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.

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.1

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.5–8 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 of opioid use disorder by 50%, whereas a history of 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.

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.
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 (i.e., 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 connotes 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.

Screening and assessment

Although rates of treatment seeking are greater for individuals with heroin use disorder than prescription opioid use disorder, overall, less than half of individuals with opioid use disorder seek help. Individuals might be unaware of the adverse consequences of their behaviours, afraid to disclose them, or have mixed feelings about stopping opioid use. 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. A useful addition is the Tobacco, Alcohol, Prescription Medications, and Other Substance Use tool, which was developed and tested in primary care. 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 criteria for opioid use disorder1

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. Hazardous pattern of use of opioids 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 or Diagnostic and Statistical Manual of Mental Disorders 11th revision criteria for opioid use disorder1

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.4 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.5

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.6 Increases in the prevalence of opioid use in the general US population have led to a rise of opioid use in pregnancy7 and in the number of infants treated for neonatal abstinence syndrome.7 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.8 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. However, a large study published in 2018 suggested that treatment with methadone could be superior to morphine9 whereas a smaller study showed superior effects for low-dose buprenorphine in comparison to morphine. Additional research suggests that environments where stimulation is minimised, in general, yield better outcomes than treatment in standard neonatal intensive care units.10 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.7 There are currently no published randomised trials on the benefits of naltrexone treatment during pregnancy.
household, should also be carefully evaluated, as this factor has been shown to decrease the likelihood of remission and increases the risk of relapse. 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. 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. 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.

### 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 α₂-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. Most patients who undergo medically supervised withdrawal without the subsequent support of opioid use disorder medications relapse shortly thereafter. 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. 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. 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.

### Maintenance

Ongoing outpatient medication for opioid use disorder leads to better retention and outcomes. 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). These medications also reduce the risk of death by overdose. 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

<table>
<thead>
<tr>
<th>Time after last use</th>
<th>Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Early withdrawal</td>
<td>Short-acting opioids: 8–24 h; long-acting opioids: up to 36 h</td>
<td>Mydriasis, piloerection, muscle twitching</td>
</tr>
<tr>
<td>Fully developed withdrawal</td>
<td>Short-acting opioids: 24–72 h; long-acting opioids: 72–96 h</td>
<td>Tachycardia, tachypnoea, hypertension or hypotension, dehydration, hyperglycaemia</td>
</tr>
</tbody>
</table>

Table 1: Withdrawal symptoms
### Table 2: Medications for opioid use disorder, withdrawal, and overdose

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage</th>
<th>Provider</th>
<th>Clinical management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid use disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone*</td>
<td>Full μ-opioid receptor agonist</td>
<td>Dispensed mainly by so-called methadone clinics</td>
<td>Discontinuation requires slow tapering to avoid withdrawal; reduces illicit opioid use and overdoses and improves other outcomes</td>
</tr>
<tr>
<td>Buprenorphine*</td>
<td>Partial μ-opioid receptor agonant and κ-opioid receptor antagonist</td>
<td>Dispensed by physicians or nurses</td>
<td>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</td>
</tr>
<tr>
<td>Naltrexone*</td>
<td>μ-opioid receptor antagonist that interferes with the binding of opioid drugs, thus inhibiting reward and analgesia</td>
<td>Dispensed by physicians</td>
<td>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</td>
</tr>
<tr>
<td>Heroin (diamorphine)*</td>
<td>μ-opioid receptor agonist</td>
<td>Dispensed by physicians</td>
<td>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</td>
</tr>
<tr>
<td>Slow-release morphine*</td>
<td>μ-opioid receptor agonist</td>
<td>Dispensed by physicians</td>
<td>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</td>
</tr>
<tr>
<td>Hydromorphone*</td>
<td>μ-opioid receptor agonist</td>
<td>Dispensed by physicians</td>
<td>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; requires supervised administration; not approved for use in the USA</td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lofexidine* or clonidine</td>
<td>α₂-adrenergic receptor agonants</td>
<td>Dispensed by physicians or nurses</td>
<td>Indicated for the treatment of withdrawal symptoms, not for maintenance treatment</td>
</tr>
<tr>
<td><strong>Overdose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone*</td>
<td>μ-opioid receptor agonant that displaces opioid drugs (eg, heroin, fentanyl, or morphine) interfering with their respiratory depressant effects</td>
<td>Dispensed by physicians or nurses</td>
<td>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)</td>
</tr>
</tbody>
</table>

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

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.\(^{[5,6,8,10,13]}\) Higher methadone doses are associated with better outcomes.\(^{[4,23]}\) 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.\(^{[4,23]}\) 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.\(^{[5,9]}\) Continued buprenorphine is superior to buprenorphine taper in decreasing illicit opioid use.\(^{[5,66]}\) 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.62 However, buprenorphine can still be lethal when combined with other CNS depressant substances.63 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.64,70

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.7 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.52,57,58 The formulation has been particularly useful in justice system settings that are reluctant to use agonist therapies,51 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.75 A Cochrane review concluded that flexible-dose methadone leads to greater retention than does sublingual buprenorphine.51 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).52 The other study52 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.70–79 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.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.31 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.72,85 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, the individual characteristics that might predict greater benefit for one medication over another, needed for personalised treatment of opioid use disorder, are currently unknown. A need also exists to compare the cost-effectiveness of each treatment option and to determine whether this varies by sub-population (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. 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. 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. 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 stabilisation with lofexidine or clonidine, if needed, to counteract withdrawal. The emergency room offers an excellent opportunity to start patients on medications for opioid use disorder and link them with ongoing services.

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). 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
role of interdisciplinary teams, and the coordination or integration of opioid use disorder treatment with other medical, psychiatric, and psychosocial services and interventions. 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, Williams and colleagues 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 50000 (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. 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 it.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Development of self-assessment or screening tools</td>
<td>Encouragement or incentivisation of screening high-risk populations, use of prescription drug monitoring programs, combatting of stigmas held by many stakeholders (eg, clinicians, system administrators, other patients); electronic health record screening and identification</td>
<td>Identification of high-risk populations and settings; integration of mental health and substance use disorders services; combatting of stigmas held by many stakeholders (eg, clinicians, system administrators, other patients); electronic health record screening and identification</td>
</tr>
<tr>
<td>Treatment engagement</td>
<td>Use of non-judgmental approaches; motivational interviewing; harm reduction approaches; treatment of medical and psychiatric comorbidity</td>
<td>Improvement of reimbursement and use of non-prescribing clinicians to do initial engagement</td>
<td>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)</td>
</tr>
<tr>
<td>Opioid use disorder medication initiation</td>
<td>Psychoeducation, reduction of induction time, use of α2-adrenergic receptor agonist to treat withdrawal symptoms, expansion of insurance or reduction of medication cost</td>
<td>Training and supervision; elimination of barriers to prescribing medications for opioid use disorder</td>
<td>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</td>
</tr>
<tr>
<td>Retention</td>
<td>Use of extended-release medications; contingency management</td>
<td>Provision of incentives to clinicians</td>
<td>Provision of wrap-around services and incentives</td>
</tr>
<tr>
<td>Remission</td>
<td>Modification of social network; provision of alternative reinforcers</td>
<td>Use of booster sessions either in person or through the use of technology (eg, telemedicine or apps)</td>
<td>Adoption of chronic disease model</td>
</tr>
</tbody>
</table>

Table 4: Models of care for opioid use disorder medications

Table 6: Interventions to improve the cascade of care by step of the cascade and target of the intervention
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, which is a crucial component of a comprehensive approach to opioid use disorder. In the USA, most preventive efforts for opioid use disorder have focused on improving prescription practices for opioid analogics 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, 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, 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 factors, such as policies and socioeconomic conditions. Changes in tobacco policies have been effective in reducing the prevalence of smoking, 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.

**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. 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). However, no specific genes have yet been identified that could serve as biomarkers for opioid use disorder. 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.

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. 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). 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), 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. 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. 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. 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. 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, 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 widespread 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 induced 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), and there is great interest in the development and validation of alternative endpoints for clinical trials of opioid use disorder.

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. 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. 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) 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 or use of oxytocin to modulate reward and stress. Vaccines and passive immunisation with antibodies have been encouraging in preclinical studies, 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. 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. 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. Not enough research exists to assess the potential role of cannabidiol or tetrahydrocannabinol for the treatment of opioid use disorder.

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. 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. 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. Some national organisations offer a combination of didactics, supervision, and mentoring to provide training beyond residency. Evidence does show that many individuals trained to provide medications for opioid use disorder do not offer that treatment, 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, 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. 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. Methadone and buprenorphine do not appear to be associated with birth defects or clinically significant neurodevelopmental delays. 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.

www.thelancet.com Published online March 13, 2019 http://dx.doi.org/10.1016/S0140-6736(18)33078-2
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. 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.

Acknowledgments
The views and opinions expressed in this Review are those of the authors and do not necessarily represent the views of the National Institutes of Health or the US Government.

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