Opioid use disorder

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Abstract | Opioid use disorder (OUD) is a chronic relapsing disorder that, whilst initially driven by activation of brain reward neurocircuits, increasingly engages anti-reward neurocircuits that drive adverse emotional states and relapse. However, successful recovery is possible with appropriate treatment, although with a persisting propensity to relapse. The individual and public health burdens of OUD are immense; 26.8 million people were estimated to be living with OUD globally in 2016, with >100,000 opioid overdose deaths annually, including >47,000 in the USA in 2017. Well-conducted trials have demonstrated that long-term opioid agonist therapy with methadone and buprenorphine have great efficacy for OUD treatment and can save lives. New forms of the opioid receptor antagonist naltrexone are also being studied. Some frequently used approaches have less scientifically robust evidence but are nevertheless considered important, including community preventive strategies, harm reduction interventions to reduce adverse sequelae from ongoing use and mutual aid groups. Other commonly used approaches, such as detoxification alone, lack scientific evidence. Delivery of effective prevention and treatment responses is often complicated by coexisting comorbidities and inadequate support, as well as by conflicting public and political opinions. Science has a crucial role to play in informing public attitudes and developing fuller evidence to understand OUD and its associated harms, as well as in obtaining the evidence today that will improve the prevention and treatment interventions of tomorrow.

Our understanding of opioid use disorder (OUD) is complicated by strong public and political opinions about drug use behaviours. It is, therefore, particularly important to use science to guide our response to the global burden of the disorder (FIG. 1), to understand the aetiology of OUD and to critically examine the scientific evidence for the effect of interventions. OUD is now recognized as a chronic relapsing disorder from which it is nevertheless possible to achieve successful recovery whilst remaining alert to the propensity to relapse. The disorder can involve the use of opiates in naturally occurring compounds such as the resin of the opium poppy (used to derive morphine or codeine), synthetic or semi-synthetic pharmaceutical opioids (such as hydrocodone or oxymorphone), and illicitly manufactured or distributed substances (such as heroin, fentanyl and analogues). Opioid use outside of its appropriate clinical applications (that is, in the management of severe acute pain or anaesthesia) is an important public health issue given the potential addictiveness of these drugs, the extent of associated harms (such as overdose deaths) and the potential health sequelae of drug-use behaviours (for example, HIV and hepatitis C virus (HCV) infection and transmission, bacterial endocarditis, and neonatal abstinence syndrome). In addition, opioid use outside clinical indications is associated with wider societal costs, such as harms to family cohesion, reduced employment and economic contribution, and increased risk and costs of crime (both from the illegal drug market per se and individuals using crime to fund their drug use).

Over the past few decades, the understanding of the mechanisms underlying the development of dependence, addiction and other complications from opioid use has greatly improved, and more is understood about the interconnected nature whereby harms are associated with drug-use behaviours. OUD is best understood as a biopsychosocial disorder in which genetic factors, adverse early development, mental illness, social norms, drug exposure and market availability can influence the extent of exposure and the opportunity for drug use, as well as the progression and development of OUD and associated harms. Indeed, polygenic influences on observed familial transmission are being increasingly identified, the brain effects of drugs and the nature of the neuronal circuits underlying the aberrant behaviours in addiction can be imaged and measured, factors that protect from, or aggravate, progression of OUD can be recognized, and influences that create specific drug epidemics at particular points in time, space and context can be understood.

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There is a diversity of targets for potential interventions for OUD, including primary prevention initiatives, which target first use and include interventions to strengthen resilience and buffer vulnerabilities, and initiatives that target progression to regular use and addiction. Other interventions address the development of tolerance and management of withdrawal phenomena or the driving force of craving. An additional target may be the prevention of health-critical transitions (such as the transition from oral or inhaled use to injected drug use) or the reversal or lessening of harmful practices that appear entrenched, an approach often referred to as harm reduction. Interventions can also address the effects on a damaged family, treatment of medical comorbidities (including mental illnesses), employment and societal contribution, including reintegration of those caught up in the criminal justice system.

Several treatments of proven efficacy and effectiveness are available for OUD. The robustness of the evidence varies, as do the observed effect sizes[1–3]. Treatments of OUD include several pharmacological strategies (μ-opioid receptor agonists such as methadone, partial agonists such as buprenorphine, antagonists such as naltrexone, and other approaches such as lofexidine to manage withdrawal). Harm reduction interventions, seeking to reduce damage caused by ongoing use, include needle and syringe exchange programmes, dispensing of naloxone for overdose reversal, drug courts and other diversion schemes. Other interventions also exist outside mainstream medical practice, including mutual aid groups and residential rehabilitation houses, although these interventions, in general, have not been subject to the same degree of rigorous research scrutiny. Some psychological, psychosocial and behavioural approaches have been shown to produce independent benefit as well as, in some cases, to work synergistically with pharmacological approaches[4]. In addition, interventions at societal and public policy level influence the extent of OUD and associated harms, requiring attention to macro-level issues such as medical prescribing practices for pain relief as well as criminal justice policies, law enforcement and interdiction strategies. The OUD field strongly illustrates the need for integration of individual treatment approaches, public health and public policy.

This Primer discusses the changing epidemiology of OUD as well as the efforts to improve the prevention and treatment of this disorder. It also discusses the biological and social mechanisms underlying the development of OUD and touches upon how this disorder affects patients, peers and society in general.

Epidemiology

Prevalence

Accurate estimation of the population-based prevalence of OUD is challenging, particularly in countries where illicit drug use can lead to incarceration and where confidentiality is absent or disclosure could trigger reprisals. Despite these shortcomings, a variety of imperfect methods can be used to estimate prevalence, including household surveys of non-institutionalized populations and capture–recapture approaches[5,6]. The availability and quality of data on OUD varies geographically[7], making prevalence estimates uncertain for many countries. In the 2016 Global Burden of Disease study, 26.8 million people were estimated to be living with OUD worldwide[8]; the age-standardized prevalence of OUD varied substantially across countries, with the highest estimated prevalence observed in the USA[8] (FIG. 1).

Types of drug use

The types of opioids used and the typical routes of administration vary between countries and have changed over time. For example, opium (by smoking or ingestion) was historically the most common opioid consumed in countries in the Middle East, such as in Iran[9], although injection of opioids has become a more prominent feature of illicit opioid use in Iran in recent decades[10,11]. By contrast, prescription opioid use is more common in North America; in the USA, prescriptions for opioid analgesics quadrupled between 1999 and 2010 (REF.[12]), with a sharp increase in deaths over the same period[13] (FIG. 2). In 2015, 37.8% of adults in the USA used prescription opioids in the year prior, 4.7% engaged in non-medical opioid use (that is, use outside a doctor's direction) and 0.8% were estimated to have a prescription OUD[14].

In parallel to increasing prescription use, heroin use in the USA has been increasing since at least 2002 (REF.[15]), with the range of efforts to restrict the availability of prescribed opioids along with the increased availability of high purity, low cost heroin likely contributing to this increase since 2010 (REF.[13]). Population surveys suggest that the prevalence of lifetime heroin use in the USA increased from 0.33% in 2001–2002 to 1.6% in 2012–2013 (REF.[16]). Additionally, there is evidence of dramatic increases in the use of synthetic opioids (including illicit fentanyl) in the USA, with an estimated more than six times increase in overdose deaths caused by synthetic opioids from 2013 (~3,105 deaths) to 2016 (~20,000)[17].

The course of OUD

The likelihood of OUD following opioid use is high compared with most other drugs[18]. Some individuals are highly vulnerable to OUD following opioid use, whereas others do not develop OUD and cease within a year of

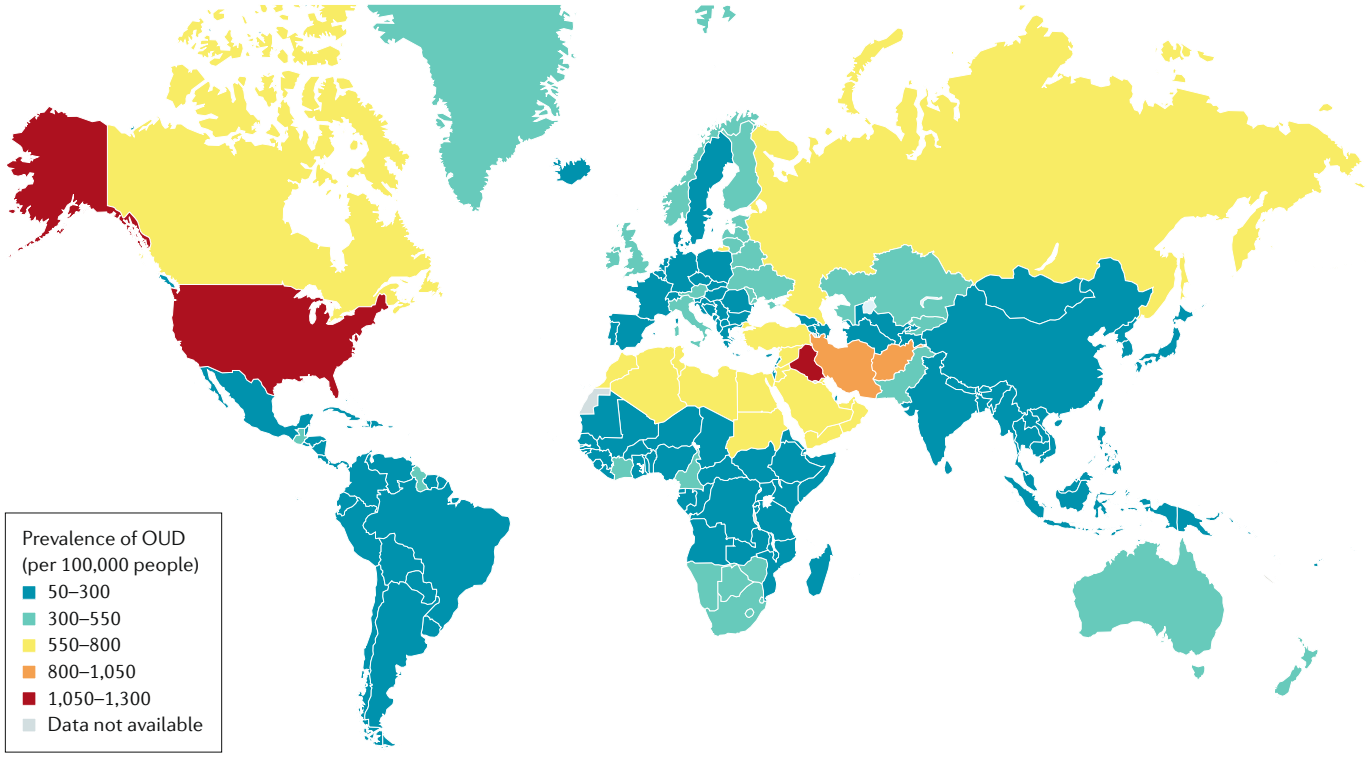

Fig. 1 | **Age-standardized prevalence of OUD per 100,000 people.** Age-standardized prevalence of opioid use disorder (OUD) per 100,000 people, based on data from the 2016 Global Burden of Disease study[8].

first use[19]. There are anecdotal accounts of individuals who manage to use opioids infrequently (such as persons who engage in 'chipping', defined as occasionally using heroin or other illicit opioids)[20], although they remain at risk of acquiring blood-borne virus infections (and the subsequent morbidity and mortality), even if other health and social problems associated with OUD do not develop.

Many people who develop OUD have a chronic remitting course of the disorder. Data from cohorts of individuals with heroin dependency suggests that they can cycle in and out of active OUD over years or decades, interspersed with periods of exposure to treatment, incarceration and abstinence[21]. The often chronic and also dynamic course of the disorder also places people with OUD at heightened risk of serious adverse outcomes at important points; for example, periods of increased risk for overdose, suicide and injuries occur following return to use after a period of abstinence such as during treatment induction, after treatment cessation and following release from incarceration[22–24].

The proportion of individuals who use opioids and do not develop OUD or those with short periods of use versus those with chronic use is difficult to estimate[25,26]. Population surveys tend to sample people who have ceased opioid use and may not have developed OUD[27], whereas cohort studies of individuals who use opioids over-represent people with OUD and prolonged periods of use[28–30]. In one small study in the UK, approximately two-thirds of individuals who used opioids reported chronic use, whereas one-third reported acute use[25]. The average duration of OUD is uncertain and can differ between populations and environments[21,31], with some cohorts indicating that average duration might be >10–20 years[32]. This uncertainty complicates estimates of the total population of persons using opioids and models of the effect of different interventions to prevent opioid-related harm[26,33].

Risk factors for OUD

A complex interplay of structural, social, developmental and behavioural risk factors is likely have a role in the development of OUD. Most of our understanding on the risk factors for OUD comes from retrospective studies of treatment populations rather than from prospective studies although, given the high prevalence of the disorder and the increased attention it has received in the USA, a range of population-based surveys have been carried out[34]. OUD has a moderate to high heritability[35]; the involvement of genetic factors are discussed in greater detail in the Mechanisms/pathophysiology section below.

An important risk factor for OUD and for overdose deaths is the availability and volume of prescriptions of opioid pain medication[36,37]. The availability of opioids for analgesic purposes varies substantially across the globe and it is not surprising that countries that have much higher prescribing rates for opioids have greater rates of non-medical use and opioid overdose deaths such as in North America, Western Europe and Australia[38]. Indeed, the USA and Canada have experienced an epidemic of opioid prescribing, which has been a driver of the current public health emergency of OUD. For example, in 2012, there were enough opioid prescriptions in

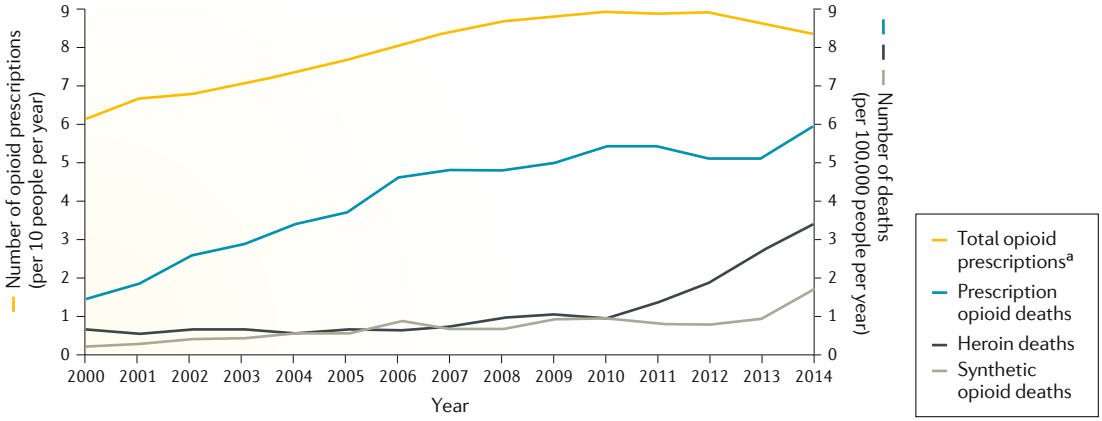

Fig. 2 | **Opioid prescriptions and deaths.** Correlation between opioid prescriptions and prescription opioid-related deaths in the USA between 2000 and 2014. The total number of opioid prescriptions increased between 2000 and 2012, during which time the number of deaths due to opioid use also increased. [a]Note that some individuals may have a prescription for more than one opioid.

the USA (~259 million) for "every adult in the United States to have a bottle of pills" (REF.[39]). This situation arose, in part, because of lobbying efforts for pain to be considered the fifth vital sign and for chronic pain to be aggressively treated with prescription opioids. Indeed, regulatory bodies such as the Joint Commission for Hospital Accreditation released new pain standards in 2001, which endorsed the "Pain is the Fifth Vital Sign" campaign and urged providers to increase the identification and treatment of pain, particularly with prescription opioids[40]. In addition, aggressive and, in some cases, deceptive marketing of opioids for the management of non-cancer chronic pain (defined in 2016 Centers for Disease Control and Prevention guidance[41] as pain lasting >3 months) from pharmaceutical companies promoted opioid prescribing throughout the USA. Direct-to-physician marketing of opioid products has been associated with increased opioid prescribing at the provider level[42], which in turn has been correlated with county-level opioid overdose mortality rates[43]. These efforts created substantial geographical variations in opioid prescribing and some cases of criminal prescribing by physicians[39,44]. The consequences of this over-prescribing have been severe. Prescription sales of opioids for pain management have increased alongside increases in opioid-related deaths (FIG. 2), with >165,000 deaths in the USA between 1999 and 2014 (REFS[45–47]).

The social and contextual factors that increase the risk of illicit substance use in general are also risk factors for non-medical prescription or illicit opioid use[48], and include drug availability, social stressors, peer substance use[49,50], mood disorders and social norms tolerating substance use[51]. In particular, affiliation with antisocial peers and those that use drugs is one of the strongest predictors of adolescent illicit drug use[52], which likely operates independently of individual and family risk factors[53]. Socioeconomic background is another important correlate of illicit drug use, with people from more disadvantaged backgrounds being more likely to use and misuse illicit and prescription opioids[34,49,54]. Several family factors increase risk of illicit drug use during adolescence such as poor quality of parent–child interactions (neglect) and relationships[55], parental conflict[56], childhood maltreatment (abuse)[57], parent incarceration, and parental and sibling drug use[58].

Individual risk factors for OUD include male sex[49,59], externalizing disorders in childhood (such as conduct disorder)[60], poor school performance, low commitment to education and non-completion of secondary education[61]. In addition, there is increasing recognition of the potential importance of co-occurring mental disorders, such as depression and post-traumatic stress disorder, and physical health problems, such as chronic non-cancer pain, in the development of OUD[34,62], both in and outside the context of medical treatment. These risk factors often co-occur, which increases the risk for OUD; for example, among people with chronic non-cancer pain who were prescribed opioids, those with a higher number of comorbidities (such as major depression) had a greater risk of receiving higher opioid doses and developing OUD[59] (termed adverse selection)[63].

Of the externalizing disorders, conduct problems in childhood and early adolescence are a key pathway to substance use in young people[64,65] and are a feature of the onset of OUD. Indeed, in one case–control study, people who inject opioids were over four times more likely to have experienced early conduct problems that were severe enough to become known, in most circumstances, to local government social services[66]. In addition, there is consistent evidence that the prevalence of childhood physical and sexual abuse are increased in people with a history of opioid use; however, the quality of the evidence is not strong owing to a lack of robust studies[67,68]. More widely, it is hypothesized that OUD might develop in some individuals as a form of self-medication for mood and anxiety disorders[57,66,69,70], although the fact that opioid use might precipitate such disorders makes disentangling these mechanistic pathways challenging[71]. Similarly poorly defined is the contribution of structural factors to non-medical opioid use such as a lack of economic opportunities and eroded social capital[72].

Risk factors for OUD are likely to differ between countries, although few studies have directly investigated this point[73]. One study that assessed the initiation

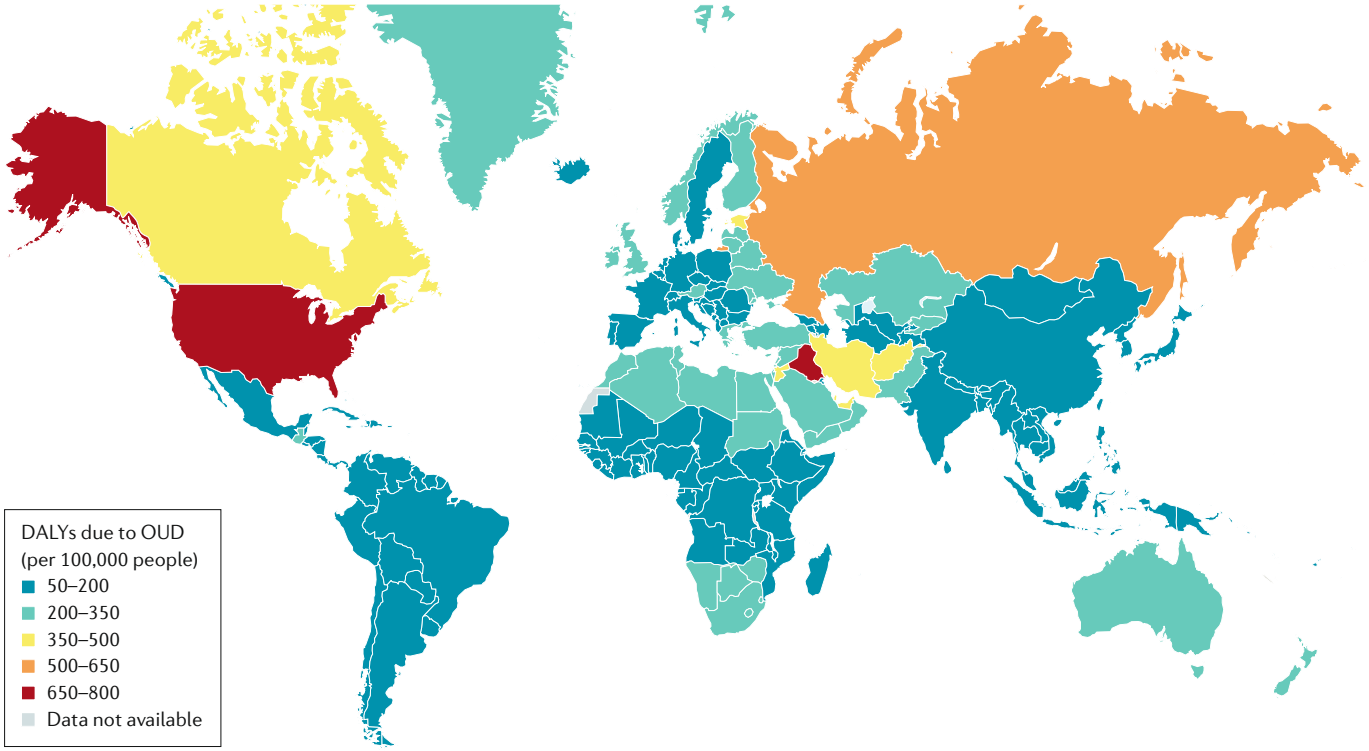

Fig. 3 | **Age-standardized DALYs due to OUD.** Age-standardized disability-adjusted life years (DALYs) due to opioid use disorder (OUD) per 100,000 people, based on data from the 2016 Global Burden of Disease study[8].

and progression to illicit drug dependence in 17 countries demonstrated that earlier onset of drug use, using more types of illicit drugs, and having already developed externalizing or internalizing disorders predicted the development of dependence in individuals who use drugs[73].

Burden of disease and sequelae of OUD

Several consequences of prescribed and non-medical opioid use cause substantial burden to the individual, their families and the broader community. For example, OUD itself carries a substantial health burden owing to the disability associated with OUD and the risk of overdose. The health burden from OUD varies dramatically across countries, with the highest burden observed in the USA[8] (FIG. 3).

The swift and concerning shifts in the types of opioids being consumed in some countries (such as the USA and Canada) have dramatically increased the risk of opioid overdose and opioid-related mortality. For example, since 2010 in the USA, deaths due to prescribed opioids have stayed relatively constant, whereas illicit opioid-related overdose deaths have increased substantially[74]; this effect was first attributable to heroin[13] but has more recently been due to fentanyl[75] (FIG. 2). The latter is highly concerning given the widespread penetration of fentanyl adulteration in the illicit drug market in North America[76,77] and evidence suggesting that many people who experience opioid overdose due to fentanyl might have unknowingly consumed the drug[78,79].

People who have developed OUD have an increased risk of a range of other social and health-related harms, including incarceration, injuries, suicide, homicide and blood-borne virus infections, compared with the general population (TABLE 1). In the USA, the number of reported cases of acute HCV infection doubled between 2011 and 2015 (REF.[80]), and multiple outbreaks of acute HCV among people who inject prescription opioids have been reported[81,82]. Similarly, the number of cases of opioid neonatal abstinence syndrome (a term used to describe a cluster of signs and symptoms in infants experiencing withdrawal from opioid drugs) increased from 1.20 per 1,000 live births in the year 2000 to 3.39 in 2009, whereas the percentage of days spent in intensive care because of neonatal abstinence syndrome increased from 0.6% to 4.0% between 2004 and 2014 (REF.[83]).

In addition, there is an increased rate of road traffic injuries, falls, drowning and related injuries in people with OUD compared with the general population. For example, one review found that pooled estimates of accidental injury-related and suicide crude mortality rates were very similar (both 0.1 per 100 person-years; 95% CI 0.1–0.2)[84]. Furthermore, compared to the general population of the same age and sex, the rate for accidental injuries was 6.9 times higher (95% CI 4.4–10.6) and that for suicide was 7.9 times higher (95% CI 5.7–11.0) in people with OUD[84]. Rates of self-reported suicide attempts among those with OUD are also much higher than among peers of the same age, sex and socioeconomic status[85]. This association may be mediated by depression, rates of which are increased among people with OUD.

Globally, opioids are the main type of injected drug, and are estimated to be used by ~80% of people who currently inject drugs[86], although the extent of injecting

Table 1 | **Excess mortality of people with an opioid use disorder across all major diseases**

Disease description	ICD-10 codes	Observed deaths	CMR, per 10,000 pys (95% CI)	Expected deaths	SMR (95% CI)
Infectious/parasitic	A00–B99	159	2.9 (2.5–3.4)	12.6	12.6 (10.8–14.8)
Viral hepatitis	B15–B19	82	1.5 (1.2–1.9)	1.4	57.2 (46.1–71.1)
HIV	B20–B24	31	0.6 (0.4–0.8)	4.4	7 (5.0–10.0)
Cancers	C00–D48	296	5.5 (4.9–6.1)	166.3	1.8 (1.6–2.0)
Liver cancer	C22	38	0.7 (0.5–0.9)	4.1	9.2 (6.7–12.7)
Endocrine	E00–E90	29	0.5 (0.4–0.8)	12.5	2.3 (1.6–3.3)
Mental and behavioural[a]	F00–F99	31	0.6 (0.4–0.8)	7.2	4.3 (3.0–6.1)
Nervous system	G00–G99	47	0.9 (0.7–1.2)	27.4	1.7 (1.3–2.3)
Circulatory system	I00–I99	418	7.7 (7.0–8.5)	134.1	3.1 (2.8–3.4)
Respiratory system	J00–J99	259	4.8 (4.2–5.4)	29	8.9 (7.9–10.1)
Influenza and pneumonia	J09–J18	102	1.9 (1.6–2.3)	11.6	8.8 (7.2–10.7)
Chronic lower respiratory diseases	J40–J47	130	2.4 (2.0–2.8)	10.4	12.6 (10.6–14.9)
Digestive system	K00–K93	423	7.8 (7.1–8.6)	65.7	6.4 (5.9–7.1)
Diseases of liver	K70–K77	345	6.4 (5.7–7.1)	49.5	7 (6.3–7.8)
Alcoholic liver disease	K70	249	4.6 (4.1–5.2)	37.1	6.7 (5.9–7.6)
Fibrosis and cirrhosis	K74	66	1.2 (1.0–1.6)	6.9	9.6 (7.5–12.2)
Skin and subcutaneous tissue	L00–L99	19	0.4 (0.2–0.5)	1.1	17.2 (11.0–27.0)
Musculoskeletal system and connective tissue	M00–M99	12	0.2 (0.1–0.4)	2.7	4.5 (2.6–7.9)
External causes[b]	V01–Y98	482	8.9 (8.1–9.7)	146.3	3.3 (3.0–3.6)
Homicide[c]	X86-Y09	77	1.4 (1.1–1.8)	6.3	12.2 (9.8–15.3)
Suicide, excluding drug-related poisoning	X65–X84 & Y15–Y34	199	3.7 (3.2–4.2)	68.2	2.9 (2.5–3.4)
Suicide, including drug-related poisoning	X60–X84 & Y10–Y34	351	6.5 (5.8–7.2)	81.9	4.3 (3.9–4.8)
Not classified elsewhere[d]	–	66	1.2 (1.0–1.6)	12.2	5.4 (4.3–6.9)
Other[e]	–	18	0.3 (0.2–0.5)	19.6	1 (0.6–1.5)

CMR, crude mortality rate; ICD-10, International Classification of Diseases, 10th Revision; pys, person–years; SMR, standardized mortality rate. [a]Excluding 916 categorized as drug-related poisonings (ICD-10 codes F11–16; F18–19)[386]. [b]Excluding 799 categorized as drug-related poisonings (6 homicides and 152 suicides: ICD-10 codes X40–X44, X60–X64, X85, Y10–Y14[386]. [c]Including 14 cases of 'accelerated registration' where the coroner's inquest is adjourned until legal proceedings are completed. [d]Including 61 cases of 'other ill-defined and unspecified causes of mortality'. [e]Other deaths: congenital malformations, deformations and chromosomal abnormalities ($n = 8$); diseases of the blood ($n = 6$) and the genitourinary system ($n < 5$); pregnancy, childbirth and the pueriperium ($n < 5$) and conditions originating in the perinatal period ($n < 5$). Table adapted from REF.[177], CC-BY-3.0 (https://creativecommons.org/licenses/by/3.0/).

drug use in individuals with OUD is likely to vary considerably geographically[86]. Globally, 52.3% of people who currently inject drugs are estimated to have been exposed to HCV (anti-HCV-positive, UI 42.4–62.1%), 9.0% have chronic hepatitis B virus infection (HBV; hepatitis B surface antigen positive, UI 5.1–13.2%) and 17.8% are living with HIV infection (UI 10.8–24.8%)[86]. Chronic and untreated HIV, HBV and HCV infections cause substantial premature mortality and disability[87]; in particular, injecting drug use is thought to be responsible for a substantial proportion of the burden due to HCV globally[87]. Unsterile drug injecting also increases the risk of a range of other injection-related injuries and diseases such as thrombosis, cellulitis and bacterial endocarditis[88].

Mechanisms/pathophysiology

Abused μ-opioid agonists override the reward function of endogenous opioids, lead to tolerance and withdrawal via alterations within the reward, brain stress and pain systems, and engage glutamatergic pathways from the frontal cortex and allocortex to drive craving. Chronic opioid administration generates intense reactivity to opioid-conditioned cues whilst also producing hyperalgesia and hyperkatifeia (increased emotional distress in individuals with OUD during withdrawal), as well

as intense reactivity to opioid withdrawal-conditioned cues, all of which drive pronounced drug-seeking behaviour via processes of negative reinforcement that exacerbate the compulsivity of drug-taking in opioid addiction. Returning these motivational circuits from an allostatic negative hedonic setpoint to a homeostatic positive hedonic setpoint through the use of medication for OUD (MOUD) helps strengthen executive function, including self-regulation, and improves mood, facilitating the recovery from opioid addiction.

Findings regarding the mechanisms of OUD are drawn from animal and human studies, with explicit effort in animal models to replicate human behaviours. All behavioural data and neuroanatomical and functional frameworks discussed in this section are derived from preclinical (mostly rodent) and clinical brain imaging studies, as well as some human genetic studies. For clarity, human studies will be designated in the text. The translation of neurocircuitry, neurochemical and molecular advances to the human condition remain a substantial challenge for future advances in the diagnosis, prevention and treatment of OUD.

Stages of the addiction cycle

Opioid addiction can be defined as a compulsion to seek and take an opioid drug, loss of control in limiting drug intake and the development of a negative emotional state (hyperkatifeia) when opioid drug is not available. Building on conceptual frameworks derived from neurobiology from animal models, clinical brain imaging studies and social psychology, a three-stage cycle of OUD has been hypothesized, consisting of binge/intoxication, withdrawal/negative affect and preoccupation/anticipation stages[89]. These three stages represent dysregulation in three functional domains that are mediated by three major neurocircuits: the binge/intoxication stage represents dysfunction with incentive salience/pathological habits and is mediated by the basal ganglia; the withdrawal/negative affect stage represents negative emotional states and is mediated by the extended amygdala; and the preoccupation/anticipation stage represents dysfunction in executive function, which is mediated by the prefrontal cortex (PFC). Excessive drug-taking in the binge/intoxication stage drives an allostatic-like process that generates the withdrawal/negative affect stage and the preoccupation/anticipation stage[90]. With chronic drug exposure, the three stages feed into each other, become more intense and ultimately lead to addiction (FIG. 4).

Endogenous opioid peptides

Opioid addiction involves the hijacking of the endogenous opioid system; a complex neuromodulatory system composed of a family of endogenous opioid peptides (β-endorphins, enkephalins and dynorphins) and receptors. Endogenous opioids have a distinct polypeptide precursor and a differential but overlapping distribution

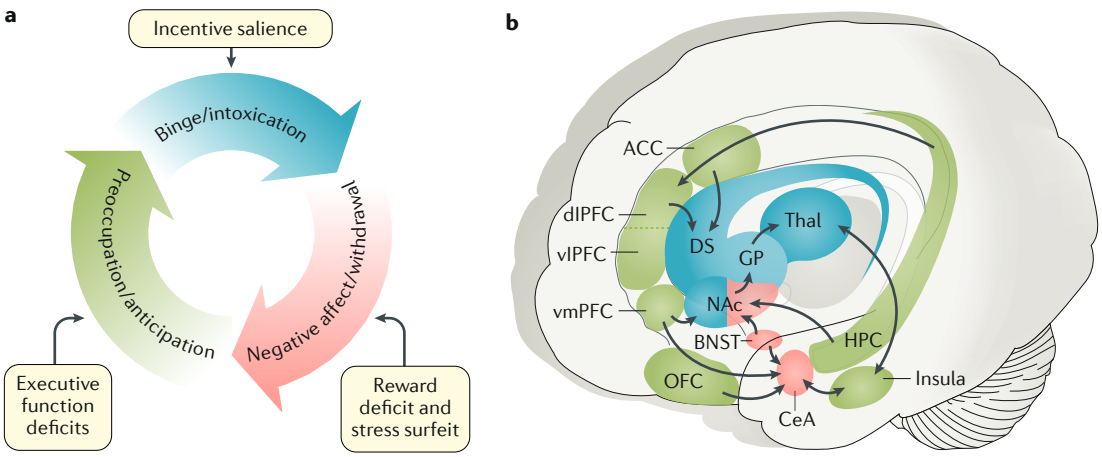

Fig. 4 | **Conceptual framework for the neurobiological basis of addiction and vulnerability. a** | A three-stage cycle has been proposed to underlie addiction. **b** | The binge/intoxication stage involves brain circuits that are involved in incentive salience (increased motivation for the drug produced by cues associated with the drug) and pathological habits. During this stage, the reinforcing effects of drugs may involve neurotransmitters that have a role in reward, associative learning mechanisms and stimulus–response habits in the basal ganglia, including the nucleus accumbens (NAc) shell and core and dorsal striatum (DS), respectively. The withdrawal/negative affect stage involves brain circuits that have a role in negative affect. During this stage, the negative emotional state that occurs during drug withdrawal may reflect the loss of reward function in the basal ganglia (including the striatum and the NAc) and the activation of aversive brain stress systems in the extended amygdala (comprising the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala (CeA) and possibly a transition zone in the medial portion of the NAc), and engagement of the habenula (not shown), which mediates negative reward signals. The preoccupation/anticipation (craving) stage involves brain circuits that are involved in executive function, including the processing of cues and contexts that trigger craving, together with compromised executive control that depends on the dysregulation of the prefrontal cortex (PFC) together with other cortical and allocortical regions. Additionally, the activity of the default mode network, which engages in interceptive awareness, is enhanced during this craving stage. One hypothesis regarding the involvement of prefrontal areas is that the top-down PFC control to reduce impulsivity and compulsivity is underdeveloped in adolescence, contributing to greater vulnerability to substance use disorders early in life. ACC, anterior cingulate cortex; dlPFC, dorsolateral PFC; GP, globus pallidus; HPC, hippocampus; OFC, orbitofrontal cortex; Thal, thalamus; vlPFC, ventrolateral PFC; vmPFC, ventromedial PFC. Adapted with permission from REF.[387], Elsevier.

throughout the brain[91], and undergo preferential binding to the three opioid receptors: μ-opioid receptors (endorphins), δ-opioid receptors (enkephalins) and κ-opioid receptors (dynorphins) receptors. Opioid peptides and their receptors are expressed throughout the peripheral and central nervous systems. These peptides regulate many aspects of physiology, including pain processing, stress reactivity, reward sensitivity, mood, respiration, and gastrointestinal, endocrine and immune functions[92].

Neurocircuitry of opioid addiction

Binge/intoxication stage: opioid intoxication and incentive salience. μ-Opioid agonist drugs are profoundly rewarding to both animals and humans, independent of pain or discomfort. As such, the reward induced by opioids leads to the association of the reward with drug-associated stimuli, such as a smell, a visual cue, any white powder or a specific context (for example, a street corner), triggering drug craving (conditioned reinforcement/incentive salience). In humans, incentive salience has been studied in laboratory settings that measured craving and drug-like urges with exposure to drug-related cues (historically termed 'needle freak' behaviour)[93,94]. Opioid drugs, such as heroin, are self-administered intravenously by mice, rats, monkeys and humans[95]. When provided under restricted conditions, animals maintain stable levels of opioid intake without major signs of physical dependence; however, when given under unlimited-access conditions, animals rapidly escalate their opioid intake[95]. Opioid drugs also support conditioned place preference (whereby an animal spends more time in a region containing the drug than a region without it), reflecting the reinforcing effects of opioids[96]. Conditioned responses trigger the 'expectation of reward' (that is, learned associations) in environments where the drug has been experienced[96]. Preclinical studies demonstrated that these reinforcing effects are mediated in the ventral tegmental area (VTA) and nucleus accumbens (NAc) via both dopamine-dependent and drug-independent mechanisms (FIG. 5). Other brain areas where μ-opioid agonists produce rewarding effects as measured by place preference include the amygdala, hippocampus, ventral pallidum and hypothalamus[97].

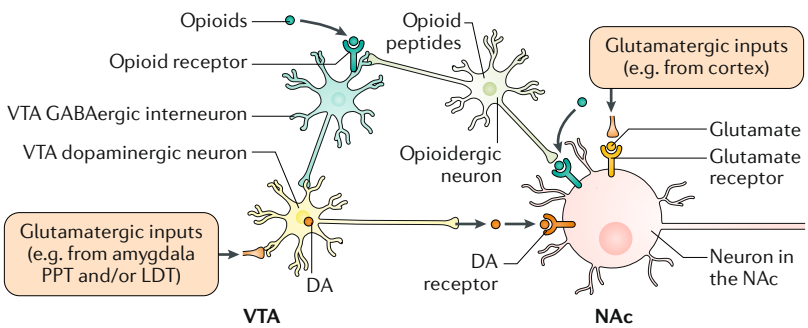

Fig. 5 | **Acute actions of drugs of abuse on the VTA and NAc.** Despite varied properties, drugs of abuse, such as opioids and psychostimulants, have some shared effects on the ventral tegmental area (VTA) and nucleus accumbens (NAc). Opioids inhibit γ-aminobutyric acid (GABA)ergic interneurons in the VTA (predominantly through μ-opioid receptors but also δ-opioid receptors)[73], leading to disinhibition of VTA dopaminergic neurons and activation of reward circuitry in the NAc. In addition, opioids also directly act on opioid receptors on NAc neurons to activate reward circuitry. These circuits likely mediate the rewarding actions of opioids. DA, dopamine; LDT, laterodorsal tegmentum; PPT, pedunculopontine tegmentum. Adapted from REF.[383], Springer Nature Limited.

Withdrawal/negative affect stage: opioid tolerance and withdrawal. Dramatic tolerance (that is, a lower response to a drug following repeated administration of the drug or the need for larger doses to produce the same effect) develops to the analgesic, euphorigenic, sedative and other effects of opioids, including their lethal effects, and can develop after a single administration[98,99]. The lethal effects of μ-opioid agonists are primarily due to respiratory depression via their actions in brainstem respiratory nuclei, specifically the pre-Bötzinger complex and the parabrachial nucleus. Interestingly, clinical studies have revealed differential tolerance levels for the different opioid effects, such that individuals become very tolerant to the rewarding, analgesic or respiratory depressant effects, whilst still showing sedation, miosis (constriction of pupil) and constipation[100,101]. Most opioid tolerance is thought to be pharmacodynamic and not dispositional, meaning that tolerance involves neuronal adaptations rather than increased opioid metabolism[101].

Neurobiological mechanisms of tolerance range from opioid receptor desensitization and downregulation to cellular and circuitry allostasis[102,103]. In the descending pain processing pathways, G proteins that are activated by μ-opioid receptors following opioid peptide binding can modulate the activity of several second messengers and cellular effectors, triggering μ-opioid receptor desensitization, μ-opioid receptor internalization, transcriptional changes in the expression of both opioid receptors and other proteins, and structural changes (such as dendritic spine remodelling)[104], all of which collectively lead to cellular tolerance[102]. Dissecting the role of one of the major non-G protein signal transduction pathways for μ-opioid receptors has revealed a key role for the β-arrestin pathway in opioid receptor desensitization and resensitization. μ-Opioid agonists typically cause activation of the arrestin 3 pathway downstream from the G-protein cascade[105]. Indeed, mice deficient in arrestin 3 (also known as β-arrestin 2) have greater analgesia, but significantly less antinociceptive tolerance, dependence, constipation and respiratory suppression compared with wild-type mice[105–107], suggesting that drugs that activate μ-opioid receptors without activating the β-arrestin pathway (such as biased opioid agonists) may have high analgesic potential and lower adverse effects[107].

In all mammals, the abrupt or gradual termination of opioids or the administration of competitive opioid receptor antagonists (such as naloxone or naltrexone) produces an opioid withdrawal syndrome. This withdrawal syndrome is characterized by physical and affective signs that can be dissociated phenotypically and by their underlying neural substrates. Symptoms of physical withdrawal in humans include piloerection, chills, insomnia, diarrhoea, nausea, vomiting and aches, and the severity and duration vary based on the dose and duration of opioid exposure and the pharmacological

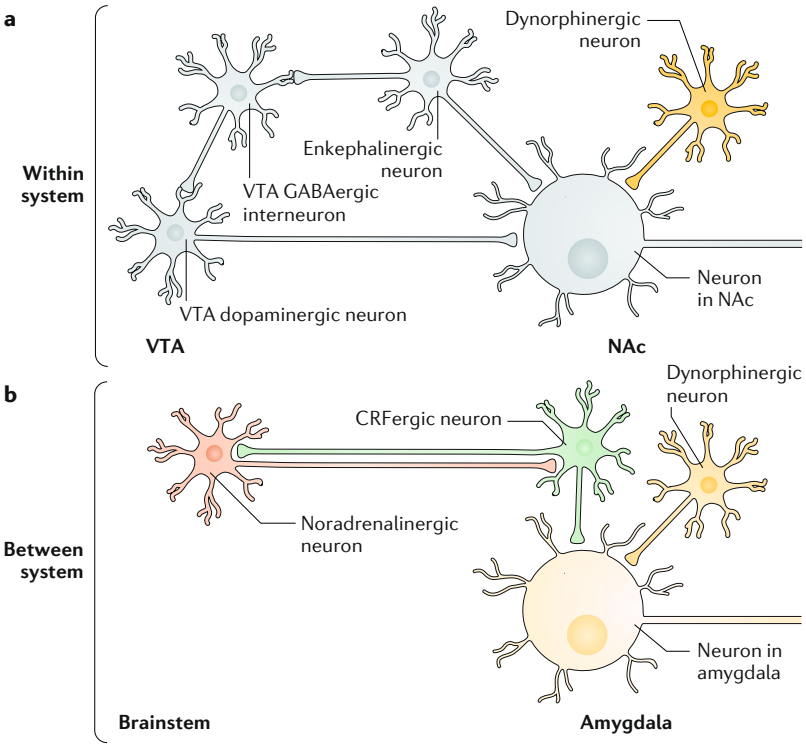

Fig. 6 | **Hypothetical neurocircuitry for the negative emotional states associated with the withdrawal/negative affect stage. a** | Excessive activation of parts of the brain reward system (that is, ventral tegmental area (VTA) dopaminergic neurons and μ-opioid receptors) following opioid use and/or chronic opioid use in turn activates dynorphin release in dynorphinergic neurons in the ventral striatum, which leads to the suppression of dopamine release in the nucleus accumbens (NAc) and contributes to the negative emotional effects of drug withdrawal (that is, the dysphoric-like effects). **b** | The activation of parts of the extended amygdala during withdrawal (corticotropin-releasing factor (CRF), noradrenaline and dynorphin) sensitize stress-like fight or flight-like responses via feed-forward mechanisms and contribute to the negative emotional effects of drug withdrawal (that is, the anxiety-like or emotional pain-like effects). GABA, γ-aminobutyric acid. Adapted with permission from REF.[384], Elsevier.

properties of the opioid used, including efficacy and pharmacokinetics[108]. The most severe acute physical withdrawal syndrome is observed with full opioid agonist drugs (compared with partial opioid agonists) and for opioids with fast pharmacokinetics such as fentanyl or heroin. In humans, affective symptoms of withdrawal (which we refer to as hyperkatifeia), are longer lasting than non-affective symptoms, and include irritability, dysphoria, insomnia, anxiety, sleep disturbances and social withdrawal[109]. Withdrawal symptoms have a major role in relapse[109,110] and can also be conditioned to cues and context in the environment[110]. Indeed, negative emotional symptoms associated with acute withdrawal, protracted abstinence and conditioned withdrawal significantly improve with the use of MOUD[109].

Studies of the neurobiological substrates of physical withdrawal in animal models have revealed the involvement of multiple regions, including the periaqueductal grey, dorsal thalamus and locus coeruleus[17]. Brain regions that are responsible for affective (motivational and emotional) withdrawal have a focal point in the extended amygdala[111]. Two neuroadaptations have been hypothesized to produce the negative emotional state (such as malaise) that contributes to the negative reinforcement associated with opioid withdrawal: a loss of function in reward systems (in the VTA and NAc) that mediate the acute reinforcing effects of opioids and a gain of function in the extended amygdala, which mediates stress-like responses[112].

Precipitated opioid withdrawal (that is produced by the administration of an opioid antagonist that abruptly leads to withdrawal signs or symptoms) in animals is associated with a decrease in extracellular dopamine in the NAc[113] and a decrease in dopaminergic neuron firing[114]. Chronic morphine use in animals is also associated with a smaller dopaminergic neuron size in the VTA and a greater sensitivity to dopamine D_2 receptor antagonists; PET studies of people with opioid dependence have revealed lower levels of D_2 receptors across the entire striatum compared with controls, which was associated with years of opioid use[115,116]. However, a decrease in dopamine release in the striatum was not observed after naloxone-precipitated withdrawal; instead, a trend for dopamine increases in the dorsal striatum was noted[115].

Gain of function of the brain stress systems during opioid withdrawal is mediated by neurochemicals in the extended amygdala that are involved in the aversive effects that act in opposition to the acute effects of opioids to reduce stress (for example, corticotropin-releasing factor (CRF), dynorphin and noradrenaline)[112,117]. The blockade of CRF receptors in the central nucleus of the amygdala blocks compulsive opioid seeking in animals that were allowed extended access to the drug (known as the long-access model)[118–120] (FIG. 6). In addition, administration of a κ-opioid receptor antagonist into the shell of the NAc blocked the stress-induced potentiation of opioid reward and reinstatement of opioid-seeking behaviour, and prohibited the escalation of drug consumption in long-access models[121,122]. Dynorphin–κ-opioid receptor activation may also explain the hypodopaminergic state that is driven by excessive opioid administration, either of a single, large dose or chronic administration[123] (FIG. 6). The activation of neuropeptide Y and the endocannabinoid systems and other anti-stress systems in the extended amygdala may modulate the increase in stress reactivity associated with opioid withdrawal and, as such, could buffer endogenous pro-stress systems[124].

Preoccupation/anticipation stage: opioid craving and relapse. The preoccupation/anticipation stage of the addiction cycle in humans involves dysfunction of executive function. Executive function is mediated by the PFC and impairments in response inhibition, salience attribution and self-regulation were conceptualized as underlying relapse and bingeing in humans[125,126].

Animal models of craving have historically used paradigms of drug-induced, cue-induced and stress-induced reinstatement of drug-seeking behaviour in non-dependent animals that are allowed limited access to opioids. In these models, administering μ-opioid receptor agonists injected systemically or directly in the VTA reinstates opioid-seeking behaviour during extinction, and reinstatement of opioid-seeking behaviour during

extinction is blocked by naloxone[127]. Re-exposure to a previous heroin-paired cue or context after extinction can reinstate heroin-seeking behaviour in nondependent rats[128,129]. In addition, in rodents, cue-induced reinstatement engages neurocircuitry from the medial PFC to the NAc[128], and context-induced reinstatement engages projections from the ventromedial PFC and subiculum to the NAc shell[129] (FIG. 7). One key molecular mechanism of cue-induced reinstatement of opioid seeking involves the dysregulation of glutamatergic homeostasis and particularly of metabotropic glutamate receptors 2 and 3 (REF.[130]). In rats, the stress-induced (via foot shock) reinstatement of opioid self-administration can be blocked using CRF receptor antagonists and α_2-adrenergic receptor agonists, which inhibit noradrenaline release[131]. Brain regions that are critical for the role of CRF and adrenergic drugs in the foot shock-induced reinstatement of opioid self-administration include parts of the extended amygdala[131].

In humans, individuals with OUD have a dysregulated hypothalamic–pituitary–adrenal stress axis; this dysregulation persists during cycles of addiction[132,133] and may drive brain stress systems as identified in animal studies. Cues that are paired with opioid withdrawal, such as places and smells, also have motivational significance. Such conditioned withdrawal cues can produce craving in humans with opioid addiction and can produce place aversions and increase drug-seeking for heroin in dependent animals[134–136]. The neurobiological substrates for conditioned withdrawal include the extended amygdala and brain stress systems therein[112]. In humans, craving and cue exposure frequently precede relapse and drug use[137], and meta-analyses of functional MRI studies have identified reliable activation of amygdala, ventral striatum and medial PFC in mediating cue-elicited craving in humans[138,139].

Long-term cellular molecular perturbations may contribute to the vulnerability to relapse in OUD. Acute opioid receptor activation leads to inhibition of adenylyl cyclase and lower protein kinase A activity[140], whereas chronic exposure increases adenylyl cyclase and protein kinase A activity[140,141]. Such perturbations eventually elicit long-term adaptations, including increased expression of the transcription factor cyclic adenosine monophosphate response element binding protein (CREB) in the NAc, which may mediate aspects of tolerance and withdrawal[142]. Subsequent ΔFosB activation could facilitate initiation and maintenance of the state of addiction and could be a common long-term molecular motivational change across drug classes[142].

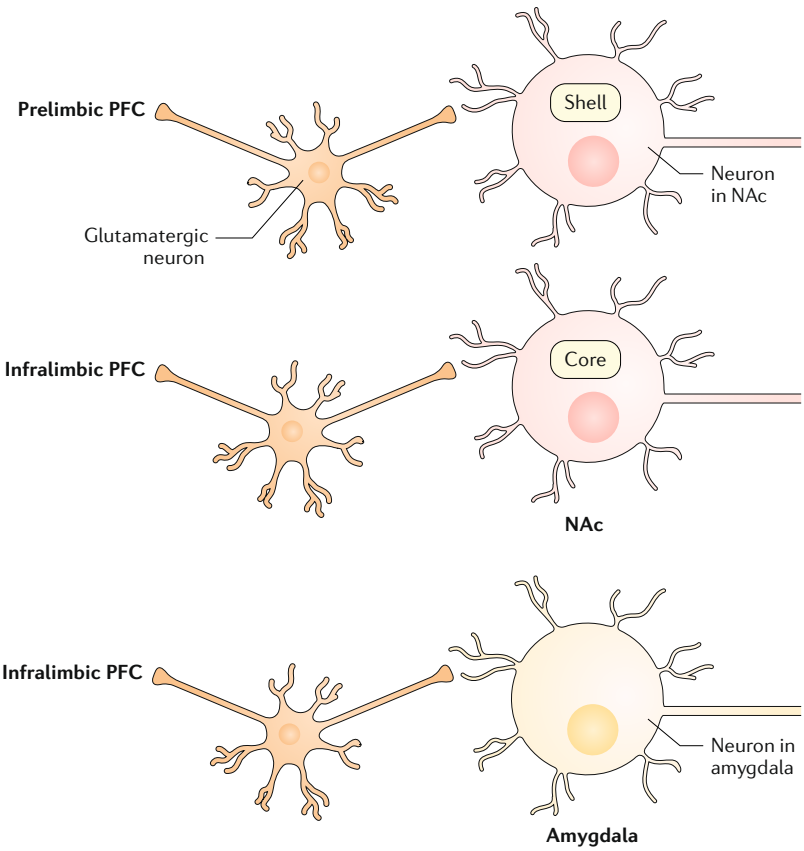

Fig. 7 | **Role of the PFC in initiating and inhibiting the reinstatement of drug-seeking behaviour.** Prelimbic glutamatergic projections to the nucleus accumbens (NAc) shell are speculated to contribute to incentive salience and habit formation, whereas the inhibition of drug-seeking behaviour is speculated to be mediated by infralimbic glutamatergic projections to the NAc core. In addition, infralimbic glutamatergic projections to the amygdala are hypothesized to contribute to the inhibition of brain stress systems. A combination of high prelimbic and low infralimbic glutamatergic activity could drive drug-seeking behaviour by driving craving and disinhibiting restraints on impulsivity and compulsivity, behaviours that are mediated by the NAc and the amygdala. PFC, prefrontal cortex.

Genetics

OUD, similar to other substance use disorders, has high heritability[143]. The A118G (or single-nucleotide polymorphism (SNP) rs1799971-A) polymorphism in *OPRM1* (encoding the μ-opioid receptor) might influence the expression of μ-opioid receptors in the brain[144], the sensitivity to opioid receptor agonist drugs[145] and vulnerability to opioid addiction[144,146], although not all studies have demonstrated these associations[146]. Indeed, cis-expression quantitative trait loci analysis has demonstrated that other SNPs, such as rs3778150, and nearby SNPs, may underlie the inconsistent associations between rs1799971 and heroin addiction. Here, SNP rs3778150 was strongly associated with an increased risk of heroin addiction and the functional SNP rs1799971-A was associated with heroin addiction only in those with rs3778150-C[146].

Based largely on case studies, a substantial genetic variation in the metabolism of opioid drugs has been reported, particularly of those that use the cytochrome P450 enzyme system, such as codeine, oxycodone, tramadol and fentanyl[145,147]. This variation leads to extreme cases of poor metabolizers (who have very high drug levels in plasma) or ultra-rapid metabolizers (who need much higher drug doses for therapeutic efficacy). Poor metabolizers could be vulnerable to overdose with ill-founded self-medication attempts and ultra-rapid metabolizers could be vulnerable to excessive intake that makes them vulnerable to addiction. Genome-wide association studies with pathway analyses have identified several loci and gene networks that might account for the heritable vulnerability to OUD, including genes encoding potassium channels,

Box 1 | **OUD criteria**

In the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5)[174], a minimum of 2–3 of the criteria below are required for a 'mild disorder' diagnosis, whereas 4–5 criteria are required for a 'moderate disorder' diagnosis, and 6–7 criteria are required for a 'severe disorder' diagnosis. A different approach is taken with the *International Classification of Diseases*, 10th Revision (ICD-10)[386], which requires ≥3 of the following criteria 1, 2, 11, 10, progressive neglect of alternative pleasures (as measured by a combination of 3, 5, 7) or persistence despite harm (as measured by 6 and 9). Adapted from REF.[174].

1. Taking the opioid in larger amounts and for longer than intended
2. Wanting to cut down or quit but not being able to do so
3. Spending a lot of time obtaining the opioid
4. Craving or a strong desire to use opioids
5. Repeatedly unable to carry out major obligations at work, school or home due to opioid use
6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by opioid use
7. Stopping or reducing important social, occupational or recreational activities due to opioid use
8. Recurrent use of opioids in physically hazardous situations
9. Consistent use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using opioids
10. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount[a]
11. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal[a]

[a]This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision. OUD, opioid use disorder.

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, calcium channels and glucocorticoid receptors[148–150].

Sex differences

More men misuse and are addicted to opioids than women[151]. Indeed, in the USA in 2017, there were 32,337 opioid overdose deaths in males and 15,263 in females[45,152]. The prevalence of OUD in the USA also shows sex differences; the 2017 National Survey on Drug Use and Health reported that, of those aged ≥12 years with opioid abuse or dependence, 1,162,090 were men (0.96% of men in this age group in the overall population) and 779,050 were women (0.62% of women in this age group in the overall population)[152].

Clinical reports suggest that, for opioids, similar to other drugs of abuse, women progress from initial use to addiction at a faster rate than men[153]. Sex differences in the opioid system have been reported in preclinical studies, which might underlie sex differences in the sensitivity to pain or addiction (for a review, see REFS[154,155]). In addition, PET studies in humans demonstrated higher levels of μ-opioid receptors in several brain regions (neocortex, caudate, amygdala, thalamus and cerebellum) in women than in men[156], and that women had less pain-induced activation of μ-opioid receptors than men in the thalamus, basal ganglia and amygdala[157]. Preliminary PET studies in humans have also reported significantly higher availability of κ-opioid receptors in the brain of men than women[158]. However, much more preclinical and clinical work is needed to characterize sex differences in the opioid system, which are relevant to both pain and addiction.

Opioids, pain and addiction

Animal and human studies have revealed hyperalgesia during spontaneous opioid withdrawal (that is, when drug administration simply ceases) and during precipitated opioid withdrawal following acute or chronic opioid exposure[159,160]. Other alterations in the pain system have been reported, such as low pain tolerance in patients who are receiving methadone maintenance[161], and pain is one of the main triggers of relapse to addiction in those receiving methadone[162]. Indeed, in abstinent individuals with a history of opioid addiction, the hyperalgesic state can persist for up to 5 months, and individuals with greater pain sensitivity also have greater cue-induced craving[163]. In a systematic study of the interaction between negative emotional states and withdrawal-associated hyperalgesia, individuals in acute withdrawal (24–72 hours) from opioids or protracted abstinence (average of 30 months) had lower pain thresholds and lower pain tolerance, and these effects were exacerbated by negative emotional states[164]. The neurobiological targets for opioid-induced hyperalgesia in animal studies include the activation of glutamatergic[165] and brain stress systems such as CRF[166] and dynorphin[102].

One hypothesis to explain the misery associated with opioid addiction is that the set point for experiencing a negative emotional state is lowered, driven by low reward, high stress and impairments in executive function[167,168], all of which are mediated by specific neurocircuitry dysregulations. Conceptually, a hypersensitive negative emotional state (hyperkatifeia) has also been hypothesized to parallel the opioid-induced hyperalgesia associated with physical pain[169]. Indeed, evidence suggests that the neural alterations that are associated with addiction could overlap with alterations in emotional aspects of pain processing in the amygdala via the spino(trigemino)-ponto-amygdaloid pathway[170–173]. One could argue, from an opponent process perspective, that any means of increasing the bolus amount of μ-opioid agonist that enters the brain, including overdosing, rapid escalation (overshooting), pharmacokinetic variables and genetic sensitivity, can trigger the involvement of the processes of hyperalgesia and hyperkatifeia that are mediated by crosstalk between the central nucleus of the amygdala and the periaqueductal grey nucleus, among other brain regions. Such a framework suggests that opioid-induced hyperalgesia or hyperkatifeia may be an important clinical marker of vulnerability to opioid addiction.

Diagnosis, screening and prevention

Diagnostic criteria

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the two previous diagnoses of opioid abuse and dependence were combined into a single disorder, OUD, with the number of symptoms signifying severity[174] (BOX 1). Many countries still use the International Classification of Diseases 10th Revision (ICD-10) classification system in which abuse and dependence remain distinct disorders, with

ICD definitions of opioid dependence requiring more symptoms than abuse (BOX 1) and with opioid abuse in the absence of dependence generally classified as harmful use if people are at risk of infection or physical or mental harm (see below). The critical factors in OUD are that people persist in using opioids despite incurring extra physical, mental, social or criminal problems as a result of their opioid use, that tolerance to the effects of the opioid develop, and that there is a switch and preoccupation with minimizing the effects of withdrawal (dysphoria) over achieving euphoria[64,65].

Detection of OUD

Individuals with OUD may come to clinical attention through a wide variety of avenues. For example, they might approach their primary care physician or other healthcare provider seeking help for their addiction or drug problem or, depending on the arrangement of services (which differ greatly within a country as well as internationally), they might approach specialist addiction services directly. However, the point of first real contact with treatment services is often oblique and might arise through another event whereby the drug use becomes evident, such as from enquiry during routine screening or from specific enquiry triggered by a clinical complication (such as injection abscess) or unexpected blood test result (for example, HBV-positive) or trauma. At such times, there is often greater receptivity to advice and a therapeutic window of opportunity that should be harnessed. Family involvement is common at the initial presentation (such as concern from a partner or from parents) and clinicians need to ascertain the extent to which the newly identified patient with OUD has their own intrinsic motivation to address their problem. However, clinicians also need to be aware that fear of change and ambivalence are almost universal characteristics of response to any such situation, and the support of the clinician, family and friends helps the individual with OUD address their problem acutely and in the long term. When an individual with OUD does not wish to engage in formal treatment, it is important to inform them of self-help options and to ensure they understand the risks associated with opioid use and advise them of behaviour changes to reduce the risks (such as HBV vaccination and avoiding needle and syringe sharing), an approach often referred to as harm reduction.

Other instances of oblique identification of OUD may be, for example, through concerns from social welfare services or school, or following apprehension for a criminal offence (sometimes drug possession or shoplifting). In these cases, the provision of treatment with accompanying requirements from courts or from professional regulatory bodies can enhance the benefits achieved from treatment[175]. A high prevalence of OUD (and other substances) is found among individuals given a prison sentence (sometimes identified, sometimes concealed), which can be an opportunity to help the individual address the OUD. Of note, some individuals at the earlier stages of OUD can overcome this disorder without formal treatment or support from self-help or mutual aid groups whereas, for others, the commencement of formal treatment is essential.

Prevention of use and prevention of harm

As previously mentioned (see Burden of disease and sequelae of OUD, above), several complications are associated with OUD and secondary prevention approaches need to be included when planning prevention initiatives. These complications include premature mortality (particularly from overdose[176]), self-harm and suicide[177,178], transmission of blood-borne viruses and increased risk of bacterial infections[87,88] (TABLE 1). Social problems, including adverse family environments and drug-related crime, are associated with OUD. Social problems are both a feature of the disorder in relation to people neglecting their other roles and responsibilities (BOX 1) and can also interact with the disorder and worsen the socio-behavioural problems that were present before opioid use was initiated. This issue is further aggravated by a severe criminal justice response to drug use, with periods of incarceration and permanent criminal records that can lead to severe limitations on future opportunities[179,180].

Primary prevention. Evidence that universal school-based interventions, some delivered through peer networks, are effective at reducing onset and progression of substance use (such as alcohol, tobacco and cannabis) in young people is growing[181–184]. However, one systematic review found either no or insufficient evidence for the effectiveness of these interventions in preventing opioid use in young people[183]. Equally, the effectiveness of prohibition or criminal justice interventions for reducing opioid use in young people has no supporting evidence[183], and mounting evidence suggests that criminal justice sanctions alone — especially imprisonment — could cause more health harms than benefit in adults who use opioids[179](see below).

In theory, interrupting the drug supply and increasing the cost of illicit drugs will reduce consumption, but such interventions are generally difficult to maintain and costly to implement[185]. There are examples of excess supply leading to opioid epidemics, such as in the USA[186], but there is little robust evidence supporting the effectiveness of interdiction or supply-based interventions reducing consumption over the long term[2]. Although some natural experiments have shown that reductions in supply can reduce opioid use and related harm[187,188], the effect is short lived and is rarely replicable. Accordingly, further study is needed to actually measure any specific effect from the interruption of drug supplies and of increased pricing as well as the duration of their effect. A potentially more promising alternative to so-called supply-based interventions is to undertake a 'whole-of-society' approach towards addressing the exclusion of marginalized and vulnerable populations from social and health services[189], although robust evidence is yet to emerge in support of this approach.

Prescription opioids. Prescription of opioids for the short-term treatment of pain (including cancer pain) does not necessarily lead to tolerance or withdrawal features; in addition, even medium-term use does not inevitably lead to development of OUD. Internationally, it is recognized that many countries continue to under-prescribe opioids for acute and cancer

pain because of a lack of training of clinical staff and fears by practitioners and policymakers of diversion and dependence, as highlighted by the International Narcotics Control Board[190]. The prescription of opioids for chronic pain, especially neuropathic pain, is more complex than treatment of acute pain (see below), and increases the risk of OUD and associated problems[36,37]. A more integrative approach is required regarding the use of opioids for pain management and to retain the undoubted benefits of opioids in some circumstances without inadvertently increasing the risk of OUD.

Patients using opioids for chronic pain experience both tolerance and a lack of efficacy within 1 month[36,37,191]. The risk of overdose is associated with several factors: high prescription doses, multiple prescribers and co-prescription with other drugs such as benzodiazepines[192,193]. Critically, there is no good evidence of any long-term benefit of prescribing opioids for chronic pain relief in the majority of patients, of the benefit of high-dose opioid prescriptions or on reliable screening tools to identify patients that are more likely to develop OUD if prescribed an opioid. Current guidance[194] recommends a 'harm reduction' or 'precautionary principle' approach for the management of chronic non-cancer pain that includes principally avoiding the prescription of opioids as the potential harms outweigh the benefits and, instead, using non-pharmacological interventions or non-opioid pharmacological symptom relief. Although the guidelines are based on existing evidence and good intentions, the reality is that many people do not have ready access to non-pharmacological interventions owing to a lack of funding, facilities and trained practitioners.

Reduced opioid prescribing for chronic pain has occurred in some countries, such as the USA, through the increased awareness by physicians that lax prescribing has contributed to the current overdose crisis and by new guidelines handed down by national and regional agencies. The US Centers of Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain was released in 2016 with the stated purpose of "reducing the number of people who misuse, abuse, or overdose from these drugs"[195]. In Canada, opioid prescribing guidelines were released in 2017 and endorsed by the Canadian Medical Association[196]. These guidelines emphasize alternative strategies for pain management and suggest restrictions on the quantity and duration of opioids. A more direct way of monitoring opioid use has been introduced in the USA through Prescription Drug Monitoring Programs (PDMPs), which aim to track responsible opioid prescribing and clinical practice, and improve patient safety. PDMPs are managed by individual states, and the uptake, enforcement and effect of these programmes vary by states, therefore affecting their efficacy[197]. For example, states with mandatory use of PDMPs have been reported to have reduced levels of opioid prescriptions and doses[198] than states where PDMP participation is voluntary, although the extent of the influence is not yet clear[199,200].

Although the effect of programmes to reduce opioid prescribing has shown early downward trends in overall prescribing[201], a major outcome has been a decreased availability of diverted pharmaceutical drugs to those who are already opioid dependent. Indeed, as the demand for opioids has remained high, the illegal market has predictably filled in the gap with more potent and less regulated products such as heroin and synthetic opioids (mainly fentanyl). However, the situation varies greatly between countries and this increased restriction needs to find a place alongside recognition of the need, in other countries, to improve the poor access to opioids for cancer pain and for severe acute pain[190].

Thus, it is too early to tell whether the guidance on restricting opioid prescription for pain relief has reduced OUD and overdose deaths. The epidemic of OUD in North America is ongoing and, although it was initially triggered by opioid prescriptions, it subsequently expanded to include heroin and, more recently, illicit fentanyl and its analogues[202]. Accordingly, clinical and public health policy needs to adapt and introduce new interventions, scale-up the coverage and intensity of interventions, and evaluate effectiveness at the same time as reducing opioid-related harm[203]. The current surge in overdose deaths in North America is complicated by the increasing use of heroin and potent synthetic opioids and drug combinations (opioids with psychostimulants)[204]. A relationship between the rise in overdose deaths and restrictions on prescription for opioids has been postulated[205] but needs careful temporal analysis as, for example, increases in heroin use among prescription opioid users preceded the implementation of policies to reduce the misuse of prescription opioids[206].

Public health approach to prevent opioid use-related harm. The Institute of Medicine recommended the adoption of a comprehensive public health approach in its review of drug abuse research that prioritizes interventions and research that prevent drug-related harms as the key policy goal, rather than focusing on drug consumption per se[64]. Similarly, harm reduction was central to a successful response to the HIV epidemic in the 1980s and early 1990s among people who inject drugs in many countries[207]. A public health or harm reduction approach to preventing opioid-related harm encompasses the full range of drug treatments along with needle and syringe provision, vaccination and treatment of blood-borne viruses, and naloxone distribution. In support of harm reduction approaches, some countries, such as Switzerland and Canada, have shown benefits for OUD and HIV treatment engagement and prevention of adverse effects of opioid injection (such as overdose fatalities) with access to supervised injecting facilities and with strategies that reduce structural risk factors associated with adverse drug policies[2,179,189,208]. The WHO and organizations in Europe and North America recommend a comprehensive approach to the prevention of HIV and HCV for people who inject drugs, comprising multiple interventions from antiviral treatment, opioid substitution treatment, needle and syringe programmes (NSPs), peer education, outreach and case-finding in the community[209]. Harm reduction policies need to

be reimagined and revitalized in response to the epidemic of opioid overdose deaths that is affecting North America in particular.

Opioid agonist therapy (OAT) can play an important role in reducing the adverse health consequences of OUD. Although a randomized controlled trial (RCT) designed or sufficiently powered to measure the effect of medications on drug-related mortality or transmission of HIV would need to have an unrealistically large sample size[210,211], there is good evidence from observational studies, and in particular cohort studies, that MOUD (BOX 2) consistently reduces mortality, reduces transmission of HIV and HCV, improves HIV treatment coverage and prognosis, and is associated with reductions in drug-related crime[22,212–217]. In addition, several systematic reviews have suggested that MOUD reduces overdose mortality by 3–4-fold[22], halves the incidence of HIV[214] and HCV[215,216], and doubles adherence to HIV antiviral therapy[218]. The health benefits of MOUD occur during exposure (that is, whilst patients are on MOUD (BOX 2)). MOUD is highly cost-effective when delivered both in the community and in prison[219,220]. Economic models that include the wider societal benefits of MOUD — specifically a reduction in drug-related crime — should be prioritized as this option tends to be less costly and generates more benefit than steady-state strategies or minimizing access to MOUD[217,221].

People with OUD have a high risk of relapse[222,223]. Two particular periods of high risk are when people with a current or recent OUD leave prison or when they cease drug treatment[24,224]. Indeed, the risk of fatal overdose within the first month of leaving prison or drug treatment can be 4–8-times higher than the general risk of overdose death in the community[23,225]. Incarceration is a key risk for people with OUD; systematic reviews suggest that one-quarter to one-third of prisoners worldwide have a history of problem drug use, particularly opioid use[179,226]. Observational studies in the UK and Australia have shown that people with OUD that leave prison on MOUD have an overdose mortality risk that is 75–80% lower in the first month after release compared with prisoners with OUD that were untreated or detoxified during prison[224,225]. These observational studies and a trial in the USA also show that leaving prison on MOUD increases the uptake of community drug treatment programmes[227]. In addition, MOUD treatment in prison reduces self-harm and is associated with lower HCV incidence in prison[228–230].

Studies of OAT on incidence of HIV and HCV suggest that greater benefit is generated through increasing both the coverage and duration of MOUD, and combining it with other interventions[231,232]. Studies of MOUD in UK primary care have suggested that the average duration (approximately ≤6 months) is too short to counter the elevated risk of death at the beginning and end of MOUD, and to achieve a population-wide effect on reducing the number of drug-related deaths[233,234]. In addition, there is good theoretical evidence from model projections and some ecological studies that antiviral treatment is critical for the prevention of HIV and HCV in people with OUD who inject drugs[231,235]. Model projections (FIG. 8; TABLE 2) hypothesize that scaling up HIV or HCV treatment in combination with MOUD and other interventions can minimize transmission of HIV or HCV and reduce prevalence of HCV towards elimination levels.

A comprehensive approach to prevention of OUD and drug-related harm — adjunct interventions. Another primary prevention intervention for HIV and HCV in people with OUD who inject drugs is the distribution of sterile injecting equipment through NSPs[215,216,236]. The evidence base is weaker for the effect of NSPs on HIV and HCV than with OAT, especially in North America. However, there is stronger evidence that the combination of NSP and MOUD reduces viral transmission[236].

Adjunct interventions to MOUD include the community distribution of naloxone (an effective antagonist treatment that can block the effects of opioids, treat respiratory depression and reverse opioid overdose) and introducing supervised injecting facilities. The community distribution of naloxone among people with OUD (and key family members) has expanded, and is an intervention which is acceptable to peer users and family members for them to administer[237–240]. In addition, good model evidence shows that scaling up community naloxone averts overdose deaths[241]. Public and professional attitudes to these harm reduction approaches vary greatly between countries and communities. In some countries, such as Switzerland and Australia, the approach is public policy, whereas in others, such as the USA and UK, it remains contentious and politically highly charged. Notwithstanding these diverse positions, the number of supervised injecting facilities has increased worldwide in response to an increase in drug-related deaths and harms[242]. Although rigorous scientific evaluation of these approaches is difficult, the clinical experience from some of the well-established sites has generally been very positive[243–245]. Going forward, the establishment of new

Box 2 | **OUD treatment terminology**

There is a confusion of terminology for medications used in the treatment and management of opioid use disorder (OUD). The term 'medications for OUD' covers all medications that are used specifically to treat OUD and includes opioid agonist therapies (OATs), opioid antagonist treatments (naltrexone) and medications for acute withdrawal.

OATs address the repeated need to seek drugs by stabilization on a maintenance dose of a prescribed opioid (usually long acting and usually taken orally under supervision on a daily basis). OAT is also described by some individuals as opioid substitution treatment, opioid replacement therapy or with terminology associated with the specific opioid used such as methadone maintenance treatment or buprenorphine maintenance treatment. Heroin assisted treatment would also be in this category.

Opioid antagonist treatments, of which the only medication in regular clinical use is naltrexone, are used to offer blockade of the effect of any exogenous opioid that may be taken by the patient. The intention of this therapy is to support a recently achieved abstinent state and allow stabilization of lifestyle without repeated intermittent further opioid use.

Medications for acute withdrawal are used to reduce the distress from physical dependence that emerges upon abrupt opioid discontinuation. This is sometimes achieved by tapering the opioid dose to avoid the most intense expression of opioid withdrawal symptoms (for example, reducing doses of methadone or buprenorphine). A different approach involves treatment with α-adrenergic agonists (lofexidine or clonidine) to relieve the intensity of the withdrawal symptoms.

In addition to the above therapies, naloxone, an opioid antagonist, is used to reverse opioid-induced overdose.

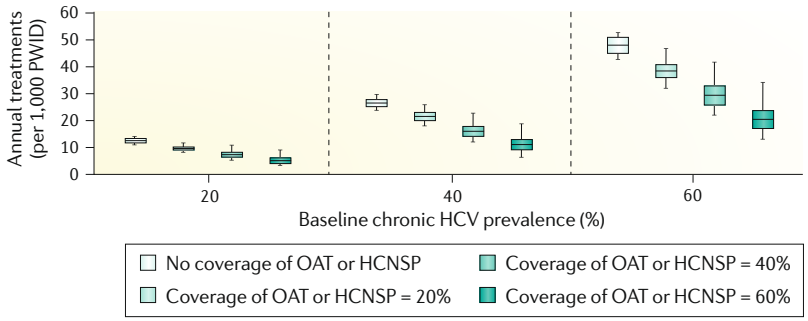

Fig. 8 | **Model projections of the effect of various treatments on transmission of HCV in people with OUD.** Hepatitis C virus (HCV) treatment rates required to halve HCV prevalence. HCNSP, high-coverage needle and syringe programmes; OAT, opioid agonist therapy; OUD, opioid use disorder; PWID, people who inject drugs. Adapted from REF.[385], CC-BY-3.0 (https://creativecommons.org/licenses/by/3.0/).

natural experiments that can characterize the intensity (dose) of the public health approach (comprising multiple interventions) are needed as is testing of whether exposure is associated with a reduction in opioid overdose deaths and other negative outcomes in the population.

As previously mentioned, the root of many of the harms associated with opioid use is criminalization, which is associated with a range of social issues and fails to recognize OUD through a health and social lens. There is increasing focus on challenging the 'war on drugs' through international commissions and innovative approaches by some countries[179,246]. For example, an earlier approach to the twin epidemics (or syndemic) of HIV transmission and drug-related deaths in people with OUD who inject drugs in Portugal was to increase the availability and access to primary prevention interventions in the community and remove criminal sanctions from people who use drugs[247–249]. This approach started in 2003 and the combination of criminal justice reforms and investment in harm reduction has been viewed as a success, with indicators suggesting lower social costs, no adverse change in the price of drugs, and reduced risks of HIV transmission and overdose.

Management

OUD is a chronic and often relapsing disorder; thus, medical and psychosocial therapy should be delivered within a framework similar to that used for the treatment of other chronic disorders. OUD requires long-term care that is adjusted to meet the needs of individual patients and allows changes in treatment intensity to address fluctuations in symptomology (FIG. 9). Management can encompass several stages, including acute intervention, stabilization and long-term care. The aim of treatment should be to stabilize the physiological and psychological disruption caused by chronic opioid exposure, which, in turn, enables reduced opioid use and the many associated physical and social harms. In this manner, patients can enter remission, providing an opportunity to address other psychosocial and medical issues related to their drug use, including infectious disease, underemployment or unemployment, relationships with loved ones, criminal justice issues and housing.

The wider health and social effects that are often associated with OUD should be addressed as part of the comprehensive management of OUD (TABLE 1). Attention to these problems is vital for the well-being of individuals with OUD as well as for the wider society. Furthermore, effective public health and public policy require this attention to be provided proactively, including to groups that are often marginalized or poorly served such as the homeless, those in prison and those involved with prostitution.

Access to treatment

Most parts of the world recognize the benefit of timely provision of treatment for OUD and many countries use treatments of proven effectiveness, including MOUD (BOX 2), often coupled with psychological and social support. However, there is a major treatment gap, with only a small proportion of individuals with a problem actually receiving treatment. For example, in the USA in 2011, out of an estimated 21.6 million persons who required treatment for an illicit drug or alcohol use problem, only 2.3 million received treatment at a specialty substance abuse facility[250]. Globally, treatment services are often inadequately funded or poorly supported, with the result that the benefits are stunted. In addition, there has been a long-standing bias against MOUD, and especially OAT, with professional and public difficulty in understanding the benefits of MOUD to reduce or eliminate opioid use, prevent relapse and reduce harmful behaviours. This bias likely arises from the failure, for many decades, to recognize substance use disorders as medical disorders that require medical treatment, instead often portraying them as moral failures or individual personality pathologies. Partly because of the bias against the use of medication for substance use disorders, there is now a large body of scientific evidence supporting the efficacy

Table 2 | **Projected effect of treatments on HIV transmission in people with OUD**

Intervention coverage (%)	Median reduction (%)	Confidence range (10–90%)
Increase OAT/NSP coverage		
10	5	2–10
25	12	5–22
50	20	9–37
Increased ART to PWID with HIV[a]		
10	3	1–5
25	7	3–11
50	10	5–17
Increased ART to PWID with HIV[b]		
10	6	3–12
25	13	6–23
50	19	9–34
Increase OAT/NSP coverage and ART to PWID with HIV[b]		
50	36	18–63

Based on data from REF.[33]. ART, antiretroviral treatment; NSP, needle and syringe programmes; OAT, opioid agonist therapy; OUD, opioid use disorder; PWID, people who inject drugs. [a]Once CD4 cell count <200 cells/μl. [b]Once CD4 cell count <350 cells/μl.

of pharmacotherapies for this indication. Nevertheless, treatment provision is often patchy even in countries with good apparent commitment, with frequent failure to capture teachable moments of influence and failure to provide treatment on demand. Moreover, there are often administrative or funding barriers to accessing MOUD, political interference with clinical judgments of duration of treatment required, and some programmes and even countries still prohibiting the use of evidence-based medications.

Attention to comorbidities

OUD rarely occurs in isolation and is more often occurring along with medical (such as infectious disease) and psychiatric comorbidities. Addressing these other co-occurring disorders is often essential for the long-term health and well-being of the patient and the effectiveness of treatment for OUD.

The ideal approach for the treatment of comorbid infectious diseases is to use an integrated care approach whereby treatment for OUD and infectious disease are provided within the same practice, decreasing the need for patients to navigate multiple care providers and clinic settings. Numerous approaches to integrating clinical care have been evaluated, including programmes that provide infectious disease care in specialty addiction settings (for example, in methadone treatment programmes and other opioid treatment programmes), providing treatment for substance use in a generalist or primary care practice, and other novel approaches such as screening and intervention in syringe services programmes. However, this type of integrated programme is not the norm, and most service delivery often remains siloed. Reviews of the features and outcomes of these integrated models[251,252] have suggested that patients are more engaged in care and are more likely to complete and/or remain compliant with medication regimens to treat their infectious disease when care is delivered in an integrated model, and that patients express a preference for integrated care. More acute problems of OUD include complications from injecting drug use such as abscesses, osteomyelitis, endocarditis and even mycotic aneurysm, which often require specialty care and hospitalization. Individuals presenting with these complicated and sometimes life-threatening problems can represent a reachable moment for providers to discuss treatment engagement.

Several psychiatric comorbidities are more prevalent in individuals with OUD than the general population, including depression, anxiety, antisocial personality disorder, suicidality, a history of abuse or sexual trauma and post-traumatic stress disorder[253–256]. As depression and anxiety can be antecedents to drug use or can be a consequence of the ongoing drug use, it is critical for the clinician to identify these disorders and develop a comprehensive treatment plan as appropriate. It is not uncommon for individuals to present for OUD treatment whilst simultaneously receiving prescription for benzodiazepines or using benzodiazepines illicitly. As the combination of any opioid agonist with benzodiazepines is a risk for fatal overdose, clinical management must be handled carefully. Patients who are willing to discontinue benzodiazepine use may require medically supervised withdrawal from benzodiazepines, whereas care must be taken in patients who are not able to discontinue benzodiazepines to ensure patient education and safety related to the co-administration of opioids and benzodiazepines. Ideally, alternative approaches for medication management should be explored for those with anxiety disorders. The need for concurrent pharmacotherapies to manage co-occurring disorders also requires careful evaluation of the risk for potential drug–drug interactions.

Medically supervised withdrawal from opioids

Abrupt (for example, immediate withdrawal) or controlled discontinuation of opioids (also known as tapering) has historically been known as detoxification; however, the terms 'medically managed withdrawal' (indicating medical supervision and treatment of withdrawal symptoms) and 'socially managed withdrawal' (indicating withdrawal in the absence of medical supervision in a counsellor or peer environment) are increasingly preferred terms. 'Detoxification' is considered stigmatizing (along with other historically applied terminology) as it suggests that the individual with OUD is toxic rather than having a medical disorder. The aim is to achieve an opioid-free state in a short time period. However, evidence for supervised withdrawal on its own as an effective treatment for OUD is lacking, even though it is commonly used. It is unsurprising that acute withdrawal is ineffective in treating OUD, particularly when evidence indicates that sustained neural adaptations occur in response to chronic opioid exposure that are not immediately reversible. In addition, supervised withdrawal, even when combined with behavioural therapies, is associated with poor treatment outcomes in the medium to longer term[257] and with enhanced risk of overdose and death in controlled studies[258,259]. Likewise, forced periods of abstinence, such as incarceration[260,261] and residential supervised withdrawal[262], are often followed by relapse with increased risk of both fatal and nonfatal overdose (likely due to loss of tolerance and sensitivity to opioid effects).

However, medically supervised withdrawal is appropriate or essential in some circumstances. For example, when patients transition from illicit opioids onto an opioid antagonist treatment (naltrexone), which requires abstinence prior to initiation to avoid precipitated withdrawal. In addition, some patients may be seeking treatment with the personal aim of being completely medication free. Indeed, the need to refrain from medication (especially OAT) is sometimes imposed as a requirement for employment. In these cases, it is critical that patients are informed about the enhanced risks associated with relapse and risk of overdose, alongside provision of overdose reversal education and naloxone and supportive therapy to facilitate their success[263].

Opioid withdrawal is characterized by autonomic hyperactivity, and treatment is generally directed at alleviating withdrawal signs and symptoms, which include anxiety, nausea, vomiting, diarrhoea, cramping, back pain, hot and cold flashes, insomnia, and lacrimation[264–266]. Historically, medically supervised withdrawal was often offered as a hospital-based treatment

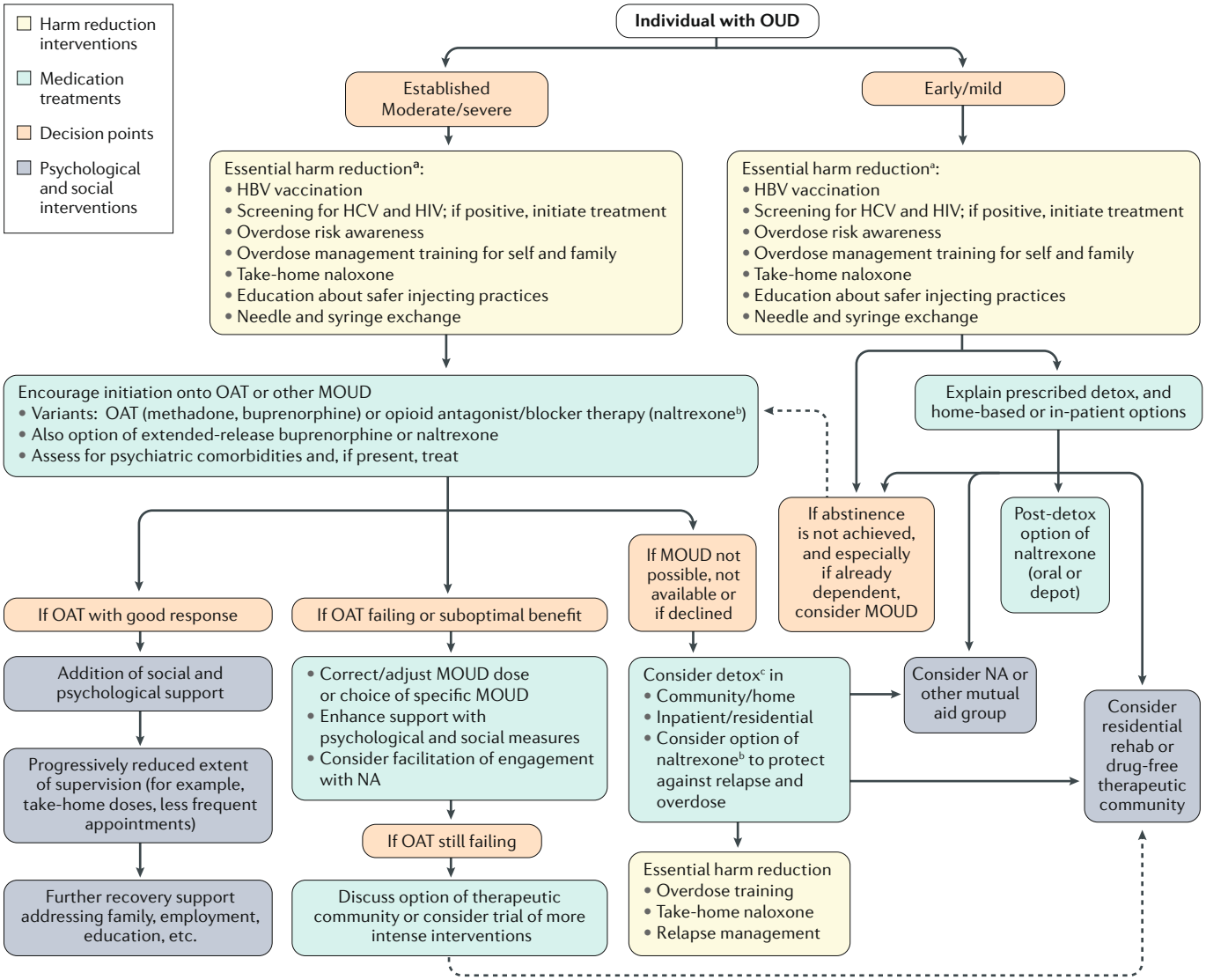

Fig. 9 | **Schematic of treatment algorithm.** Depending on the severity and chronicity of opioid use disorder (OUD), treatment can involve medications and psychological and social interventions. Management also requires consideration of harm reduction interventions. HBV, hepatitis B virus; HCV, hepatitis C virus; MOUD, medication for opioid use disorder; NA, Narcotics Anonymous ; OAT, opioid agonist therapy. [a]Harm reduction strategies are not limited to before the commencement of MOUD and should be provided to individuals not in treatment as well as throughout the duration of treatment for OUD. [b]Although approved for the treatment of OUD, naltrexone is generally associated with poor outcomes OAT is generally preferred. [c]Although evidence supporting the use of detoxification alone for the treatment of OUD is lacking, this approach is still used in many countries.

of varying duration. However, as medical costs have increased and as opioid withdrawal, although very unpleasant and uncomfortable, is rarely life-threatening, medically supervised withdrawal is now often provided in outpatient and residential treatment settings, although completion rates are typically lower in an outpatient setting[267]. Medically supervised withdrawal is often managed with tapering doses of an opioid agonist (such as methadone) or a partial agonist (buprenorphine) over a period of between 1 week and several months. Alternatively, α_2-adrenergic agonists (clonidine or lofexidine) are also used as they suppress opioid withdrawal signs[268–271]. Ancillary medications, such as anti-anxiety agents, analgesics, sleep aids, anti-emetics and anti-diarrhoeal agents, can increase comfort and decrease these predominant withdrawal symptoms. In general, slower reductions over longer periods of time lead to less illicit use during medically supervised withdrawal[272].

Treatment with MOUD

The most common pharmacotherapies for the treatment of OUD (methadone, buprenorphine and naltrexone) are most frequently used in outpatient treatment settings for adults with varying levels of supervision and intensity of care. Policies and models of care vary widely across countries from very restrictive (such as clinic-supervised medication) to extensive take-home supplies.

μ-*Opioid agonist therapies.* Methadone and buprenorphine have distinct pharmacological profiles but both exert activity through the μ-opioid receptor. These medications are the most commonly used pharmacotherapies for the treatment of OUD globally and are listed by the WHO as Essential Medicines[273]. When stabilized on an effective daily dose, both medications suppress opioid withdrawal signs and symptoms, reduce craving and produce opioid blockade (that is, the attenuation or complete blocking of effect from any non-prescribed opioid, such as heroin) at sufficiently high doses[274,275]. In cases of maintenance with opioid agonists or partial agonists, opioid blockade is a functional antagonism arising from cross-tolerance and receptor occupancy[274,275]. Although both methadone and buprenorphine are efficacious, patients might choose one therapy over the other owing to availability, convenience, the need for more or less structure (for example, unstable patients or those earlier in the treatment may require more frequent supervised dosing), therapeutic response and tolerability. In addition, there is considerable global variability in the use of buprenorphine versus methadone for OUD and in guidelines on induction and post-induction monitoring. Patients might remain on methadone and buprenorphine treatment for varying durations of time, with many continuing treatment for several years. In general, as a chronic disorder, it is commonly accepted that patients receive treatment for as long as they need and are benefiting from it. Although OAT is considered the most efficacious treatment available for OUD, it is not perfect as relapse may occur and retention in treatment is not optimal. Additionally, in many instances, the clinician and patient as well as the policymaker need to consider the wider psychosocial aspects to achieve fuller benefit.

Methadone is a full μ-opioid receptor agonist and NMDA receptor antagonist that is effective when administered orally. This medication is used in many countries and is typically delivered under direct daily supervision, at least initially. Due to its long half-life (~24 hours) and tendency to accumulate with repeated dosing, initiation of treatment begins with low dose and escalates slowly. Higher doses of methadone produce greater reductions in use of heroin and other non-prescribed opioids[276,277]. Discontinuation of methadone leads to withdrawal in all cases and, because of its long duration of action (half-life of 24–40 hours), this withdrawal syndrome can be protracted. Accordingly, stopping methadone treatment is typically carried out through slow dose reductions over several weeks or months. Methadone is primarily metabolized by CYP3A (along with CYP2D6 and CYP1A2) and plasma concentrations can alter substantially with concomitant use of other drugs with common metabolic pathways. Drugs with enzyme induction properties can accelerate methadone metabolism (such as phenytoin and rifampin, also known as rifampicin), thereby decreasing plasma concentrations and leading to withdrawal symptoms[278]. By contrast, other medications, such as P4503A inhibitors, can prevent methadone metabolism, leading to higher methadone plasma concentrations than intended and increase sedation and risk of overdose[279]. Medications that are often co-prescribed with methadone that have potential to alter its metabolism include protease inhibitors for HIV and antifungal agents[280], warranting additional safety monitoring. Another safety concern related to methadone use is its propensity to prolong the cardiac QT interval, particularly at higher doses[281], with clinical recommendations suggesting baseline electrocardiography, screening for pre-existing risk factors and periodic monitoring especially during dose escalations.

Buprenorphine is a partial μ-opioid receptor agonist as well as a κ-opioid receptor antagonist and has nociception receptor partial agonist properties. It is delivered transmucosally as a sublingual or buccal formulation (in immediate-release formulations) and as an injection or implant (in extended-release formulations). As a partial μ-opioid receptor agonist, it is generally a safer alternative to full opioid receptor agonists such as methadone[282,283]. As a partial μ-opioid receptor agonist, starting buprenorphine can initially precipitate opioid withdrawal if other opioids are still substantially occupying the μ-opioid receptor. Accordingly, the risk of precipitated withdrawal is decreased by extending the interval between the last opioid dose and commencing buprenorphine to allow mild withdrawal to emerge, introducing an initial low dose of buprenorphine, and decreasing the level of prior opioid medication before initiating buprenorphine treatment (particularly for patients on long-acting opioids like methadone who wish to switch to buprenorphine)[284–286]. Typical buprenorphine induction requires the patient to refrain from opioid use for sufficient time to allow opioid withdrawal signs to emerge (for example, this may require abstinence overnight for an individual using heroin). RCTs have found buprenorphine to be comparably efficacious/effective to methadone at treatment engagement and retention and at reducing illicit opioid use, with comparable long-term results[287,288]. Buprenorphine also exists in combination with naloxone, which is intended to deter potential misuse by the parenteral route through the precipitation of withdrawal symptoms; however, this deterrent effect does not always occur, particularly if strategies are used to avoid or minimize it. Both buprenorphine (alone as well as in combination with naloxone) and methadone are sometimes diverted and misused. The balance between methadone and buprenorphine treatment availability and the use of buprenorphine or a buprenorphine/naloxone combination vary considerably globally.

Extended-release formulations of buprenorphine are more recent developments and, therefore, only early evidence of their benefits is available. At least three extended-release formulations exist. A subdermal implant (Probuphine in North America; Sixmo in Europe, Titan Pharmaceuticals and Molteni Farma) has regulatory approval in the USA, Canada and Europe and provides stable coverage at moderate plasma levels for 6 months[289], with one RCT finding non-inferiority to daily sublingual buprenorphine for lower-dose treatment[289]. A higher-dose, subcutaneous, long-acting depot, injectable buprenorphine (Sublocade, Indivior) that is administered monthly has received regulatory approval in the USA[290,291]. In addition, a second subcutaneous, long-acting injectable formulation (Buvidal (Brixadi),

Camurus) has been approved in Europe and Australia with a range of dose formats and formulations that can be administered weekly and monthly to enable individualized dosing[292] (this formulation has also been approved in the USA but not yet marketed). Sustained-release formulations of buprenorphine may provide protection against diversion and improve patient compliance; however, these outcomes have not yet been systematically evaluated with these relatively new products.

Other opioid agonists have also been used, albeit less commonly, for treatment of OUD. For example, in Austria and elsewhere, slow-release morphine has been used in a manner similar to methadone for maintenance treatment and with similar benefits[293,294]. In addition, L-methadone (the L-enantiomer stereoisomer of methadone)[295] has been used in Germany, although the extent of benefit over racemic methadone remains uncertain[296]. Benefit from maintenance treatment with dihydrocodeine has also been reported[297].

A substantially different approach of treatment with prescribed diamorphine (pharmaceutical heroin) has gathered credence since several randomized trials in Europe and Canada demonstrated positive results. These trials from Switzerland, the Netherlands, Germany, the UK and Canada[298–301] all consistently demonstrated a substantial early and sustained benefit, disengagement from illicit heroin use and associated criminal behaviour, and reduced mortality in individuals previously classified as non-responsive to other therapies[302,303]. Diamorphine treatment is intensive, requiring attendance several times daily over many months and years for injection under supervision, and is expensive and politically challenging, but benefits in an otherwise non-responsive population have led to its introduction on at least a local basis in several countries, including Switzerland, Netherlands, Canada, the UK and Denmark, specifically for individuals with chronic refractory OUD. With a growing body of RCTs demonstrating feasibility and benefit, this approach has led to serious consideration, more widely, for unresponsive patients. Similar benefits have been reported for non-responsive patients with OUD with supervised injectable hydromorphone maintenance[304].

μ-Opioid antagonist therapy. Naltrexone, an μ-opioid receptor and κ-opioid receptor antagonist, has been available since the 1980s. Despite its highly efficacious blocking capability, oral naltrexone is rarely prescribed because of problems with initiation and poor adherence to treatment. Indeed, initiation of oral naltrexone requires opioid abstinence, otherwise withdrawal symptoms are precipitated (see Medically supervised withdrawal, above). Medication instructions suggest a period of 7 to 10 days of opioid abstinence before naltrexone initiation; yet, for many patients, successfully completing a medically supervised withdrawal to achieve this status is highly challenging or impossible. Adherence to naltrexone is improved when medication compliance is forced[305] or reinforced[306]. Despite its capacity to produce opioid blockade, a systematic review of controlled studies concluded that the evidence does not support the superiority of oral naltrexone over placebo for the management of OUD[305]. Additionally, withdrawal from naltrexone treatment can increase the risk of overdose.

Long-acting depot naltrexone[307], which is injected intramuscularly and is effective for 1 month, circumvents some, but not all, of these challenges[308]. Indeed, one study comparing this formulation of naltrexone to sublingual daily buprenorphine/naloxone highlighted the difficulty of initiating naltrexone, with 28% of individuals assigned to naltrexone failing to achieve induction, in contrast to only 6% of those failing to start buprenorphine/naloxone[309]. For subgroups who successfully initiated treatment, relapse (defined as 4 consecutive weeks of opioid use by urine drug screening or self-report or 7 days of self-reported use), did not differ between groups[309]. Implanted naltrexone products are available, but regulatory approval for these formulations has only been granted in Russia and a few other adjacent countries[308]. To date, no comparative effectiveness study of extended-release naltrexone versus extended-release buprenorphine has been conducted.

A cohort analysis evaluated the protective role of MOUD in the following 12 months after adults survived an opioid overdose. Overall, both buprenorphine and methadone treatment — but not oral or depot naltrexone — were associated with a reduction in all-cause mortality compared with those who did not receive MOUD[310]. Finally, one study found that treatment with buprenorphine, but not naltrexone, was associated with a reduced risk of opioid overdose compared with no treatment[311]. In summary, these findings support the superior efficacy of buprenorphine and methadone over naltrexone in clinical practice.

Behavioural therapies

Behavioural therapies are increasingly provided as an added component of a comprehensive treatment programme for OUD, alongside non-specific counselling and general social support. Indeed, behavioural therapies are sometimes a compulsory part of programme approval and certification[312]. An array of behavioural interventions has been used for OUD treatment, including cognitive behavioural therapy, coping skills, motivational interviewing, self-help groups, peer counselling or peer support, recovery coaches, and case management. The availability of scientific evidence supporting the efficacy of these interventions varies widely but several interventions are endorsed by national agencies.

In general, these approaches do not have the extent of underpinning robust evidence found with OAT and are mostly considered for their potential synergistic benefit[313,314]. Contingency management methods have a greater effect size than other behavioural interventions and, accordingly, this intervention has attracted particular interest[315,316]. However a Cochrane review of the benefit of psychosocial interventions alongside opioid agonist pharmacotherapy concluded that adjunctive psychosocial therapies did not result in statistically significant benefits compared with pharmacotherapy alone[317]. Various other controlled studies have attempted to parse out the relative independent contribution of counselling or behavioural therapy from MOUD but have not always demonstrated a robust contribution of

behavioural therapies[318,319]. Moreover, studies of interim care, providing OAT only when treatment slots are unavailable for a specified period as a stopgap measure, have reported significant reductions in illicit opioid use in the absence of behavioural intervention[320,321].

Mutual-aid and residential rehabilitation

Mutual-aid groups, of which Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) are the most famous, provide extensive support for many in their recovery. These programmes are distinctive as they operate outside the scope of professional services and are often coordinated by individuals who are themselves in recovery from a substance use disorder. They classically work with individuals who are already abstinent (even if fragilely), can offer invaluable support at points of crisis and can enable fuller social reintegration[322,323]. Other forms of these groups exist, sometimes including psychologist or medical input. These groups usually operate in the community, although they may also be found in specific environments such as prisons or hospitals. NA and AA adhere to working through the '12 Steps' (see https://12step.org/references/12-step-versions/na) and, although they originated from and have grown most prominently in North America, NA groups have proliferated in recent decades in more than 100 countries, including Iran and much of southeast Asia[324]. Elements of the 12-Step mutual-aid support are applicable to individuals in medication-based treatments (such as methadone or naltrexone) but this is only rarely considered[325–328]. Rigorous research on the effectiveness of NA has been scarce and only recently more seriously conducted. In a closely related field, a new Cochrane review of AA and alcohol use disorder examined not only AA but also 12-Step facilitation and found comparable or greater benefit from AA and 12-Step facilitation when compared with formal outpatient and psychological interventions, with greater cost-effectiveness[329].

Residential rehabilitation can be built around 12-Step work such as with the Minnesota Model or, for example, the Betty Ford Clinic network, which typically require residence for 28 days followed by community aftercare. Some residential rehabilitation facilities can involve longer-term residency as with therapeutic communities[330,331] such as Phoenix House or DayTop, in which the community, with a requirement to develop and work with relationships, is the therapy itself. Such residential treatment has strong champions and impressive individual successes, although there are limited controlled studies that have independently assessed the effectiveness of these programmes. As with all treatment programmes, the risks of relapse, particularly on leaving the facility, and of fatal outcome from any overdose, need to be addressed.

Overdose interventions

Opioid overdose is now one of the main causes of premature death in many countries. More than 80% of opioid overdoses occur in the presence of others persons[237] and are therefore preventable with effective early intervention. Education is essential, as is training in essential interim management of overdose whilst awaiting emergency medical care for people who use drugs, their family members and their peers to ensure they are aware of the risk of overdose. Training in overdose management, often alongside training in administration of opioid antidote (naloxone), is increasingly provided (comparable to provision of training to families and peers of those with epilepsy, diabetes mellitus or anaphylaxis) to those in treatment and, crucially, to those out of contact with addiction treatment services. However, the latter is more challenging and yet it is this population that is at the greatest risk of overdose[332]. Times and settings of particularly increased overdose mortality have been identified, such as release from prison[23] and discharge from hospital or leaving rehabilitation facilities, and these timepoints represent opportunities for focused action[262,333].

Naloxone has been used for decades, by injection, for the reversal of opioid (including heroin) overdose in hospital, emergency transport services and, now more broadly, in the community through provision and administration by laypersons. This treatment is well-established in emergency medicine and can be given through intravenous, intramuscular or subcutaneous routes. Effective concentrated naloxone nasal sprays have been developed more recently, which will likely further widen the potential for community resuscitation. At least three intranasal formulations of concentrated naloxone have been approved worldwide, with a speed of onset similar to intramuscular administration (that is, comparable time to maximum concentration and plateau plasma level achieved) (Narcan, Adapt Pharma; Nalscue, Indivior; Nyxoid, Mundipharma), with these concentrated naloxone nasal sprays now available in the USA, Canada, Europe and Australia[332]. An auto-injector device (Evzio, Kaleo) has also been approved in the USA. It is important to note that naloxone has a shorter half-life than some opioids that might be causing the overdose and, therefore, there is a risk of return of overdose symptomology, which can require further medical attention.

Treatment settings

Although most treatment for OUD is delivered in specialist or primary care (generalist) settings, initiating and/or delivering treatment in other settings is critical for reaching patients who may not yet have an established care plan. Individuals with OUD frequently present to emergency hospital services with complications from their drug use. This point of contact is a potential opportunity to engage the patient and link them to care. Accordingly, emergency room interventions have included expanded screening and diagnosis for substance use disorders, brief counselling interventions, naloxone overdose training, onsite treatment of withdrawal, induction with buprenorphine and linkage to community care[334]. Similarly, initiating treatment in a hospital setting followed by linkage to follow-up care after discharge is another strategy to engage patients who have high morbidity and mortality risk and initiate evidence-based care.

The criminal justice system, including jails, prisons, probation offices, parole offices and drug court systems, is another important point of contact for the potential

delivery of care. Owing to the significantly increased risk of fatal overdose after release from prison or jail[261,335], several countries have implemented treatment with MOUD either during incarceration or at the time of discharge, including methadone, buprenorphine and naltrexone, and have demonstrated a reduced fatal overdose rate after release[224,336,337].

Quality of life

Observing OUD trajectories

Longitudinal studies have indicated that people with OUD transition between living in the community and using drugs, incarceration, treatment and living in recovery, multiple times over the course of what has been called an addiction or treatment career[338–340]. Several studies have indicated that episodes of treatment increase in duration over time[339,341] and that the percentage of survivors who achieve abstinence with treatment also increases over time[342]. In addition, the longer the duration of abstinence, the greater the probability of continued abstinence[343]. However, the death rate in some of the longitudinal studies is up to 50% and the probability of ongoing engagement in treatment and abstinence from illicit opioid use is 10–20% of the original sample after 20–30 years[342]. Regardless of the cohort or group studied, the expected outcomes over time outside of treatment are poor[342].

Patients with OUD have a significantly greater risk of death than people without OUD. Indeed, death rates are as much as 10–14 times higher for people with OUD than age-adjusted rates for people without OUD[344,345]. The primary risk is for death due to overdose[346], but death by other causes, for example, suicide or infectious disease (both acute, such as pneumonia or sepsis, and chronic, such as hepatitis or HIV)[344–347], are also more common among people with OUD. Increases in the number of people with OUD who die of overdose have been identified as a cause of a reduction in life expectancy in white middle class and working class Americans, the first decrease since HIV had its initial effect in the 1980s[348]. Indeed, the USA has seen an unprecedented increase in deaths due to opioid poisoning since 1999, with exponential growth rates in the past 5 years[349] (see Epidemiology, above). Other countries have not been as severely affected, though increases in death rates have been reported in many countries, in particular, Canada[350], Australia[351] and the UK[352]. In the USA, deaths from the epidemic of opioid overdoses combined with increases in the rates of suicide and alcohol-related fatalities in middle-aged people have been described as 'deaths of despair'[353].

Treatment effect on OUD trajectories

MOUD has been shown to reduce the risk of death[22], contraction of infectious disease[213], engagement with the criminal justice system[354], and improved overall health[355] and quality of life (QOL)[356–358]. However, at any given point in time, < 25% of people who had active OUD in the prior year engaged in treatment during that year, and only one-third of those that received any treatment in the USA received MOUD[359], despite treatments including medications resulting in significantly better outcomes than psychosocial treatment alone[211]. In fact, despite widespread use in the USA, psychosocial interventions without MOUD have not demonstrated adequate efficacy to be recommended[360].

Ongoing MOUD retention is an essential protective factor against return to opioid use[343,361], with risk of death and other negative consequences increasing at treatment discontinuation[341]. Although initiated as long-term treatment, MOUD treatment retention is often curtailed by drop-out or programme discharge and becomes of brief duration, with average stays in methadone-maintained treatment often at <1 year[362] and for buprenorphine at <3 months in observational studies[363–365]; most studies have demonstrated a 6-month retention rate of <50%. The modal number of doses in one study of monthly naltrexone depot injections was one, with nearly 60% of patients dropping out after the first or second injection[366]. Better retention of patients in care is urgently required to increase life expectancy and to reduce the cycling between treatment, active use in the community and incarceration that leads to greater risk of death and lower QOL.

Recovery

In recent years, a focus on recovery as a multifactorial construct that includes reduced use or abstinence but also alternative coping strategies, improved relationships, purpose or meaning in life, and physical, mental and spiritual health[325,367] has built traction as the goal of treatment rather than simple remission of symptoms, particularly in the USA and the UK[368,369]. From the recovery-oriented perspective, remission from DSM-5 symptoms is not, by itself, an adequate measure of treatment outcome, which should be broader and include the additional components that define recovery[325,368]. The interest on the multifaceted aspects of recovery has led to the development of recovery-oriented systems and patient-centred care strategies.

The focus on recovery and improved QOL as treatment outcomes has led to the recognition of the need for tools that adequately measure these constructs[370–372]. Studies of what patients wish to achieve from treatment and recovery programmes correlate highly with QOL measures[373] and the concept of recovery-oriented or patient-centred care revolves around achieving patient goals for improved functioning in multiple domains. A few studies have used health-related QOL measures such as the SF-6D[357] or EQ-5D[371] to assess treatment efficacy. Efforts are underway to develop an OUD-specific QOL or recovery outcome measure[374], although there are advantages for measuring QOL using a basic instrument that covers multiple domains other than health, such as the WHOQOL-B[375], and can be used to compare the QOL of patients with OUD to that of those with other disorders or healthy people[376]. A five-factor, 21-item patient-reported outcome measurement of recovery has been developed and validated and is being adopted in the UK and other countries; this could prove to be a measure that meets the criterion of capturing patient-centred QOL outcomes that are specific to addiction recovery[377,378].

Correlates to achieving long-term recovery are engagement in ongoing treatment[379,380], social support

for abstinence[381] and engagement in meaningful life activities such as work[380]. Attempts have been made to link QOL to reduction in substance use, but early research seems to indicate that QOL improvements are more linked to abstinence-supportive social network development[382] and studies have indicated that treatment participation improves QOL regardless of whether it leads to cessation of all drug use[356,376].

Outlook

Science continues to make a vital contribution towards the advancement of the clinical, public and political understanding of OUD. This understanding is particularly important as there is often a mismatch between the public belief of impact and the actual reality of evidence of strong impact for some treatments alongside evidence of weak impact for other approaches, including primary prevention, despite their popular support. With an estimated 26.8 million people living with OUD globally, > 100,000 opioid overdose deaths annually and with 50% of people who inject drugs being HCV positive, OUD constitutes a major burden to healthcare systems as well as an individual and family burden. In addition, the extent of the problem is increasing. Public and political leadership, drawing on science, is needed to obtain the best yield from existing evidence-based interventions and to support the exploration and development of new or improved interventions.

Our understanding of OUD has leapt forward in recent years. Expanded knowledge of brain mechanisms, of the interplay between genetic and familial vulnerability, developmental pathways, and the influence of context and environment has deepened our understanding of OUD. In addition, it is increasingly recognized that these factors can exert different influences, for the same individual, at different points in time, such as influences on original initiation of opioid use, or progression to more problematic opioid use or the interplay between the development of problems and treatment-seeking. In addition, these factors will be influential on later vulnerability to relapse, even after OUD problems appear initially to have resolved.

Despite improved knowledge regarding OUD, new challenges are emerging. Problems of dependence on prescription opioids are increasingly recognized as a major challenge for individual and public health. In addition, the market in illicitly manufactured opioids now extends far beyond heroin, including increasing availability of synthetic opioids such as fentanyl and its derivatives. Internet trade further increases the diversity of routes of access to these drugs, and the line between pharmaceutically and illicitly manufactured drugs is not as clearly demarcated as previously assumed.

Fortunately, several effective treatments for OUD are available. However, there are aspects of OUD for which our influence is weaker such as the persistence of injecting behaviour, comorbidities of HIV disease and chronic HCV infection, and the high overdose mortality rate amongst individuals who use opioids. Even with effective treatments, medication adherence is poor, dropout rates are high and there is substantial risk of relapse when treatment finishes. In addition, political and professional attitudes to scientifically established treatments are highly variable between countries, and even within countries. Accordingly, scientists must engage in public and political discussion to ensure that understanding of OUD is improved and that effective treatments are available at the time of need without counterproductive deterrent effects impeding treatment-seeking. Wider healthcare links and fuller treatment engagement will undoubtedly benefit both individuals and society.

There are multiple points of potential influence on OUD. Consideration of prevention needs to include the prevention of progression (for example, from initial use to regular use, or from oral to injectable use) and the prevention of associated harms such as HIV and HCV (which can be, for example, prevented by changes in injecting and sexual behaviour). Treatment needs to integrate social and psychological interventions alongside medications of proven efficacy, where appropriate. Particular attention should be paid to health-critical transition points at which there is a danger that a move to more seriously harmful behaviour may occur, particularly because these transition points are often associated with organisational change (such as release from prison to the community, or returning home from hospital or rehabilitation). Many of the harms are associated with the pattern of drug use (that is, not necessarily deriving from the dependence per se) and harm reduction approaches are increasingly being introduced to reduce the damage that may result even when the drug-taking behaviour persists. Alongside the attention to medications, combined with family community and society efforts to support recovery, it is important that there is lifelong awareness of the risk of subsequent relapse and of the need for steps to be taken to monitor well-being and reduce risk.

We are now in the fortunate position of having high-quality science to greatly improve our understanding of OUD behaviour and to guide development and delivery of more effective interventions. This creates opportunity for smart policy to increase public good. It frequently requires coordination between different sectors (for example, between health and law enforcement or between public policy and local community) which can often prove problematic, and requires public and political commitment alongside continuing advances in scientific knowledge and improvements in prevention and treatment.

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Author contributions
Introduction (J.S. and N.D.V.); Epidemiology (L.D. and B.D.L.M.); Mechanisms/pathophysiology (G.F.K. and N.D.V.); Diagnosis, screening and prevention (M.H. and M.T.); Management (S.L.W. and J.S.); Quality of life (K.J.); Outlook (J.S. and N.D.V.); Overview of Primer (J.S. and N.D.V.). After the joint first authors, all authors are listed alphabetically, and all contributed significantly to the assigned sections.

Competing interests
J.S.'s employer (King's College London) has received, connected to his work, project grant support and/or honoraria and/or consultancy payments from the UK Department of Health, Public Health England, and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as well as research grants from (past 3 years) the UK National Institute for Health Research (NIHR), the Medical Research Council and the Pilgrim Trust. J.S. has also worked with the EMCDDA, United Nations Office on Drugs and Crime, US FDA and US National Institute on Drug Abuse (NIDA), and WHO as well as with other international government agencies. King's College London has registered intellectual property on a buccal naloxone with which J.S. is involved, and J.S. has been named in a patent registration by MundiPharma as inventor of a potential concentrated naloxone nasal spray. King's College London has also received, connected to the work of J.S., research grant support and/or payment of honoraria, consultancy payments, and/or travelling, accommodation and/or conference expenses (past 3 years) from Braeburn, Camurus, Indivior, Molteni Farma and MundiPharma, and has received trial medication supplies from Braeburn and iGen related to medications and technologies potentially applicable in the treatment of addictions and related problems. J.S. has worked with and received grant support from the charity Action on Addiction and with the Pilgrim Trust and is a Patron of DrugFAM. L.D. has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, MundiPharma and Seqirus. The Australian National Drug and Alcohol Research Centre of the University of New South Wales Sydney is supported by funding from the Australian Government Department of Health under the Drug and Alcohol Program. L.D. is supported by an Australian National Health and Medical Research Council Senior Principal Research Fellowship (#1041742, #1135991) and by US National Institutes of Health grant NIDA (R01DA1104470). M.H. has received unrestricted honoraria for presenting at scientific meetings within the past 2 years from Gilead and MSD, and acknowledges support from the NIHR Public Health and Prevention in Evaluation, NIHR School for Public Health Research and NIHR Biomedical Research Centre at Bristol. In the past year, K.J. has received funding from Johnson, Bassin and Shaw to conduct analysis of Medicare data for assessment of opioid use for a Medicare contractor. She has a subcontract to NIDA (grant no. DA035789) to write a paper on the results of a clinical trial on a mobile app to address substance use disorders. She has consulted several times for AlphaSights on opioid issues for their clients, who cannot be disclosed but are not pharmaceutical companies, pharmacies or other entities currently engaged in the industry. K.J. is the Executive Director of the International Consortium of Universities for Drug Demand Reduction, which is registered as a not-for-profit organization in the USA and is funded by the US Department of State. K.J. declares that, for the period prior, she was employed by the US government. S.L.W.'s employer, University of Kentucky, has received research support related to her work from the Braeburn Pharmaceuticals, US FDA and US NIDA (in the past 3 years). S.L.W. has worked with the FDA, NIDA, NIH and WHO on issues related to substance use disorders and opioid abuse liability; has served as a scientific advisory board member for the Addiction Policy Forum, the NIDA Scientific Advisory Council and Opiant Pharmaceuticals; and has received, connected to her work, research grant support and/or payment of honoraria, consultancy payments and/or travelling, accommodation and/or conference expenses from pharmaceutical/device companies (over the past 3 years) from Brainsway, Braeburn, Camurus, Eli Lilly and Co., Indivior, Neurocrine, Otsuka, Pfizer, Summit Biosciences, Trevi Pharmaceuticals and U.S. World Meds. All other authors declare no competing interests.

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