous use of opioids
- Mixing with fentanyl or fentanyl analogues
- Use of opioids after a period of abstinence or reduced use
- Respiratory disease

delivering buprenorphine treatment needs to be established. Such counselling is at present not required for extended-release naltrexone. Questions about the need for concurrent psychotherapy in the pharmacological treatment of opioid use disorder have led some to prefer the term medications for opioid use disorder (also known as MOUD) to the more commonly used medication assisted treatment.

The third area where further data are needed concerns whether residential or inpatient treatment is superior to outpatient treatment for detoxification and maintenance, at least for some patients. This question is important because of the greater costs of residential treatment in the absence of evidence of superior outcomes.

Finally, medications are mostly selected on the basis of practical considerations such as access to methadone treatment programmes or to insurance to cover for buprenorphine or extended-release naltrexone treatment, rather than on patient characteristics. Despite some attempts at identification,[88–91] the individual characteristics that might predict greater benefit for one medication over another, needed for personalised treatment of opioid use disorder, are currently unknown.[35] A need also exists to compare the cost-effectiveness of each treatment option and to determine whether this varies by subpopulation (eg, justice-involved populations or pregnant patients).

Preventing opioid-related overdoses

Clinicians should educate patients and their families about the disease of addiction, its treatment, and about overdose risk, identification, and response. Risk of overdose is increased when: a higher dose than prescribed is used; opioids are mixed with illicit opioids such as fentanyl or other high-potency opioids; opioids are combined with other substances, such as alcohol or benzodiazepines; they are used after a period of abstinence (eg, following medically supervised withdrawal or incarceration), which leads to decreased tolerance; used by individuals with comorbid mood disorders, suicidality, or both; and used by people with a history of overdose (panel 2). The acute treatment of overdose is immediate administration of naloxone. Until 2014, naloxone could only be administered by injection. The availability of an autoinjectable naloxone device and a naloxone spray have greatly facilitated the administration of naloxone by laypersons, and communities have seen substantial decreases in lethal opioid overdoses with its use.[92,93] A remaining challenge is to increase the availability of naloxone to ensure that it can reach those who need it at short notice. In the USA, considerable variability exists in the availability of naloxone by locality, which might represent a general state-specific response to the opioid crisis, rather than a direct association with opioid overdose mortality in a particular location.[94] Future work should estimate the optimal amount and distribution of naloxone that would maximise overdose prevention without wasting resources.

Although in most cases a single dose of naloxone is sufficient to revert overdoses, in some cases, more than one dose is necessary to restore or maintain spontaneous breathing, especially if high doses or high-potency opioids, such as fentanyl, were used. Because of its high affinity for the μ-opioid receptor, fentanyl can displace naloxone and reoccupy the receptor, triggering a return of overdose symptoms.[95] Naloxone might also fail to reverse overdoses attributable to drug combinations (eg, alcohol or benzodiazepines). For that reason and because patients will be experiencing naloxone-precipitated withdrawal, the first-responders should stay with the patient until emergency medical services arrive. The patient should then be transported to an emergency room for a more systematic evaluation and stabilised with lofexidine or clonidine, if needed, to counteract withdrawal.[45] The emergency room offers an excellent opportunity to start patients on medications for opioid use disorder and link them with ongoing services.[96]

Challenges to implementation

Although treatment of opioid use disorder has traditionally been done mostly in specialty settings, there has been growing interest in expanding the availability of treatments, particularly medications for opioid use disorder, to a broader range of settings, including primary care, emergency departments, and justice settings. A number of models have been developed to meet this need (table 3).[106] Although the models are described as distinct approaches to care, they often overlap as a result of adaptions to local needs, resources, and preferences. All models emphasise, to varying degrees, the need for provider and community educational interventions, the

	Description	Advantages	Disadvantages
Office-based opioid treatment (also known as OBOT)[97-99]	Clinicians prescribe buprenorphine in their practices; counselling and coordination with other services is done by physician, nurse, or social worker	Simplicity and relative low cost	Variability in level of coordination with other medical, and psychosocial services
Hub-and-spoke[100]	Hubs are specialty outpatient programmes with capabilities for comprehensive care; hubs provide consultation to spokes, which are community clinics that provide opioid use disorder medications and psychosocial services for less complex patients	Spokes extend the capabilities of hubs	Need to train and supervise spokes; variability in quality of care across spokes
Massachusetts nurse care[101]	Nurses provide initial assessment and ongoing management; physicians provide consultation and supervision; psychosocial services provided onsite or nearby; complex patients are transferred to a specialty clinic	Shifts many treatment tasks from physicians to other professionals (eg, nurses)	Need to train and supervise spokes; variability in quality of care across spokes
Extension for Community Healthcare Outcomes project[102-105]	Initial assessment done by nurse or physician assistant; physician prescribes opioid use disorder medication and ongoing management; consultation and mentoring provided over the internet	Extends ability to provide care in rural areas	Difficulty managing complex patients or those who live in places without internet access
Emergency department-initiated buprenorphine[96]	Buprenorphine is initiated in the emergency department and patient is linked for subsequent outpatient care	Treatment initiated at time of heightened patient motivation	Need for emergency departments to allocate resources for this activity

Table 3: **Models of care for opioid use disorder medications**

	Patient	Clinician	System
Identification	Development of self-assessment or screening tools	Encouragement or incentivisation of screening of high-risk populations; use of prescription drug monitoring programs; combatting of stigmas held by many stakeholders (eg, clinicians, family members, or other patients)	Identification of high-risk populations and settings; integration of mental health and substance use disorder services; combatting of stigmas held by many stakeholders (eg, clinicians, system administrators, other patients); electronic health record screening and identification
Treatment engagement	Use of non-judgmental approaches; motivational interviewing; harm reduction approaches; treatment of medical and psychiatric comorbidity	Improvement of reimbursement and use of non-prescribing clinicians to do initial engagement	Expansion of settings where opioid use disorder medications can be initiated and improvement of linkages (eg, between emergency or hospital care and outpatient care, and social services and treatment services)
Opioid use disorder medication initiation	Psychoeducation; reduction of induction time; use of α_2-adrenergic receptor agonist to treat withdrawal symptoms; expansion of insurance or reduction of medication cost	Training and supervision; elimination of barriers to prescribing medications for opioid use disorder	Improvement of clinician availability; improvement of availability of supervision; implementation of collaborative models; ensuring appropriate reimbursement; provision of wrap-around services; developing and implementing evidence-based measures of quality of care
Retention	Use of extended-release medications; contingency management	Provision of incentives to clinicians	Provision of wrap-around services and incentives
Remission	Modification of social network; provision of alternative reinforcers	Use of booster sessions either in person or through the use of technology (eg, telemedicine or apps)	Adoption of chronic disease model

Table 4: **Interventions to improve the cascade of care by step of the cascade and target of the intervention**

role of interdisciplinary teams, and the coordination or integration of opioid use disorder treatment with other medical, psychiatric, and psychosocial services and interventions.[106] Use of technology including telehealth and internet or mobile-application delivered treatment can also help to extend the role of busy or scarce clinicians, while increasing convenience for patients.

Cascade of care

Few individuals with opioid use disorder ever access care, and even fewer receive or remain in evidence-based treatment for a meaningful length of time. Based on the well known HIV cascade of care,[107] Williams and colleagues[108] developed an opioid use disorder treatment cascade as a population-based approach to identify potential action points that increase access and retention in evidence-based treatment for individuals with the disorder. They estimated that of the approximately 2·1–2·4 million individuals with opioid use disorder in the USA, only about 20% receive any treatment for their disorder. Of those, only a third receive medications for opioid use disorder and, during a given care episode, retention is 30–50% in most settings. As a result of these challenges, they estimated that only about 50 000 (roughly 2%) of individuals with opioid use disorder in the USA achieve long-term remission. By identifying the size of the gaps in the path to treatment, this treatment cascade provides a conceptual framework to consider where interventions could be most effective. Data from Canada published in 2018 suggest the possibility of decreasing attrition at different points of the treatment cascade.[109] Important future directions would be to identify the most effective measures to intervene at each point; to estimate the relative difficulty of implementing measures; and to do simulations and cost-effectiveness analyses to help inform choices on how best to deploy the necessary resources. A summary of potential interventions is presented in table 4. Development is needed in quality of care or outcome measures to help assess the effect of interventions, inform financing or reimbursement models, and to help monitor

progress towards decreasing the prevalence of opioid use disorder.

Future directions

Prevention

To date, most of the effort in addressing the burden of opioid use disorder has been focused on treatment approaches. Comparatively much less effort has been devoted to prevention,[5] which is a crucial component of a comprehensive approach to opioid use disorder.[30,110–112] In the USA, most preventive efforts for opioid use disorder have focused on improving prescription practices for opioid analgesics and increasing the availability of naloxone to prevent overdoses. As heroin (diamorphine), illegally manufactured fentanyl, and other synthetic opioids have become increasingly important during the opioid crisis,[113,114] it has become necessary to broaden the scope of preventive interventions. Although a wealth of research has documented the efficacy of preventive interventions for children and adolescents,[115] there are no evidence-based primary or secondary preventions for opioid use disorders for adults or for youth transitioning into adulthood. Development of these interventions is a high priority for research. Although various risk factors for opioid use disorder have been identified, conceptual frameworks are needed that articulate the associations between those risk factors and suggest intervention targets. These targets might be individual risk factors, such as psychiatric comorbidities, or broader environmental risk factors, such as policies and socioeconomic conditions. Changes in tobacco policies have been effective in reducing the prevalence of smoking,[116] although the efficacy of those approaches for opioid use disorder is unknown. Improved management and treatment of opioid use disorder in pregnant women is also a high priority because these would benefit the mother and decrease the risk of neonatal abstinence syndrome in the child.[117]

Genetics, epigenetics, and pharmacogenetics

Studies of genetic epidemiology indicate that genes contribute about 50% of the susceptibility to substance use disorders, including opioid use disorder.[118] These studies further estimate that there is substantial overlap in the risk across substances (ie, much of the risk is due to a general susceptibility towards substance use disorders rather than to a specific substance).[118,119] However, no specific genes have yet been identified that could serve as biomarkers for opioid use disorder.[120] Several factors contribute to this challenge. First, opioid use disorder, like most other psychiatric disorders, appears to be a polygenic disease, in which multiple genes each have a small influence. Thus, large sample sizes are necessary to detect single gene effects. Second, genes can act at many different levels, directly influencing reward sensitivity or drug metabolic pathways, or indirectly affecting pathways such as those involved in predisposition towards impulsivity or other personality traits (eg, novelty-seeking and negative emotionality). Third, gene variants, even if present, might not be expressed due to interaction with other (modifying) genes or incomplete penetrance. Finally, environmental and developmental factors regulate the effect of genes through epigenetic modification. Thus, the relative roles of genetic and environmental factors in increasing the risk of opioid use disorder within and across racial or ethnic groups remain to be elucidated.[121]

Despite these barriers to discovery, some genes appear likely to be connected to the cause of opioid use disorder. For example, the gene encoding the μ-opioid receptor, *OPRM1*, has been implicated in increased susceptibility to opioid use disorder.[122] Similarly, converging evidence of rodent studies, genome-wide association studies, and neuroimaging studies support a function in opioid use disorder for *CNIH3* (a gene that regulates the trafficking and gating properties of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, also known as AMPA, receptors).[123] Other genes have been proposed to influence opioid use disorder, including *KCNJ6* (which encodes a voltage-gated potassium channel), the dopamine receptor D2 gene (*DRD2*), and brain derived neurotrophic factor (*BDNF*),[124] but further study is necessary to firmly evaluate these findings.

Pharmacogenetics is also a promising approach for understanding individual responses to medication and personalised medicine in the future, although considerable work is still needed to increase the reliability of current findings.[124] Most research to date has focused on methadone because it has been available on the market for much longer than buprenorphine or naltrexone. Despite these efforts, as of yet, reliable genetic biomarkers for methadone treatment do not exist. For example, initial studies suggested that the *ABCB1* gene, which encodes an ATP-dependent transporter, was associated with methadone dose and concentration, but later studies failed to confirm these findings.[125] Similarly, several cytochrome P450 enzymes, which metabolise many opioids, among other compounds, have been linked to variations in opioid metabolism, but the results have been inconsistent.[126] The study of genetic variants that predict treatment outcomes for buprenorphine or naltrexone is very new and has not yet yielded any meaningful results. A potential promising direction is to use network approaches to identify genes jointly involved in increased risk of disorder and treatment response. This strategy, recently applied to the treatment of schizophrenia, suggested new pharmacological targets for future antipsychotics.[127] A similar approach might also help to generate new approaches for the treatment of opioid use disorder.

New medications

Because multiple factors contributed to the emergence and growth of the opioid crisis, including socioeconomic

conditions,[5] medications alone will not suffice to control the problem, but medications are powerful tools to prevent morbidity and mortality from opioid use disorder. Also, although there is wide acceptance of the efficacy of medications for opioid use disorder, there is a need for development of new medications and formulations that will facilitate adherence and retention, and that can be offered as alternatives to existing treatments. Specifically, many patients are unable to adhere to medications for opioid use disorder for sufficiently long periods of time, some cannot be inducted onto them, and some might stop responding after a period of benefit. In addition to increasing the availability of existing treatments, there is a need to develop more effective medications for opioid use disorder. In the past, most pharmaceutical companies have been reluctant to invest in medication for addictive disorders, including opioid use disorder, because of stigma, the perception that the market is small, that medications would not be reimbursed, and the requirement by the FDA to make abstinence the primary endpoint in clinical trials. Partnerships between industry and the US National Institute on Drug Abuse have already led to the development of new medications for the treatment of overdose reversal (eg, intranasal naloxone), or for supervised medical withdrawal (eg, buprenorphine and lofexidine) and maintenance (eg, buprenorphine and extended-release naltrexone),[128] and there is great interest in the development and validation of alternative endpoints for clinical trials of opioid use disorder.[129]

A promising strategy for future developments would be targeting endophenotypes associated with addiction. This approach could include developing medications to improve impulse control, reduce stress reactivity, decrease conditioning to drug cues, or for enhancing the salience to non-drug rewards.[128] There is also interest in validating the use of patient-reported outcomes for opioid use disorder treatment to prevent relapse, including craving, insomnia, and depression.[130] Repurposing existing medications, as was done with bupropion for smoking cessation, might also yield novel opioid use disorder treatments. A promising therapeutic strategy directed at medication for opioid use disorder is the use of biased agonists, such as TRV130 (Trevena, Chesterbrook, PA, USA)[131,132] already in a phase 3 trial on pain management (NCT02656875). Novel pharmacological approaches independent of the μ-opioid receptor include modulation of the reward circuit via antagonism of the neurokinin 1 receptor[133] or use of oxytocin to modulate reward and stress.[134,135] Vaccines and passive immunisation with antibodies have been encouraging in preclinical studies,[136–138] but further work is needed to make them clinically useful. Similarly, preliminary findings from brain stimulation strategies, such as transcranial magnetic stimulation and transcranial direct current stimulation need confirmation in large samples with standardised protocols.[110,112] Several ongoing epidemiological studies, although still gathering data, suggest that in US states with existing medical marijuana laws, there has been a reduction in opioid prescriptions and opioid-related deaths.[139] However, the only longitudinal study done in a nationally representative sample found that cannabis use was associated with increased risk of future opioid use disorder.[140] Not enough research exists to assess the potential role of cannabidiol or tetrahydrocannabinol for the treatment of opioid use disorder.[139]

Training of health professionals

The great need for care of patients with opioid use disorder far exceeds present treatment capacity. For example, a 2015 study estimated that in the USA, more than 30 million people were living in counties without access to buprenorphine treatment.[141] Surprisingly little is known about how best to train physicians and other health professionals on the management of opioid use disorder with the use of medications.[97] Because of the prevalence of opioid use disorder and the consequences on patients' health, medical school, or residency (or equivalent for other professions) appears the natural time to gain this competency. However, at least in the USA, few residency programmes provide training in pharmacological treatment of opioid use disorder.[142] Some national organisations offer a combination of didactics, supervision, and mentoring to provide training beyond residency.[143] Evidence does show that many individuals trained to provide medications for opioid use disorder do not offer that treatment,[144] suggesting that providing training might not be enough to solve the shortage of providers, particularly in rural settings. Combating stigma, enhancing institutional support, and increasing reimbursement rates might be necessary to encourage those who are trained to provide treatment.

Special populations

Although emerging information suggests that prescription of medication for opioid use disorder in young adults has increased over time,[143] relatively little is known about opioid use disorder (beyond some descriptive epidemiological data) in special populations such as older people, adolescents, or ethnic minorities, or about sex differences in prevention or treatment outcomes. A possible exception to this scarcity of knowledge is information on the treatment of pregnant women.[145,146] At present, treatment with methadone or buprenorphine is recommended for opioid use disorder during pregnancy because of superior maternal and infant outcome compared with no treatment or medically supervised withdrawal.[147] Methadone and buprenorphine do not appear to be associated with birth defects or clinically significant neurodevelopment delays.[148] Starting treatment with naltrexone during pregnancy is not recommended due to the risk of precipitated withdrawal, but there is controversy regarding whether women already on naltrexone at the beginning of pregnancy should continue taking it during pregnancy.[145]

The Helping to End Addition Long-term (HEAL) initiative

To address the opioid crisis, the US Congress in 2018 added US$500 million to the budget of the National Institutes of Health.[148] This funding is being used to support the HEAL initiative. HEAL will address multiple areas of opportunity, both to improve pain management and minimise reliance on opioids, and to improve treatment of opioid use disorder. Research targeting opioid use disorder will include the development of medications for treatment, optimisation of effective models of treatment in health-care and justice settings, and developing prevention interventions across the lifespan. Three major areas will be prioritised. First, substantial resources will be used to leverage existing findings from basic science to identify new pharmacological targets and to develop novel medications (including immunotherapies) or to repurpose existing ones. As part of this effort, special attention will be drawn to improving overdose reversal medications and developing new therapies for opioid-induced respiratory depression. Second, there will be an increased focus on optimising existing treatments. Attention will be drawn to enhancing the US National Institute on Drug Abuse Clinical Trials Network for opioid research, the establishment of the Justice Community Opioid Intervention Network, and the conduct of the HEALing Communities Study. Finally, a series of clinical trials (NCT01958476 now underway) will determine best practices for the treatment of neonatal abstinence syndrome. The combined results of this initiative should lead to important advances in the prevention and treatment of opioid use disorder.

Contributors

We jointly wrote and edited the manuscript. CB did the bibliographic searches.

Declaration of interests

We declare no competing interests.

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References

1 WHO. International Classification of Diseases 11th revision. Disorders due to substance use. December, 2018. https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f499894965 (accessed Feb 20, 2019).

2 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Washington, DC: American Psychiatric Association, 2013.

3 Charlson FJ, Baxter AJ, Dua T, Degenhardt L, Whiteford HA, Vos T. Excess mortality from mental, neurological, and substance use disorders in the Global Burden of Disease Study 2010. In: Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME, eds. Mental, neurological, and substance use disorders: disease control priorities, 3rd edn (volume 4). Washington, DC: The International Bank for Reconstruction and Development/The World Bank, 2016: 41–66.

4 Olfson M, Crystal S, Wall M, Wang S, Liu S, Blanco C. Causes of death after nonfatal opioid overdose. *JAMA Psychiatry* 2018; **75:** 820–27.

5 Pincus HA, Blanco C. The opioid crisis in America: an overview. In: Weil AR, Dolan R, eds. Confronting our nation's opioid crisis, a report of the Aspen Health Strategy Group. Washington, DC: The Aspen Institute, 2017: 23–46.

6 Han B, Compton WM, Blanco C, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults. *Ann Intern Med* 2018; **168:** 383–84.

7 Jones CM. The paradox of decreasing nonmedical opioid analgesic use and increasing abuse or dependence—an assessment of demographic and substance use trends, United States, 2003–2014. *Addict Behav* 2017; **65:** 229–35.

8 Oquendo MA, Volkow ND. Suicide: a silent contributor to opioid-overdose deaths. *N Engl J Med* 2018; **378:** 1567–69.

9 Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA* 2016; **176:** 1286–93.

10 Blanco C, Alderson D, Ogburn E, et al. Changes in the prevalence of non-medical prescription drug use and drug use disorders in the United States: 1991–1992 and 2001–2002. *Drug Alcohol Depend* 2007; **90:** 252–60.

11 Saha TD, Kerridge BT, Goldstein RB, et al. Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. *J Clin Psychiatry* 2016; **77:** 772–80.

12 Barnett ML, Olenski AR, Jena AB. Opioid-prescribing patterns of emergency physicians and risk of long-term use. *N Engl J Med* 2017; **376:** 663–73.

13 WHO. HIV/AIDS: people who inject drugs. 2018. http://www.who.int/hiv/topics/idu/about/en/ (accessed Aug 16, 2018).

14 Lopes M, Olfson M, Rabkin J, et al. Gender, HIV status, and psychiatric disorders: results from the National Epidemiologic Survey on alcohol and related conditions. *J Clin Psychiatry* 2012; **73:** 384–91.

15 Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. *AIDS Res Ther* 2016; **13:** 35.

16 Woody GE, Bruce D, Korthuis PT, et al. HIV risk reduction with buprenorphine-naloxone or methadone: findings from a randomized trial. *J Acquir Immune Defic Syndr* 2014; **66:** 288–93.

17 Klevens RM, Hu DJ, Jiles R, Holmberg SD. Evolving epidemiology of hepatitis C virus in the United States. *Clin Infect Dis* 2012; **55:** S3–9.

18 Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. *JAMA* 2014; **174:** 1974–81.

19 Saitz R. Medical and Surgical complications of addiction. In: Miller SC, Fiellin D, Rosenthal RN, Saitz R, eds. The ASAM principles of Addiction Medicine, 6th edn. Philadelphia: Wolters Kluwer, 2019: 1109–31.

20 Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med* 2015; **372:** 2118–26.

21 Krans EE, Patrick SW. Opioid use disorder in pregnancy: health policy and practice in the midst of an epidemic. *Obstet Gynecol* 2016; **128:** 4–10.

22 Substance Abuse and Mental Health Services Administration. Reports and detailed tables from the 2017 National Survey on Drug Use and Health. 2017. https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2017-NSDUH (accessed Nov 9, 2018).

23 Wachman EM, Schiff DM, Silverstein M. Neonatal abstinence syndrome: advances in diagnosis and treatment. *JAMA* 2018; **319:** 1362–74.

24 Davis JM, Shenberger J, Terrin N, et al. Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. *JAMA Pediatr* 2018; **172:** 741–48.

25 Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. *N Engl J Med* 2017; **376:** 2341–48.

26 Holmes AV, Atwood EC, Whalen B, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. *Pediatrics* 2016; **137:** e20152929.

27 Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction* 2016; **111:** 2115–28.

28 Wu LT, Zhu H, Swartz MS. Treatment utilization among persons with opioid use disorder in the United States. *Drug Alcohol Depend* 2016; **169:** 117–27.

29 Blanco C, Iza M, Schwartz RP, Rafful C, Wang S, Olfson M. Probability and predictors of treatment-seeking for prescription opioid use disorders: a national study. *Drug Alcohol Depend* 2013; **131:** 143–48.

30 McNeely J, Cleland CM, Strauss SM, Palamar JJ, Rotrosen J, Saitz R. Validation of self-administered single-item screening questions (SISQs) for unhealthy alcohol and drug use in primary care patients. *J Gen Intern Med* 2015; **30:** 1757–64.

31 McNeely J, Wu LT, Subramaniam G, et al. Performance of the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) tool for substance use screening in primary care patients. *Ann Intern Med* 2016; **165:** 690–99.

32 Skinner HA. The drug abuse screening test. *Addict Behav* 1982; **7:** 363–71.

33 Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. *Arch Intern Med* 2010; **170:** 1155–60.

34 Tiet QQ, Leyva YE, Moos RH, Frayne SM, Osterberg L, Smith B. Screen of drug use: diagnostic accuracy of a new brief tool for primary care. *JAMA* 2015; **175:** 1371–77.

35 Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addict Behav* 2012; **37:** 747–75.

36 Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987; **13:** 293–308.

37 Bisaga A, Mannelli P, Sullivan MA, et al. Antagonists in the medical management of opioid use disorders: historical and existing treatment strategies. *Am J Addict* 2018; **27:** 177–87.

38 Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database Syst Rev* 2011; **12:** CD003410.

39 Supervised Injectable Opioid Agonist Treatment Guidance Committee. Guidance for injectable opioid agonist treatment for opioid use disorder. 2017. http://www.bccsu.ca/wp-content/uploads/2017/10/BC-iOAT-Guidelines-10.2017.pdf (accessed Nov 9, 2018).

40 Oviedo-Joekes E, Guh D, Brissette S, et al. Hydromorphone compared with diacetylmorphine for long-term opioid dependence: a randomized clinical trial. *JAMA Psychiatry*. 2016; **73:** 447–55.

41 US Food and Drug Administration. EVZIO full prescribing information. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209862lbl.pdf (accessed July 18, 2018).

42 US Food and Drug Administration. Narcan nasal spray (naloxone hydrochloride). 2015. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000TOC.cfm (accessed July 14, 2018).

43 Chou R, Korthuis PT, McCarty D, et al. Management of suspected opioid overdose with naloxone by emergency medical services personnel. Comparative effectiveness review no. 193. Rockville, MD: Agency for Healthcare Research and Quality, 2017.

44 Substance Abuse and Mental Health Services Administration. Medications for opioid use disorder: Treatment Improvement Protocol 63. 2018. https://store.samhsa.gov/system/files/sma18-5063fulldoc.pdf (accessed July 12, 2018).

45 Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database Syst Rev* 2017; **5:** CD002021.

46 Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev* 2011; **9:** CD005031.

47 Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction* 2005; **100:** 1090–100.

48 Smyth BP, Barry J, Keenan E, Ducray K. Lapse and relapse following inpatient treatment of opiate dependence. *Ir Med J* 2010; **103:** 176–79.

49 Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry* 2017; **174:** 459–67.

50 Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 2010; **105:** 1545–54.

51 Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis* 2016; **35:** 22–35.

52 Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011; **377:** 1506–13.

53 Lee JD, Friedmann PD, Kinlock TW, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med* 2016; **374:** 1232–42.

54 Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009; **3:** CD002209.

55 Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; **2:** CD002207.

56 Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. *Am J Addict* 2004; **13:** S17–28.

57 Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend* 2009; **105:** 9–15.

58 Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction* 2008; **103:** 462–68.

59 Schwartz RP, Gryczynski J, O'Grady KE, et al. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. *Am J Public Health* 2013; **103:** 917–22.

60 Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev* 2016; **5:** CD011117.

61 Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA* 2000; **283:** 1303–10.

62 Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat* 2005; **28:** 321–29.

63 Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev* 2003; **3:** CD002208.

64 Fareed A, Casarella J, Amar R, Vayalapalli S, Drexler K. Methadone maintenance dosing guideline for opioid dependence, a literature review. *J Addict Dis* 2010; **29:** 1–14.

65 Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA* 2014; **174:** 1947–54.

66 Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry* 2011; **68:** 1238–46.

67 Volkow ND, Jones EB, Einstein EB, Wargo EM. Prevention and treatment of opioid mis-use and addiction: a review. *JAMA Psychiatry* 2018; published online Dec 5. DOI:10.1001/jamapsychiatry.2018.3126.

68 Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. *J Addict Med* 2014; **8:** 315–26.

69 Falcon E, Browne CA, Leon RM, et al. Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. *Neuropsychopharmacology* 2016; **41:** 2344–51.

70 Khanna IK, Pillarisetti S. Buprenorphine— an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res* 2015; **8:** 859–70.

71 Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial. *JAMA* 2016; **316:** 282–90.

72 Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006; **63:** 210–18.

73 Weerts EM, Kim YK, Wand GS, et al. Differences in delta- and mu-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. *Neuropsychopharmacology* 2008; **33:** 653–65.

74 Nunes EV, Krupitsky E, Ling W, et al. Treating opioid dependence with injectable extended-release naltrexone (XR-NTX): who will respond? *J Addict Med* 2015; **9:** 238–43.

75 Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 2018; **391:** 309–18.

76 Tanum L, Solli KK, Latif ZE, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2017; **74:** 1197–205.

77 Baser O, Chalk M, Fiellin DA, Gastfriend DR. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care* 2011; **17:** S235–48.

78 Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess* 2007; **11:** 1–171.

79 Lynch FL, McCarty D, Mertens J, et al. Costs of care for persons with opioid dependence in commercial integrated health systems. *Addict Sci Clin Pract* 2014; **9:** 16.

80 Morgan JR, Schackman BR, Leff JA, Linas BP, Walley AY. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. *J Subst Abuse Treat* 2018; **85:** 90–96.

81 Cushman P. Abstinence following detoxification and methadone maintenance treatment. *Am J Med* 1978; **65:** 46–52.

82 Nosyk B, Sun H, Evans E, et al. Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study. *Addiction* 2012; **107:** 1621–29.

83 Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; **357:** j1550.

84 Stimmel B, Goldberg J, Rotkopf E, Cohen M. Ability to remain abstinent after methadone detoxification. A six-year study. *JAMA* 1977; **237:** 1216–20.

85 Moore BA, Fiellin DA, Cutter CJ, et al. Cognitive behavioral therapy improves treatment outcomes for prescription opioid users in primary care buprenorphine treatment. *J Subst Abuse Treat* 2016; **71:** 54–57.

86 Schwartz RP, Alexandre PK, Kelly SM, O'Grady KE, Gryczynski J, Jaffe JH. Interim versus standard methadone treatment: a benefit-cost analysis. *J Subst Abuse Treat* 2014; **46:** 306–14.

87 Sigmon SC, Schwartz RP, Higgins ST. Buprenorphine for persons on waiting lists for treatment for opioid dependence. *N Engl J Med* 2017; **376:** 1000–01.

88 Heidebrecht F, MacLeod MB, Dawkins L. Predictors of heroin abstinence in opiate substitution therapy in heroin-only users and dual users of heroin and crack. *Addict Behav* 2018; **77:** 210–16.

89 McDermott KA, Griffin ML, Connery HS, et al. Initial response as a predictor of 12-week buprenorphine-naloxone treatment response in a prescription opioid-dependent population. *J Clin Psychiatry* 2015; **76:** 189–94.

90 Proctor SL, Copeland AL, Kopak AM, Hoffmann NG, Herschman PL, Polukhina N. Predictors of patient retention in methadone maintenance treatment. *Psychol Addict Behav* 2015; **29:** 906–17.

91 Zhu Y, Evans EA, Mooney LJ, et al. Correlates of long-term opioid abstinence after randomization to methadone versus buprenorphine/naloxone in a multi-site trial. *J Neuroimmune Pharmacol* 2018; **13:** 488–97.

92 Albert S, Brason FW 2nd, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Med* 2011; **12:** S77–85.

93 Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013; **346:** f174.

94 Freeman PR, Hankosky ER, Lofwall MR, Talbert JC. The changing landscape of naloxone availability in the United States, 2011–2017. *Drug Alcohol Depend* 2018; **191:** 361–64.

95 Substance Abuse and Mental Health Services Administration. Opioid overdose prevention toolkit. 2018. https://store.samhsa.gov/system/files/sma18-4742.pdf (accessed July 12, 2018).

96 D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA* 2015; **313**: 1636–44.

97 Levin FR, Bisaga A, Sullivan MA, Williams AR, Cates-Wessel K. A review of a national training initiative to increase provider use of MAT to address the opioid epidemic. *Am J Addict* 2016; **25:** 603–39.

98 Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med* 2006; **355:** 365–74.

99 Knudsen HK. The supply of physicians waivered to prescribe buprenorphine for opioid use disorders in the United States: a state-level analysis. *J Stud Alcohol Drugs* 2015; **76:** 644–54.

100 Brooklyn JR, Sigmon SC. Vermont hub-and-spoke model of care for opioid use disorder: development, implementation, and impact. *J Addict Med* 2017; **11:** 286–92.

101 LaBelle CT, Han SC, Bergeron A, Samet JH. Office-based opioid treatment with buprenorphine (OBOT-B): statewide implementation of the Massachusetts Collaborative Care model in community health centers. *J Subst Abuse Treat* 2016; **60:** 6–13.

102 Arora S, Kalishman S, Thornton K, et al. Expanding access to HCV treatment—Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. *Hepatology* 2010; **52:** 1124–33.

103 Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med* 2011; **364:** 2199–207.

104 Komaromy M, Duhigg D, Metcalf A, et al. Project ECHO (Extension for Community Healthcare Outcomes): a new model for educating primary care providers about treatment of substance use disorders. *Subst Abus* 2016; **37:** 20–24.

105 Patient Self-Management Education and Support members. ECHO Access opioid use disorder treatment guideline opioid abuse and addiction management protocol. Project ECHO. 2014. http://echo.unm.edu/wp-content/uploads/2014/10/Opioid-Abuse-and-Addiction-Management-Protocol.pdf (accessed July 14, 2018).

106 Chou R, Korthuis PT, Weimer M, et al. Medication-assisted treatment models of care for opioid use disorder in primary care settings. Technical brief no. 28. Rockville, MD: Agency for Healthcare Research and Quality, 2016.

107 Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. *AIDS Res Ther* 2016; **13:** 35.

108 Williams AR, Nunes EV, Bisaga A, et al. Developing an opioid use disorder treatment cascade: a review of quality measures. *J Subst Abuse Treat* 2018; **91:** 57–68.

109 Socias ME, Wood E, Kerr T, et al. Trends in engagement in the cascade of care for opioid use disorder, Vancouver, Canada, 2006–2016. *Drug Alcohol Depend* 2018; **189:** 90–95.

110 Grall-Bronnec M, Sauvaget A. The use of repetitive transcranial magnetic stimulation for modulating craving and addictive behaviours: a critical literature review of efficacy, technical and methodological considerations. *Neurosci Biobehav Rev* 2014; **47:** 592–613.

111 Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med* 2017; **167:** 293–301.

112 Lupi M, Martinotti G, Santacroce R, et al. Transcranial direct current stimulation in substance use disorders: a systematic review of scientific literature. *J ECT* 2017; **33:** 203–39.

113 Cicero TJ, Ellis MS, Kasper ZA. Increased use of heroin as an initiating opioid of abuse. *Addict Behav* 2017; **74:** 63–66.

114 Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med* 2016; **374:** 154–63.

115 Compton WM JC, Baldwin G, Harding F, Blanco C, Wargo EM. using prevention science principles to address the U.S. opioid crisis. *AJPH* (in press).

116 Perez-Warnisher MT, Carballosa de Miguel MDP, Seijo LM. Tobacco use worldwide: leg-islative efforts to curb consumption. *Ann Glob Health* 2019; **85:** pii: 9.

117 Smid M, Gordon AJ, Plumb S, Plumb J. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. *Obstet Gynecol* 2018; **131:** 163–64.

118 Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry* 2003; **160:** 687–95.

119 Wetherill L, Agrawal A, Kapoor M, et al. Association of substance dependence phenotypes in the COGA sample. *Addict Biol* 2015; **20:** 617–27.

120 Volkow ND, Boyle M. Neuroscience of addiction: relevance to prevention and treatment. *Am J Psychiatry* 2018; **175:** 729–40.

121 Ducci F, Roy A, Shen PH, et al. Association of substance use disorders with childhood trauma but not African genetic heritage in an African American cohort. *Am J Psychiatry* 2009; **166:** 1031–40.

122 Xu J, Lu Z, Xu M, et al. A heroin addiction severity-associated intronic single nucleotide polymorphism modulates alternative pre-mRNA splicing of the mu opioid receptor gene OPRM1 via hnRNPH interactions. *J Neurosci* 2014; **34:** 11048–66.

123 Nelson EC, Agrawal A, Heath AC, et al. Evidence of CNIH3 involvement in opioid dependence. *Mol Psychiatry* 2016; **21:** 608–14.

124 Crist RC, Clarke TK, Berrettini WH. Pharmacogenetics of opioid use disorder treatment. *CNS Drugs* 2018; **32:** 305–20.

125 Dennis BB, Bawor M, ThabaneL, et al. Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. *PLoS One* 2014; **9:** e86114.

126 Crettol S, Déglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther* 2006; **80:** 668–81.

127 Kauppi K, Rosenthal SB, Lo MT, et al. Revisiting antipsychotic drug actions through gene networks associated with schizophrenia. *Am J Psychiatry* 2018; **175:** 674–82.

128 Volkow ND, Boyle M. Neuroscience of addiction: relevance to prevention and treatment. *Am J Psychiatry* 2018; **175:** 729–40.

129 Volkow ND, Woodcock J, Compton WM, et al. Medication development in opioid addiction: meaningful clinical end points. *Sci Transl Med* 2018; **10:** eaan2595.

130 US Food and Drug Administration Center for Drug Evaluation and Research. Patient-focused drug development public meeting for opioid use disorder (OUD). 2018. https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm591290.htm (accessed Nov 1, 2018).

131 DeWire SM, Yamashita DS, Rominger DH, et al. A G protein-biased ligand at the mu-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *J Pharmacol Exp Ther* 2013; **344:** 708–17.

132 Singla N, Minkowitz H, Soergel D, Burt D, Skobieranda F. (432) Respiratory safety signal with oliceridine (TRV130), a novel Mu; receptor G protein pathway selective modulator (μ-GPS), vs morphine: a safety analysis of a Phase 2b randomized clinical trial. *J Pain* 2016; **17:** S82.

133 Sandweiss AJ, Vanderah TW. The pharmacology of neurokinin receptors in addiction: prospects for therapy. *Subst Abuse Rehabil* 2015; **6:** 93–102.

134 Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci* 2011; **12:** 524–38.

135 Peris J, MacFadyen K, Smith JA, de Kloet AD, Wang L, Krause EG. Oxytocin receptors are expressed on dopamine and glutamate neurons in the mouse ventral tegmental area that project to nucleus accumbens and other mesolimbic targets. *J Comp Neurol* 2017; **525:** 1094–108.

136 Bremer PT, Kimishima A, Schlosburg JE, Zhou B, Collins KC, Janda KD. Combatting synthetic designer opioids: a conjugate vaccine ablates lethal doses of fentanyl class drugs. *Angew Chem Int Ed Engl* 2016; **55:** 3772–75.

137 Bremer PT, Schlosburg JE, Lively JM, Janda KD. Injection route and TLR9 agonist addition significantly impact heroin vaccine efficacy. *Mol Pharm* 2014; **11:** 1075–80.

138 Pravetoni M, Le Naour M, Tucker AM, et al. Reduced antinociception of opioids in rats and mice by vaccination with immunogens containing oxycodone and hydrocodone haptens. *J Med Chem* 2013; **56:** 915–23.

139 Hurd YL, O'Brien CP. Molecular genetics and new medication strategies for opioid addiction. *Am J Psychiatry* 2018; **175:** 935–42.

140 Olfson M, Wall MM, Liu SM, Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. *Am J Psychiatry* 2018; **175:** 47–53.

141 Rosenblatt RA, Andrilla CH, Catlin M, Larson EH. Geographic and specialty distribution of US physicians trained to treat opioid use disorder. *Ann Fam Med* 2015; **13:** 23–26.

142 Tesema L, Marshall J, Hathaway R, et al. Training in office-based opioid treatment with buprenorphine in US residency programs: a national survey of residency program directors. *Subst Abuse* 2018; published online March 7. DOI:10.1080/08897077.2018.1449047.

143 Hadland SE, Wharam JF, Schuster MA, Zhang F, Samet JH, Larochelle MR. Trends in Receipt of buprenorphine and naltrexone for opioid use disorder among adolescents and young adults, 2001–2014. *JAMA Pediatr* 2017; **171:** 747–55.

144 Sharma A, Kelly SM, Mitchell SG, Gryczynski J, O'Grady KE, Schwartz RP. Update on barriers to pharmacotherapy for opioid use disorders. *Curr Psychiatry Rep* 2017; **19:** 35.

145 Substance Abuse and Mental Health Services Administration. Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants. 2018. https://store.samhsa.gov/system/files/sma18-5054.pdf (accessed July 12, 2018).

146 The American College of Obstetricians and Gynecologists, Women's Health Care Physicians. Opioid use and opioid use disorder in pregnancy. 2017. https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Opioid-Use-and-Opioid-Use-Disorder-in-Pregnancy?IsMobileSet=false (accessed July 14, 2018).

147 Fajemirokun-Odudeyi O, Sinha C, Tutty S, et al. Pregnancy outcome in women who use opiates. *Eur J Obstet Gynecol Reprod Biol* 2006; **126:** 170–75.

148 Collins FS, Koroshetz WJ, Volkow ND. Helping to end addiction over the long-term: the research plan for the NIH HEAL initiative. *JAMA* 2018; **320:** 129–30.