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Global patterns of opioid use and dependence: Population harms, interventions, and future action

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Abstract

This paper summarises evidence for medicinal uses of opioids; harms related to the extra-medical use and dependence upon these drugs, and for a wide range of interventions to address the harms related to extra-medical opioid use. Finally, we use mathematical modelling to estimate harms and explore the overall health benefits of opioid agonist treatment (OAT) in a range of settings that vary in levels of opioid use and associated harms (overdose, HIV, HCV, suicide, accidental injuries) and responses. Estimates in 2017 suggest 40.5 million people were dependent upon opioids (40.5 million people, 95%UI 34.3–47.9 million) and 109,500 people died from opioid overdose (10.5,800–113,600). OAT can be highly effective in reducing illicit opioid use and improving multiple health and social outcomes, including reduced overall mortality and key

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Author contributions

LD and SL drafted the initial outline of the paper, which was reviewed by MH, JG, PV. JS, PV, MH, SL, LD and JG conceived of the modelling. JS led the modelling work with supervision from PV. LD, SL, JG oversaw the reviews of reviews and systematic reviews. LD, SL, JG, BDLM, MH, GH drafted specific sections of the paper. SL, LD, RA, JB, JG, BDLM, JS and PV contributed specific inputs into drafts of the panels. LD led the writing of the full draft of the paper.

causes of death including overdose, suicide, and other injuries. Modelling suggested scaling-up and retaining people in OAT, including providing OAT in prison, could avert a median of 7.7%, 14.5% and 25.9% deaths over the next 20 years (compared to scenarios without OAT) in Kentucky, Kyiv and Tehran, with more impact achieved in Tehran and Kyiv due to the added benefits on HIV mortality.. Other pharmacological and non-pharmacological treatments have varying levels of evidence for effectiveness and patient acceptability. Other effective interventions are those focused on preventing harms associated with problematic opioid use. Despite strong evidence for the effectiveness of a range of interventions to improve the health and well-being of people who are dependent on opioids, coverage is low even in high income countries. Treatment quality may be less than desirable, and considerable human, social, and economic harms arise from the criminalisation of illicit opioid use and dependence. Alternative policy frameworks are recommended that adopt a human rights and public health-based approach, do not make drug use a criminal behaviour and seek to reduce drug related harm at the population level.

Background

Opioids are among the world's oldest known psychoactive drugs, with the use of derivatives from the opium poppy recorded for thousands of years. A wide range of opioids are used for medicinal and recreational purposes, and include natural (i.e., plant-based), semi-synthetic, and synthetic opioids (see webappendix A). Opioids are WHO-listed essential medicines for acute and cancer pain, palliative care, and treatment of opioid dependence[1] (throughout this review we use the term dependence to be consistent with WHO's International Classification of Diseases [ICD]; see Panel A for terminology). Use of opioids for extra-medical purposes is illegal in most countries, with punishments ranging from fines to incarceration. In many countries, people who are opioid dependent comprise a significant proportion of people who are incarcerated for drug-related offences or other crimes[2].

We use *extra-medical use* to refer to use of illicit opioids, and/or pharmaceutical opioid use either without a prescription or not as directed by a doctor, while allowing that the user may have medically driven reasons for using the opioid. Extra-medical opioid use occurs worldwide. Many people use opioids initially because they enjoy their effects (see Panel B for some perspectives from people who use drugs), without necessarily choosing opioid dependence and long-term health and social consequences. The complex intersection of illicit opioid use with increased rates of prescribing for medical purposes in many high-income countries, most notably the United States (US), has brought increasing attention to extra-medical opioid use and opioid-related harms.

Opioid dependence (as defined in ICD) involves a cluster of symptoms including impaired control over use, prominence of use of a substance in a person's life and physiological symptoms including tolerance and withdrawal[3,4]. In North America, the term opioid use disorder (OUD) (from the American Psychiatric Association's DSM-5[5]) is often used in preference to opioid dependence.

This paper summarises evidence for medicinal uses of opioids, and harms related to the extra-medical use of and dependence upon these drugs. We also summarise the evidence for a wide range of interventions to address harms related to extra-medical opioid use. Finally,

we use mathematical modelling to estimate harms and explore the overall health benefits of opioid agonist treatment (OAT) in a range of settings with varying levels of opioid use and associated harms (overdose, HIV, HCV, suicide, accidental injuries) and responses. The approaches used in reviewing literature for each of the sections are detailed in the appendix.

Medicinal uses of opioids

WHO lists opioids as essential medicines for acute and cancer pain, palliative care, and opioid dependence[1] (see webappendix B including Panel B1 for a discussion of evidence for medicinal use of opioids). In some countries, particularly the United States (US) and Canada, there have been considerable increases in the prescribing of opioids for a wide range of chronic non-cancer pain (CNCP) conditions over the past two decades. Evidence for the long-term use of opioids for CNCP is limited,[6,7] and subject to considerable controversy.

International Narcotics Control Board (INCB) data on country-level use of pharmaceutical opioids (Figure 1; appendix C details how data are collected), shows opioid analgesic use is low in Africa, Asia, Central America, the Caribbean, South America, eastern and south-eastern Europe[8].

In countries with the highest opioid consumption (Figure 1), most use is for CNCP. The US far exceeds other nations, consuming 68% of the world's prescribed opioid analgesics between 2011–2013[8]. These levels of overprescribing are in part responsible for the unprecedented increase in opioid dependence and overdose in the US.[9]

Epidemiology of extra-medical opioid use and dependence

There are varied trends across countries in patterns and harms of extra-medical opioid use and dependence. Illicitly produced heroin has traditionally been the dominant opioid used extra-medically. The notable exceptions have been source countries and their close neighbours such as Afghanistan and Iran, where opium has been the most common and heroin use and injecting are now increasing [10].

In many parts of South America, the Middle East and Africa opioids like tramadol are prescribed for pain. There are also reports of significant extra-medical use of tramadol, accompanied by dependence, overdose, and death[11]; there is some suggestion that much of this is illicitly produced tramadol[12]. Similarly, problems related to extra-medical use of over-the-counter codeine are reportedly common in Nigeria, Kenya, Zimbabwe, and Chad[13]. There is evidence that substantial amounts of opioids, including fentanyl, are illicitly manufactured in Mexico[14], China and India[15].

In high-income countries, increased prescribing of opioids for CNCP has produced iatrogenic dependence and subsequent increases in illicit opioid use, most prominently in the US and Canada. From the 1990s to around 2011[16] aggressive promotion, under-regulation, and overprescribing of pharmaceutical opioids, increased opioid dependence and overdose deathssubstantially[17]. In the US, interventions were introduced from 2010[18] to reduce the supply and extra-medical use of prescribed opioids (e.g., limits on prescribing, prescription

monitoring programs, “pill mill” laws, abuse-deterrent reformulations,). These privileged reducing supply over reducing demand and increasing access to interventions for people who had developed problematic opioid use. From the late-2000s onwards[16], there were increases in heroin supply and transitions to heroin use and injection [19–21]. A “third wave” from around 2013[22] involved an influx of highly potent synthetic opioids such as illicitly manufactured fentanyl[23,24] (see also **Peacock et al**[22] in this series.) The severity of the opioid problem has reduced adult life expectancy in the US for two consecutive years, a first since 1964. In British Columbia in Canada increased use of fentanyl and carfentanyls has reduced life expectancy despite access to universal health care and considerable harm reduction and treatment services. There have been similar but far less dramatic shifts in opioid prescribing, illicit opioid use and overdose in some other countries[25].

Prevalence of opioid dependence

The Global Burden of Disease (GBD) study estimated national, regional, and global prevalence of opioid dependence in 2017[26] (Figure 2a; see Appendix F for methods and Table F1 for regional and global opioid dependence estimates). Globally, the age-standardised rate of opioid dependence was 510 people per 100,000 population (95% uncertainty interval [UI] 430–605; 40.5 million people, 95%UI 34.3–47.9 million). The highest estimated prevalence in 2017 was in the US (age standardised rate of 1,347 per 100,000 (95%UI 1,136–1,609; 4.8 million people, 95%UI 4.1–5.6 million). High rates of opioid dependence were also estimated in the Middle East and East Asia.

Not everyone who uses opioids extra-medically develops opioid dependence[27]. A 1991 US population survey suggested that around one in four people who had used opioids (largely heroin) experienced dependence at some time prior to interview[28], whereas a UK study adjusting for potential biases estimated that two in three heroin users might become dependent[27]. A recent study of US population-based surveys over 15 years suggested that approximately 30% of people had developed heroin dependence within a year of initiating use[29]. A 2011 Iranian population survey found half (49%) of those who had used opioids (mainly opium) in the past year were opioid dependent[30]. Dependence can also be context-specific: a seminal 1974 study of US Vietnam war veterans found one in three used heroin in Vietnam, of whom 59% were dependent during that time, but 98% remitted from dependence upon returning to the US[31].

Estimates of the risk of developing opioid dependence among people prescribed opioids vary widely. In studies of people prescribed opioids for any pain condition, the median risk developing dependence has been estimated at 5% (range 0–31%)[32]; among people with CNCP prescribed opioids long-term in primary care, estimates vary between 3–26%[7]. A systematic review (n=15, mostly US surveys) estimated that 15% of people with past-year extra-medical opioid use (95%CI 14–17%) might be dependent[33] (see appendix E for methods).

The course of opioid dependence

Opioid dependence is best characterised as a chronic, relapsing condition with periods of active use, abstinence and relapse over years or decades, interspersed with periods of

treatment and/or incarceration[34]. These periods place individuals at heightened risks of serious adverse consequences. There is an elevated risk of mortality from overdose,[35–37] during treatment initiation or discontinuation, or when tolerance is reduced after a period of abstinence, treatment cessation, and release from incarceration.

There are few studies on the natural history of pharmaceutical opioid dependence. Some data from the US suggest elevated risk of transition from extra-medical prescription opioid use to injectable heroin[19–21].

Risk factors for opioid dependence

Risk factors include genetic, early life, and environment. The social and contextual risk s for extra-medical prescription opioid and illicit opioid use[38] include: drug availability, peer substance use[30,39,40]; social norms about substance use[41]; adverse childhood experiences, including social disadvantage, family history of drug use[42], childhood maltreatment[43], parental conflict[44] and problematic parental relationships[4530,46–48]. Individual risk factors include being male, externalising disorders in childhood[49] and poor educational attainment[50]. Drug dependence is partially heritable, but probably a genetic disposition to drug use disorders in general rather than opioids in particular[51].

Comorbid substance use and mental health problems

People who use extra-medical opioids typically use multiple substances and often have comorbid polysubstance use disorders[52,53] and mental illnesses[54]. These relationships are not necessarily causal but problematic non-opioid use[47,55] and depression, anxiety and post-traumatic stress disorders[47,55] markedly increase the risk of opioid dependence. Similarly, use of alcohol, stimulants, benzodiazepines[52] and mental health problems[56] reduce positive treatment outcomes for opioid dependence and increasing overdose risk (see later section on overdose risk). Additional interventions are required when psychiatric comorbidity is present (see **Hall et al**[57] and **Farrell et al**[58] in this series).

Opioid overdose

Prevalence of fatal opioid overdose

Fatal opioid overdose is a major adverse outcome of prescribed and extra-medical opioid use that is increasing in the US, the United Kingdom, Canada, Australia and across Europe[59]. Globally, GBD 2017[60] estimated that there were around 109,500 opioid overdose deaths (see appendix F, Table F1), 43% of which were in the US. As shown in Figure 2b, the highest estimated fatal opioid overdose rates per 100,000 population were in the Russian Federation, Eastern European countries and the US.

Not all overdoses are fatal; many more non-fatal overdoses occur than fatal overdoses. A cohort of people prescribed opioids in Washington State, US, found a rate of 0.13 non-fatal opioid-related overdoses per 100 person-years (PY), and 0.017 fatal overdoses per 100PY (7.6:1 ratio).[61] By contrast, in a cohort of PWID in Vancouver, Canada, there were 12.0 non-fatal overdoses per 100PY[62] and 0.89 fatal overdoses per 100PY – a ratio of 13.5:1.[62]

Mechanisms of opioid overdose

At higher doses, opioids suppress respiratory rhythm generation and reduce normal physiological responsiveness of central and peripheral chemoreceptors (more detail on overdose mechanisms is presented in webappendix G). As a result, CO_2 levels rise and hypoxia develops,[63] breathing rates decrease and eventually stop.

People who use opioids long-term develop tolerance to euphoria faster than to respiratory depression.[64] Fentanyl and its structural analogues rapidly enter the brain after intravenous injection, accelerating respiratory depression[65] and inducing “respiratory paralysis.”

Risk factors for fatal opioid-related overdose

Systemic disease comorbidity may increase the risk of fatal opioid overdose e.g. via increased sensitivity to respiratory depressive effects impaired cardiac function, or impairment of opioid metabolism because of impaired liver or kidney function. Prolonged hypoxia and loss of consciousness from multiple overdoses may aggravate systemic disease[66,67].

Fatal opioid-related deaths often involve alcohol, benzodiazepines, cocaine and amphetamines[68]. Concomitant or polydrug use greatly increases the risks of opioid overdose[69–74] via synergistic respiratory depressant effects[70,74]; reverse tolerance to respiratory depression[73,75]; and 3) increase risk of relapse in abstinent heroin users[76]. The use of gabapentinoids prescribed to treat chronic pain, has increased amongst heroin users, [74,77–81] and have been found along with opioids at post mortem[74,82,83]. An increased risk of opioid-related deaths has also been reported for patients prescribed opioids and gabapentin for the treatment of pain[84].

Other health and social harms among people who use opioids

Non-fatal harms among people with opioid dependence

Table 1 summarises evidence for opioid dependence as a risk factor for a range of adverse outcomes (see webappendix H for methodology). Much of the evidence comes from studies of people who use heroin, most of whom inject; there are fewer studies among people who use pharmaceutical opioids extra-medically, and who use opioids without injecting.

HIV and HCV are a major risk for people who inject drugs (PWID).[85] The prevalence of opioid injecting varies widely geographically and in the main type of opioid used e.g. in South Asian countries, non-injecting routes of administration have been the most common. Table 1 also shows that skin and soft tissue infections[86], as well as infective endocarditis[86], are significant risks among PWID. Other consequences associated with opioid dependence, include poorer quality of life[87], mental health problems[88], increased criminal activity[89], and involvement with the criminal justice system[89].

Prolonged heroin use is associated with damage to brain white matter[90–92], changes in the connectivity between cortical and subcortical regions[93] and a decrease in grey matter density[94,95]. Chronic extra-medical opioid use results in repeated periods of hypoxia during non-fatal overdoses. The number of non-fatal heroin overdoses predicts neurocognitive

impairment[96], though less than other drugs[97], head injury, psychiatric comorbidity, and chronic infection (HCV and HIV)[98,99].

Mortality in people with using illicit opioids and prescribed opioids for chronic pain

A systematic review of mortality among people who use opioids (see webappendix I) found 97 eligible cohorts of people using opioids extra-medically [100] and nine cohorts of people prescribed opioids for chronic non-cancer pain[101]. The pooled all-cause crude mortality rate (CMR) in people using extra-medical opioids was 1.7 per 100 person-years (PY; 95%CI 1.5–1.9), nearly 10 times the expected rate for people of that age (standardised mortality ratio (SMR 9.9; 95% CI 7.5–13.1)). Among people injecting extra-medical opioids, the pooled SMR was 14.1 (95% CI 10.1–19.7), highlighting a higher risk among injectors. CMRs were highest for overdose deaths (0.5 per 100PY; 95% CI 0.5–0.6), but AIDS and liver disease were major causes of mortality (AIDS CMR 0.2 per 100PY; 95% CI 0.1–0.3; liver-related CMR 0.2 per 100PY; 95% CI 0.1–0.3).

In people prescribed opioids for CNCP, the pooled all-cause mortality rate was high (2.4 per 100PY PY; 95% CI 0.9–6.2) owing to the age and poor health of these samples. Overdose comprised a small proportion of mortality (pooled overdose CMR 0.06 per 100PY; 95% CI 0.01–0.2). T

Reducing harms among people who use opioids

Impact of methadone or buprenorphine treatment on outcomes

Varying terms (and their acronyms) are used to describe long-acting opioid agonists or partial agonists for the treatment of opioid dependence, including ‘methadone maintenance treatment’ and opioid agonist treatment (OAT[102]. In this paper we use OAT to refer to methadone or buprenorphine specifically, though all terms have limitations[103].

OAT is the most effective treatment for opioid dependence and a WHO Essential Medicine[1]. It reduces harms across multiple health outcomes (Table 2 (see webappendix J **for methods** and the searches undertaken, and **modelling** Panel E). Other opioids can be used in the treatment of opioid dependence; these are summarised in webappendix J in Panel J1). A range of other services are often provided in addition to OAT, depending upon the setting, and may include other medical care, mental health services, vocational and other assistance, and provision of naloxone.

The best evidence for OAT and other interventions is in people using illicit opioids (especially heroin) and/or PWID. Some evidence suggests that outcomes are also positive for OAT for people with any pharmaceutical opioid dependence[104]; evidence is less clear for opium dependence[105].

Table 2 summarises the evidence for the impact of OAT on outcomes in people who are opioid dependent (. It reduces injecting risk behaviour[106] and risk of HIV and HCV acquisition[107,108], increases engagement in the HIV[109] and HCV cascade of care, reduces criminal activity[110] and reduces all-cause[111] and overdose[111] mortality. There is weaker

evidence that it may reduce o suicide and accidental injuries[112]. OAT is highly cost-effective, and cost-saving when costs of crime are included[113].

The protective effect of OAT on mortality is marked in people who experience incarceration, especially during the highest risk periods in the first weeks post-incarceration, and after release from prison[114,115]. This could reduce HIV and HCV transmission, which is also elevated at these times[116]. However, OAT is rarely available in these settings. Our modelling (Panel E) shows that scaling-up OAT in prisons and the community could avert up between 23.9% and 75.0% more deaths over 20 years than only scaling-up in the community, suggesting that interruptions in OAT during incarceration may limit its population benefits.

Methadone and buprenorphine differ on some outcomes. Retention is higher in patients on higher doses of methadone (>80mg daily) and lower for buprenorphine and lower methadone doses (<60mg daily)[117]. Two studies have found lower risk of mortality during induction onto methadone vs. buprenorphine, but evidence is unclear on differences at other points in or out of treatment[111,118]. Among opioid dependent women who are pregnant, neonatal outcomes may be superior for women maintained on buprenorphine[119].

Higher doses of methadone and buprenorphine increase retention in treatment[120]. There is low quality evidence that supervised dosing (i.e. doses provided as directly observed doses by a pharmacist or other clinical worker) does not improve retention[121]. There is insufficient evidence to assess the effectiveness of urine drug screening (UDS) during OAT upon retention[122]. Guidance on quality OAT provision developed by WHO is based on evidence more than a decade old (Panel C summarises WHO guidance; text in bold indicates guidance based on more recent evidence).

Current OAT provision around the globe

A 2017 review[123] found very low levels of OAT coverage among PWID (Figure L1). Only 86 of 179 countries with evidence of injecting drug use provided OAT. Coverage was most often low according to WHO indicators (defined as <20 OAT recipients per 100 PWID per year); only 20 countries (5% of the global PWID population) were implementing high-coverage OAT (>=40 OAT recipients per 100 PWID)[123]. Retention in OAT can also be poor (Figure L2 in webappendix L presents data on retention in cohorts in multiple countries). Our mathematical modelling (see Panel E) demonstrates that scaling-up OAT from low to high coverage among PWID could avert 2.4–8.1% of all deaths, 9.8–19.3% of overdose deaths and 21.8–34.9% of HIV deaths in people who injected drugs in Kentucky, Tehran and Kiev over the next 20 years if OAT achieved 40% coverage of PWID outside of prisons. Even greater impacts are projected if OAT retention was improved (to 2 years) and OAT was provided in criminal justice settings (see Panel E and below).

In a systematic review of OAT in routine clinical practice (search details in Appendix L) sub-optimal dosing of methadone and buprenorphine was common.[124] There was greater access to unsupervised dosing with buprenorphine than methadone[124]. Limiting access to unsupervised dosing can mean daily clinic attendance which interferes with employment, education and family responsibilities, and is a barrier to treatment entry and retention. Use of urine drug screening in OAT is widespread but there is little evidence that it improves

clinical outcomes [122]. Requirements in some countries that OAT client details are reported to law enforcement agencies are a significant barrier to treatment [124]. OAT could be improved by greater involvement of clients in service design and delivery. Panel D discusses a range of ways in which OAT access, retention and outcomes could be improved.

There are few data on the impacts of flexible OAT provision on the diversion of OAT medications. The safety profile of buprenorphine (especially in comparison to illicit opioids such as fentanyl and heroin) means that these harms are limited. In the UK supervised community pharmacy provision of methadone reduced methadone-related overdoses despite an almost 400% increase in patient numbers[125].

Modelling impact of OAT scale-up on health outcomes

Panel E presents model projections for 3 global settings (Kiev (Ukraine), Perry County (Kentucky, USA) and Tehran (Iran) to evaluate the overall health benefits of OAT among PWID (model details are presented in webappendix M). Scaling-up OAT to UNAIDS/WHO recommended coverages of 40% among PWID in the community (current coverage in each setting is 5–11%) could prevent 2.4–8.6% of all deaths among PWID and people who previously injected drugs over 2020–2040, with overdose deaths accounting for 22.1–43.7% of all deaths averted. These mortality reductions would increase up to 1.8-fold if OAT treatment duration increases to 2 years) and up to 3.2-fold if retention was improved (to 2 years) and access provided to OAT in prisons and on release. Increasing OAT coverage, improving retention, and providing OAT in prisons could reduce 57.0% of all overdose deaths among PWID in Kentucky and 58.7% of HIV deaths among PWID and people who previously injected drugs in Tehran.

Our modelling shows that OAT also reduces other causes of mortality and the risk of HIV and HCV transmission, and rates of incarceration while improving HIV treatment outcomes. The mortality benefits vary across settings depending upon whether the major causes of death are due to HIV, as in Kiev and Tehran (where the impact of OAT is greatest), or overdoses, such as Kentucky. Our findings also highlight the importance of improving OAT retention (confirmed elsewhere[118,126]), and increasing the availability in prisons for maximising reductions in mortality. Importantly, our analyses focused on the impact of OAT on mortality rather than quality of life which will likely underestimate the population-level impact of OAT on HIV and HCV morbidity and other aspects of quality of life[87]. Nevertheless, our findings still suggest that it is imperative to expand OAT and improve the quality of OAT provided to PWID globally.

Opioid antagonist treatment

Oral naltrexone is ineffective and has little appeal for many people who are opioid dependent.[127] Extended-release naltrexone (XR-NTX) reduces extra-medical opioid use more than placebo or treatment referral. The need to withdraw from opioids before initiating XR-NTX limits its use, e.g. 37% of persons in studies of people withdrawing from opioids before XR-NTX induction did not start treatment.[128] Among those who initiate, XR-NTX treatment may have similar efficacy to buprenorphine in reducing opioid use short-term.[128] Reviews have concluded there is very limited and “inconsistent” evidence[128] on adherence

and retention in XR-NTX compared to OAT.[128] An economic evaluation in a clinical trial comparing XR-NTX to sublingual buprenorphine-naloxone concluded that buprenorphine was more cost-effective than XR-NTX at 24 and 36 weeks[129].

As with OAT[35], mortality risk increases after cessation of XR-NTX [130]. This suggests that relapse to opioid use is likely after treatment cessation, and the increased risk of overdose need to be clearly communicated to people leaving treatment.

Other interventions and policies to reduce opioid-related harms

Table 3 **summarises** our review of reviews of the effects of various interventions on injecting risk behaviour, extra-medical opioid use, HIV and HCV incidence, quality of life, and fatal overdoses, suicides and accidental injuries (Appendix J). There are several limitations in the evidence. First, the amount and quality of evidence for many interventions is much lower than for OAT. Second, few interventions had evidence on their impacts on all the outcomes we considered and most had a limited impact on a limited number of outcomes (in contrast to the wider impacts for OAT).

The provision of clean injecting equipment via needle and syringe programmes (NSP) reduces injecting risk in PWID[131]. There is stronger evidence for reduced HIV [132] than HCV incidence[108]. Testing for and treating HIV and HCV had positive impacts in people who use drugs[133–135]. Many countries are increasing access to naloxone to reverse opioid overdose. The rationale for this intervention is clear[136];it is uncertain what scale of provision is required to reduce opioid-related overdose mortality in the population.

Despite their low efficacy, psychosocial interventions remain the most commonly delivered interventions. Evidence suggests benefits of contingency management, cognitive behavioural therapy and relapse prevention in substance use disorders[137]. Evidence for their use in opioid dependence is more mixed[137], including whether they improve outcomes over OAT alone[137,138]. The more important factors may be quality of clinician training and supervision, the therapeutic alliance between the clinician and client and integration of clinician and peer-led psychosocial support services.[137]

Peer-led groups such as Narcotics Anonymous (NA) are one of the most common interventions globally. These abstinence-oriented programs involve peer support and regular attendance at group meetings. There is some evidence that of efficacy of Alcoholics Anonymous in reducing alcohol use for people who are alcohol dependent[139], but less for NA.

Medically supervised opioid detoxification using tapered doses of opioids assists people to complete withdrawal[140] but most people relapse to opioid use without additional interventions[140] with an increased risk of overdose. Supervised withdrawal is often followed by inpatient treatment in a therapeutic community. There was insufficient evidence to assess whether these are more effective than other interventions because of very high dropout before completion [141].

Compulsory drug detention centres (CDDCs) are used in some East and Southeast Asian countries. For example, in Malaysia[142], people may be forced to enter a CDDC after a positive urine drug test, police suspicion of drug use, or at family's request; detention is for 2 years, with few effective treatments provided and 18 months' supervision post-release. A review concluded that there was no evidence for positive outcomes and some evidence of harm[143]; a recent study reported a swifter relapse to opioid use among opioid users leaving CDDCs than among people leaving methadone treatment[142].

"Abuse-deterrent" formulations (ADF) of pharmaceutical opioids have been introduced to reduce extra-medical opioid use (e.g. making them more difficult to inject). A systematic review[144] concluded that there was promising but inconclusive" evidence that a tamper-resistant sustained-release formulation of oxycodone was "comparable or better" in reducing extra-medical use, and other opioid ADF". The evidence was insufficient to assess its effectiveness in reducing overdose[144]. Cost-effectiveness modelling suggested that ADF opioids costs $231,500 to prevent one new case of extra-medical opioid use, $80,500 to prevent one abuse-year, and $1.36 billion to prevent an overdose death[144].

Evidence for prescription drug monitoring programs (PDMP) and "pain clinic laws" (e.g. requiring registration, physician ownership, prescribing restrictions, and detailed record-keeping) is mixed[145] and insufficient given the low-strength evidence, high risk of bias and some evidence of increases in heroin overdoses[145]. Unless it is obligatory for prescribers to use the system, PDMPs are unlikely to be of benefit. These interventions at best reduce new cases of opioid dependence but are an insufficient response to opioid use dependence and related harms[146].

A recent systematic review of associations between indicators of criminalisation of drug use (e.g. exposure to incarceration and street-level policing) and patterns of injecting drug use, risk behaviours and HIV prevalence[147]. A formal synthesis was not possible but 86% of studies found that criminalisation of drug use was associated with greater injecting risk and HIV prevalence, and reduced engagement with OAT, harm reduction services, and the HIV care cascade[147]. Incarceration also increases risks of HCV infection[116]. People who use drugs see decriminalisation – as distinct from legalisation - of drug use as critical in reducing drug related harm and improving quality of life (e.g. Panel B).

The future of opioids: What are the anticipated changes, opportunities and challenges for the coming decade?

Improving access to prescribed opioids as essential medicines requires advocacy and collaboration of multiple organisations and agencies clear guidance on opioid use for pain and alternative strategies for managing non-cancer pain.

A comprehensive and evidence-based public health response is required to significantly reduce opioid dependence and related harms over the coming decades. We need drug policy to be driven by public health and prevention of health harms; which will require decriminalisation of drug use and dependence. The global research enterprise should be supported to develop and evaluate novel interventions to prevent opioid overdose, improve

the quality of treatment for opioid dependence, and identify novel treatments for opioid dependence and chronic pain.

International attention should be devoted to eliminating the marketing strategies that contributed to the sharp increase in opioid prescription and harms in North America. The presence of synthetic opioids in the illicit stimulant drug supply[148] poses grave public health challenges (see **Farrell et al**[57] in this series) because many people who use stimulants are opioid-naïve and at high risk of opioid overdose. If a public health approach will be essential to address problems arising from illicitly manufactured fentanyls and other synthetic opioids We need more research on the effectiveness and cost-effectiveness of novel interventions to prevent inadvertent exposure to synthetic opioid substances such as drug checking programs [149–151]. Developing the technical capacity to detect and measure these drugs will present a significant challenge in responding to public health issues raised by highly potent synthetic opioids (see **Peacock et al**[22] in this series).

We need to increase the global coverage and quality of care in f effective interventions such as OAT and NSP. Continua of care [152–154], such as the “cascade” of care for the treatment of HIV infection[155] could be used to address gaps in OUD treatment engagement[156–158]. The pursuit of abstinence or “recovery” should not be the immediate or ultimate goal. Overdose prevention — and prevention of drug related harm more broadly –are more appropriate public health objectives.

We need research on how to optimise treatments for opioid dependence by listening to the views of people who use drugs on what treatments are required at different stages of dependence, i.e. population-stratified medicine (see Panel B for perspectives from people who use drugs). We need to know whether novel models of treatment and care provision (e.g., in primary care, community-based and criminal justice settings) increase access and improve population-level outcomes. Particularly, we need research on how to improve retention in treatment and how to design OAT programmes (unsupervised dosing, dedicated pharmacies etc.) to best prevent overdose. This should include innovative “low threshold” OAT, including street-based outreach programs, mobile clinics, and home-based induction that shown promise[159]. Finally, we need to quantify the impact of interventions other than OAT on overdose and other health outcomes to design a population-based approach to treatment choices for people who are opioid dependent.

Opioid agonist and antagonist medications for the treatment of opioid dependence may not be effective for all patients[160]. Extended-release formulations of OAT may overcome challenges posed by the need for daily or near-daily dosing. In the United States, the first buprenorphine implant for the treatment of opioid dependence was approved by the FDA in 2016[161] and depot buprenorphine in 2017. Implementation research is needed to determine their attractiveness to patients[162], improve patient and population outcomes (including retention), and provide them to scale. We need to identify patient characteristics that predict successful induction and adherence to XR-NTX and reduce overdose risks during and after treatment with XR-NTX.[128]

Finally, the optimal policy and regulatory framework for opioids is one that minimises the health and social harms arising from extra-medical opioid use and dependence, while ensuring access to prescribed opioids as essential medications. Further work is needed to identify ideal policy and regulatory frameworks.

Opioid dependence is the third most important substance use disorder (after tobacco and alcohol) in terms of contribution to morbidity and premature mortality. The coverage of interventions to prevention opioid-related health harms is woefully inadequate in most countries. National and international drug policy, clinical guidance and research is needed to reduce the scale of opioid-related harm in the world. Drug policies need to move from a focus on criminal justice to public health. Prevention of harm should be the goal of clinical guidance and strategies – led by research into how to optimise combinations of pharmacological, psychological, and harm reduction interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest

LD has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma and Seqirus. SL has received investigator-initiated untied educational grants from Indivior. JG is a consultant and adviser for and has received research grants from Abbvie, Cepheid, Gilead Sciences, and Merck/MSD. MH reports personal fees from Gilead, Abbvie, and MSD. JS reports non-financial support from

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Common terminology used to describe patterns of opioid use

A range of terms are listed below that are used in the opioid literature[137].

Medical opioid use:

use of opioids as prescribed for pain and in the treatment of opioid dependence.

Extra-medical opioid use:

Encompasses use of pharmaceutical opioids either without a prescription (i.e. obtained from outside the formal medical system) or not as directed by a doctor, without excluding the possibility that the user may have medically driven reasons for using the opioid.

Illicit opioid use:

use of non-pharmaceutical opioids for extra-medical purposes.

Diverted opioids:

this term can be used in varied ways, some of which are more stigmatising (e.g. use in a broad sense, including if a patient does not take medication "as directed"). We propose a more restrictive definition,[137] which denotes medications diverted from licit sources to unintended individuals or the illicit marketplace: selling/trading, sharing, or giving away of prescription medications to others (either intentionally or involuntarily).

Aberrant opioid behaviours:

a range of patient practices that fall outside those usually expected in treatment of pain or opioid dependence; could have varied reasons including ambivalence about treatment, under-treatment, side-effects or emerging opioid-related problems.

Non-adherent opioid use:

use of opioids by the individual to whom they were prescribed, but are not taken in accordance with prescription directions or other conditions of treatment not met[137].

Hazardous opioid use:

a pattern of opioid use that increases the risks of harmful consequences (physical, psychological) for the user or others. It has been defined under "Factors influencing health status and encounters with health services" in ICD-11.

Opioid addiction:

a term widely used by the public and health-care professionals, and in the pain literature. It is mainly used as a synonym for opioid dependence but is not a current diagnostic term. In common usage, this term invokes a range of social constructs that are value-laden; many people prefer not to use this term.

Opioid abuse:

a historical term used to refer to a drug use disorder (DSM-IV); it is also a more general term denoting use that is disapproved of.

Opioid use disorder:

can have varied definitions: in DSM-IV, ICD-10 and ICD-11, denotes either abuse/harmful use or dependence; in DSM-5 denotes any use disorder (mild, moderate or severe) and may be further classified as in early or sustained remission or in a controlled (e.g., prison, hospital) environment. ICD differs from DSM-5 in that DSM-5 criteria are met when any two of 11 criteria are endorsed (including criteria previously categorised as DSM-IV abuse); ICD-11 retains the concept of dependence.

Opioid dependence:

a maladaptive pattern of opioid use involving a constellation of behaviours including physiological signs of dependence, loss of control over use, craving and preoccupation with non-therapeutic use, and continued use despite causing harm (used in ICD-10, ICD-11, DSM-IV). This term is not used in DSM-5.

Harmful opioid use:

used by WHO in its ICD classification of use disorder (similar to DSM-IV abuse).

Illicit opioid dependence:

dependence upon illicitly produced opioids, including heroin and illicitly manufactured synthetic opioids.

Pharmaceutical opioid dependence:

dependence upon pharmaceutical opioids, which may develop under medical supervision[138]. It may also occur via use of diverted pharmaceutical opioids.

Abstinence:

no longer using the drug that was causing problems; may still be taking agonists as prescribed.

Recovery:

definitions vary; however, can refer to a process of change through which people improve their health and wellness, live self-directed lives, and strive to reach their full potential[139].

Some perspectives from people who use drugs*

What would you like people to know about people who use drugs?

He/she could be anyone: their brother, sister, fiancé, professor they like the most, singer or actor they've a crush on or anyone…people who use drugs are simply not bad people. *(Male, 39, Nepal)*

We are human we are OK people. We are parents, good and bad like everyone else. We are not demons. We hold down responsible jobs, we care, we're intelligent, we love, we are creative, we have the same faults as others. *(Male, 65, France)*

All professions, all governments etc would have significant numbers of drug users among them. People who use drugs are just the same as everyone else - human beings. *(Unidentified)*

I am, and other people who use drugs are, capable complex multifaceted human beings, capable of being trustworthy, responsible, with ethics, in loving relationships, managing career, education, hobbies, a home, animals. I am smart and I make decisions about my drug use and my drug choices and my breaks…I am a sentient being trapped by laws that makes one drug legal and the next illegal. One route of administration [is] socially acceptable and topical and the other a pariah. *(Female, 43, Australia)*

There are many different reasons why people from many walks of life choose to take drugs including to self-medicate, alleviate pain, stress, boredom, to relax, have fun, socialise, escape… *(Female, 53–58, Australia)*

What are the current gaps in the availability, quality and suitability of drug treatment services, health services, and harm reduction services for people who use drugs?

Violation of the rights of PUD, absence of PUD in planning & designing of the program results in to low-quality services and involvement. *(Male, 39 years, Nepal)*

In terms of health, we just need access to the same as non-drug users but with added expertise so that specific health problems that may occur are not excluded from the treatment package and are delivered by people who know what they are doing. *(Male, 65, France)*

Most of the drug treatment services in North-east are in the form of Rehabilitation Facilities and all of them does not provide evidence based systematic treatment module. Again, some of the treatment centre and their service providers are not well educated about the psychotherapy and base concept of addiction as a disease. Here, patients are used to suffer and deprived from all necessary amenities inside the rehab in the name of treatment. *(Male, 33, India)*

Drug treatment services, health services, and harm reduction services need to value and prioritise peer & lived experience for staff, more drug positivity and total abstinence

*These perspectives were submitted by people who use drugs in response to an email inviting input circulated in March 2019.

should not be seen as the only goal, some people might just want to get to a healthier place with their use. *(Female, 36, Australia)*

What do services need to have in place to make people who use drugs feel welcome and want to access services?

Sympathy, non-judgmental and welcoming environment *(Male, 39 years, Nepal)*

Active involvement of drug using community, gender responsiveness. *(Unidentified) (Male, 43, South Africa)*

How can people who use drugs and other stakeholders work together to improve the health of people who use drugs?

Remove the prejudice and stigma from both sides and we might actually get somewhere. *(Male, 65, France)*

Create an environment of trust. *(Male, 39, Nepal)*

Share experiences and networking of organisations *(Male, 42, Burundi)*

Promote, allow and listen to feedback by people who use drugs…without bias, stereotype…create and maintain avenues for feedback, suggestions, comments, compliments within services and agencies. *(Female, 53–58, Australia)*

What is the single best thing that could be done to improve the lives of people who use drugs?

Decriminalisation of drug use. *(Male, 49 years, Nepal; Unknown; Female, 43, Australia; Male, 43, Wurundjeri country; Male, 43, South Africa; Female, 36, Australia; Male, 35, USA; Male, 53, Australia;; Male, 58, Australia; Male, 54, Australia);*

Legalisation of drug use *(Male, 51, UK; Male, 35, USA; Female, 41, Australia; Female, 61, Australia)*

Promote human rights of people who use drugs (*Male, 42, Burundi);* recognise the humanity of people who use drugs *(Female, 53–58, Australia; Female, 35, India)*

Guidance for opioid agonist treatment (OAT) for the treatment of opioid dependence

The most recent international guidelines for OAT for opioid dependence were released by the World Health Organization (WHO) in 2009[176], and do not reflect current practice or guidelines elsewhere, including several treatment modalities like slow-released morphine and injectable and implantable forms of OAT that are now included in standard of practice and national guidelines in many countries. The below text combines older recommendations from the WHO guidelines along with **some key updates (noted in bold text)** guided by more recent evidence and featured in national guidelines. It will be important for WHO to update the WHO guidelines given the developments in this field in the decade since the guidelines were published.

Due to better retention and greater cost effectiveness, higher-dose methadone might be considered the preferred OAT medication[176]. There are multiple reasons why buprenorphine may be preferred, including less rigid supervision and client preference, better safety profile, experience of adverse effects or medication interactions with methadone and poor response to methadone[176].

Initial methadone dose depends upon level of tolerance and is 10mg to 30mg (not more than 30mg) per day. **Doses should be escalated rapidly with monitoring for symptoms of opioid excess to promote lower relapse and higher retention**. Higher maintenance doses (range 60–120mg per day) result in reduced extra-medical opioid use and better retention. Initial buprenorphine dose for clients will vary; for those with moderate neuroadaptation it should be 4–8mg, and maintenance doses should **minimally be at least 8mg (range: 8mg to 24 mg)**[176]. **Buprenorphine doses higher than 24mg per day are associated with diversion of the medication.**

Doses should be directly supervised early in treatment, especially with methadone. **Supervision of buprenorphine doses should be variable, and in some cases, home inductions can occur with experienced clinicians.** Take-away doses (i.e. doses provided to the patient for unsupervised dosing) should be provided especially when benefits of reduced frequency of attendance outweigh medication diversion risks, and this should be regularly reviewed[176].

The WHO recommendations do not address urine drug screening during OAT. **Urine drug testing requirements are variable based on settings. When deployed, however, they should be used to guide OAT dosing and concomitant psychosocial counselling – not discontinuation of OAT, which may result in relapse, overdose and death.**

Clients on methadone can be successfully transferred to buprenorphine, but only when methadone doses have been lowered sufficiently, generally below 40mg.

Pharmacological treatment of opioid dependence should be widely accessible. OAT can be successfully provided in multiple settings, including specialty addiction treatment, hospitals, primary care and other office-based settings, pharmacies and in criminal justice settings.

Best practice is considered to involve a range of other interventions as needed by clients, including counselling, psychiatric treatment and social supports including assistance with housing, employment, education and legal problems. **Psychosocially assisted pharmacological treatment should not be compulsory because not all patients need it**[138]. Links to psychosocial counselling, HIV, TB and hepatitis treatment should be available[176].

Synthesis of available evidence suggests that in many settings, delivery of OAT in routine clinical practice may be sub-optimal. Average doses in some countries appear to be below the minimum recommended dose, and access to unsupervised dosing is often limited, particularly for methadone.

Improving opioid agonist treatment access, retention and outcomes

There are many opportunities to improve the quality of care provided in OAT. Key barriers to treatment entry include: lack of unsupervised dosing, extensive assessment processes, delays to treatment following presentation, mandatory engagement in psychosocial counselling, siloing of OAT in specialist clinics, and geographically distant clinics and pharmacies for medication delivery.

In many countries, there is a requirement for official registration of a patient due to the scheduling of opioid medications. This information can sometimes be shared with police (either by law, or in practice), and clients may be targeted by police, lose their driver's license, experience restrictions on employment, and other adverse consequences[177,178].

Opportunities to improve OAT access, retention and outcomes:

- Rapid access to OAT with minimal assessment to establish opioid dependence in several settings such as emergency rooms, community-based settings, primary care and criminal justice settings
- OAT prescribing in a range of settings, beyond specialised settings including primary care, and OAT dispensing in community pharmacies
- Elimination of compulsory counselling requirements (e.g. in the US); instead, make provision of psychosocial services that may be accessed on a voluntary basis
- Minimise intensity of care as people stabilise in treatment (e.g., transition to less supervision as patients become clinically stable)
- Increased and rapid access to unsupervised dosing, particularly for people prescribed buprenorphine or stabilised on methadone
- Minimise use of urine drug screening; use results of such screening to improve care (i.e. dose adjustment) rather than to terminate treatment
- Low-threshold and adapted care for disengaged individuals, such as those who are homeless or with mental health issues (e.g., many required assessments can be obtained after starting OAT)
- Access to alternative agonist treatments such as slow release oral morphine and injectable opioid agonist therapy for individuals who do not respond to methadone or buprenorphine

Mathematical modelling of the impact of improving coverage and quality of OAT on multiple health outcomes across three global settings

We performed modelling to comprehensively evaluate the overall health benefits of OAT amongst PWID in 3 global settings: Kiev (Ukraine), Appalachian Kentucky (USA) and Tehran (Iran) (for details see Webappendix M). The single-sex, dynamic model, calibrated within a Bayesian framework to data from each setting, captures effects of OAT on all-cause mortality, injury, overdose and self-harm/suicide deaths, HIV and HCV transmission, HIV treatment outcomes, and incarceration (which has been linked to greater risk of HIV and HCV transmission among PWID[116]). The contrasting settings were chosen because of differences in HIV and HCV epidemics, overdose mortality and intervention coverage, their geographical spread and data availability (Figure E1).

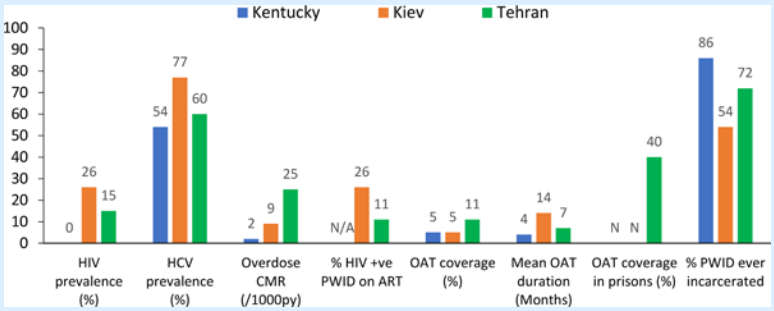

Figure E1:
Summary of parameters across modelled settings

Model analyses estimated the lives lost due to an individual's drug use, and the contribution that different harms (overdose, injury, suicide, HIV and HCV mortality) have to this health loss (with current OAT coverage). Analyses then evaluated how scaling-up the coverage of OAT or increasing the duration of OAT can reduce this health loss and which beneficial effects of OAT are most important for improving health in each setting. Model analyses evaluated the percentage of deaths averted and life years gained (LYG) compared to a scenario with **no OAT**, of: current OAT coverage (**Status Quo Scenario**); scaling-up OAT coverage to 40% in the community, as recommended by WHO/UNAIDS (**Scale-up Scenario A**); additionally, increasing the average duration of OAT to 2 years (**Scale-up Scenario B);** additionally, scaling-up OAT in prison (**Scale-up Scenario C**).

Figure E2 shows that current levels of OAT are projected to have negligible impact on mortality in Kentucky and Kiev but substantial impact in Tehran where OAT coverage is greatest and provided in prisons (Figure E2); averting 0.8% (95%CrI: 0.5–1.4), 0.3% (95%CrI: 0.1–0.6) and 6.5% (2.5 – 12.1) of deaths and gaining 119.6 (95%CrI: 61.8–206.1), 18.5 (95%CrI: 9.1–32.8) and 1062.6 (95%CrI: 385.0–2003.3) life-years per 1,000 PWID over the next 20 years in Kiev, Kentucky and Tehran, respectively.. Scaling-up OAT in the community (Scale-up Scenario A) could avert between 2.4% (Kentucky; 95%CrI: 1.2–4.5) and 12.5% (Tehran; 95%CrI: 6.0–18.0) of deaths and gain between 161.3 (Kentucky; 95%CrI: 84.6–258.9) and 1878.9 (Tehran; 95%CrI: 859.9–3262.8) life-years per 1,000 PWID over the next 20 years. This equates to between 12.7% (Tehran; 6.6–18.5) and 19.3% (Kiev; 95%CrI: 16.3–21.6) of overdose deaths averted (Figure E2 and Table E1). Model analyses suggest that extending the average duration of OAT (Scale-up Scenario B) would have additional benefits, particularly on reducing overdose deaths; with between 4.4% (Kentucky; 95%CrI: 2.4–8.5) and 16.7% (Tehran; 95%CrI: 9.1–22.4) of all deaths averted and 1.6–2.3 times more overdose deaths averted compared to scaling-up OAT without improving retention. Model projections also show that interruptions in OAT due to incarceration may limit the impact of OAT; in Tehran, for example, 25.9% (95%CrI: 16.7–33.2) of deaths and 56.2% (95%CrI: 19.4–78.6) of HIV deaths could be averted if OAT is also provided in prisons with retention upon release (Scale-up Scenario C). However, limited impact on HCV deaths is achieved due to many of the HCV deaths occurring among those with existing infections prior to OAT scale-up.

The impact of scaling-up OAT on all-cause mortality varies substantially between the three settings primarily because of differences in how the varied harms associated with drug use contribute to mortality among PWID. This impact is greatest in Kiev and Tehran where the primary cause of death associated with drug use is projected to be HIV (27.8% (95%CrI: 20.1–36.5) and 21.3% (95%CrI: 6.5–42.7) of all deaths in Kiev and Tehran, respectively). Lower impact of scaling-up OAT is achieved in Kentucky, where overdose is the primary cause of death associated with drug use and only accounts for 8.1% (95%CrI: 4.4–15.7) of all deaths. This is further demonstrated by how each effect of OAT contributed to the overall impact of scaling-up OAT in each setting. For Scale-up Scenario C, for example, the effect of OAT on HIV transmission was the most important effect in reducing mortality in Kiev and Tehran accounting for 41.3% (95%CrI: 28.6–60.1) and 69.1% (95%CrI: 31.7–92.9) of deaths averted, respectively, whilst in Kentucky, the most important effect was the effect of OAT on overdose, accounting for 55.0% (95%CrI: 32.7–75.8) of deaths averted.

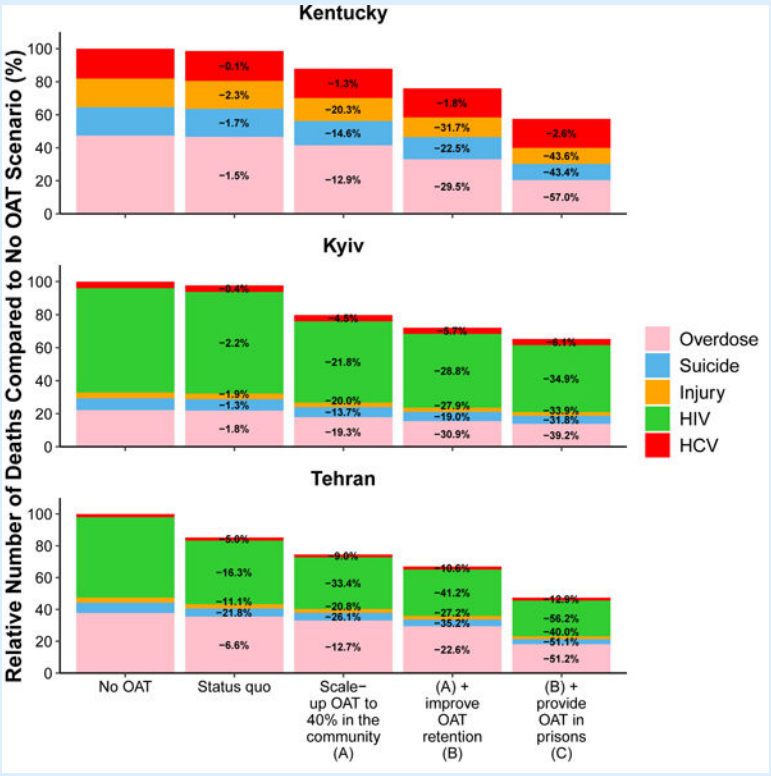

Figure E1: Causes of death among PWID and ex-PWID; 2020–2040.

Figure shows the median percentage of deaths due to overdose, suicide, injury, HIV, HCV or other causes under the following strategies: if there were no OAT from 2020; if OAT was scaled-up to 40% coverage among PWID in the community; if OAT was scaled-up to 40% coverage among PWID in the community and the average duration of OAT is increased to 2-years; if OAT was scaled-up to 40% coverage among PWID in the community, incarcerated PWID enrol onto OAT at the same rate and the average duration of OAT is increased to 2-years. Deaths from other natural causes which account for 22%, 54% and 82% of deaths in Tehran, Kiev and Kentucky in Status Quo projections, respectively, are not shown.

Table E1:

Deaths averted with current and scaled-up OAT coverages compared to no OAT scenario. Cells show median relative reduction in preventable deaths due to different causes with 95% credibility intervals in parentheses. Negative reductions (i.e. increases) in deaths are possible for some causes due to competing risks.

	Status quo	Scale-up OAT to 40% in the community (A)	(A) + improve OAT retention (B)	(B) + provide OAT in prisons (C)
	Median % reduction in deaths (95%CrI)	Median % reduction in deaths (95%CrI)	Median % reduction in deaths (95%CrI)	Median % reduction in deaths (95%CrI)
Kentucky				
HCV	0.1% (0 – 0.3)	1.3% (−0.3 – 3.1)	1.8% (−0.7 – 4.7)	2.6% (−1.4 – 7)
Overdose	1.5% (0.2 – 2.1)	12.9% (2.2 – 17)	29.5% (23.1 – 38)	57% (48.1 – 62.9)
Suicide	1.7% (1.2 – 2.3)	14.6% (12.1 – 17.7)	22.5% (18.2 – 29)	43.4% (35.8 – 50.8)
Injury	2.3% (1.8 – 3)	20.3% (18.1 – 22.7)	31.7% (25.7 – 37.1)	43.6% (39.1 – 50)
Other	0% (0 – 0.2)	0.2% (−0.4 – 2)	0.1% (−0.7 – 2.9)	0% (−1.3 – 3.6)
Total	0.3% (0.1 – 0.6)	2.4% (1.2 – 4.5)	4.4% (2.4 – 8.5)	7.7% (4.4 – 13.3)
Kiev				
HIV	2.2% (1.2 – 3.7)	21.8% (15.2 – 30.1)	28.8% (19.6 – 39.5)	34.9% (24.4 – 45.8)
HCV	0.4% (0 – 0.9)	4.5% (0.4 – 8.2)	5.7% (0.3 – 10.9)	6.1% (−1 – 12)
Overdose	1.8% (1.1 – 3)	19.3% (16.3 – 21.6)	30.9% (22.4 – 35.4)	39.2% (29.7 – 43.5)
Suicide	1.3% (0.8 – 2)	13.7% (11.6 – 15.3)	19% (14.1 – 23)	31.8% (25.4 – 40.1)
Injury	1.9% (1.2 – 3)	20% (18.3 – 21.4)	27.9% (22.3 – 31.9)	33.9% (27.1 – 37.9)
Other	−'0.1% (−0.2 – 0.1)	−'0.6% (−2.2 – 0.7)	−'0.7% (−3.2 – 0.9)	−'1% (−3.9 – 1.1)
Total	0.8% (0.5 – 1.4)	8.6% (6.8 – 11.5)	11.7% (8.8 – 16.4)	14.5% (11.3 – 20.4)
Tehran				
HIV	16.3% (5.2 – 44.4)	33.4% (11.2 – 63.4)	41.2% (14.0 – 70.3)	56.2% (19.4 – 78.6)
HCV	5.0% (0.6 – 17.6)	9.0% (1.6 – 25.7)	10.6% (1.0 – 30.0)	12.9% (−2.9 – 35.6)
Overdose	6.6% (1.6 – 10.2)	12.7% (6.6 – 18.5)	22.6% (16.6 – 28.1)	51.2% (43.3 – 56.5)

	Status quo	Scale-up OAT to 40% in the community (A)	(A) + improve OAT retention (B)	(B) + provide OAT in prisons (C)
	Median % reduction in deaths (95%CrI)	Median % reduction in deaths (95%CrI)	Median % reduction in deaths (95%CrI)	Median % reduction in deaths (95%CrI)
Suicide	21.8% (16 – 25.6)	26.1% (21.9 – 30.1)	35.2% (29.5 – 39.4)	51.1% (40.2 – 57.6)
Injury	11.1% (4.6 – 14.5)	20.8% (18.1 – 23.3)	27.2% (23.2 – 30.3)	40.1% (33.8 – 45.2)
Other	−'2.0% (−3.5 - −0.7)	−'3.8% (−6.4 - −1.8)	−'5.1% (−8.9 - −2.8)	−'8.3% (−14.5 - −4.5)
Total	6.5% (2.5 – 12.1)	12.5% (6.0 – 18.0)	16.7% (9.1 – 22.4)	25.9% (16.7 – 33.2)

Key messages

1. Opioids are essential medicines for the treatment of acute and cancer pain and opioid dependence. Access to opioids for medicinal purposes varies widely across the globe and is often inadequate.
2. By contrast, ready access to illicit opioids and in some countries, overprescribing of pharmaceutical opioids, mean that extra-medical opioid use and dependence are increasing globally, and causing substantial loss of health and life.
3. There is an increasingly diverse number and sources of opioids both naturally and synthetically produced. The proliferation of highly potent opioids in some countries is substantial increasing in overdose mortality.
4. Many people with problematic or dependent use of opioids will experience a long-term cycle of use, abstinence, and relapse, including periods in and out of treatment. The criminalisation of illicit opioid use in most countries means that many face arrest and incarceration, which increases health harms.
5. Manifold adverse health outcomes are elevated among people with problematic or dependent opioid use e.g. overdose, suicide, accidental injuries and infectious diseases, including HIV and hepatitis C virus. Mortality risk in people using illicit opioids around 10 times higher than the general population. Overdose risk is elevated after a period of abstinence from use and loss of tolerance, as may occur following incarceration, and in the context of polydrug use.
6. Opioid agonist treatment (OAT) is the most effective treatment for opioid dependence. It reduces illicit opioid use and reduces overall mortality and deaths from overdose, suicide, and other injuries. Modelling suggests that compared to a scenario with no OAT, scaling-up OAT to 40% coverage in the community, increasing average duration of OAT to two years and providing OAT in prisons would avert between 7.7–25.9% of all deaths, 39.2–57.0% of overdose deaths and 34.9–56.2% of HIV-related deaths over the next 20 years by also preventing incarceration, reducing the risk of HIV and HCV transmission, and improving HIV treatment outcomes.
7. Other pharmacological and non-pharmacological treatments are available, with varying levels of evidence for effectiveness and patient acceptability. Other effective interventions include those focused on preventing harms associated with problematic opioid use.
8. Despite strong evidence for the effectiveness a range of interventions to improve the health and well-being of people who are dependent on opioids, coverage is low even in high income countries and treatment quality suboptimal. Policy changes that prioritise prevention of opioid-related harms and scale-up evidence-based programs, health care services, and drug treatment services are urgently needed.

9. The criminalisation of illicit opioid use and dependence produces considerable avoidable human, social, and economic harms. Policy frameworks need to adopt a human rights and public health-based approach, by not making drug use a criminal offence and seeking to reduce drug related harm at the population level.

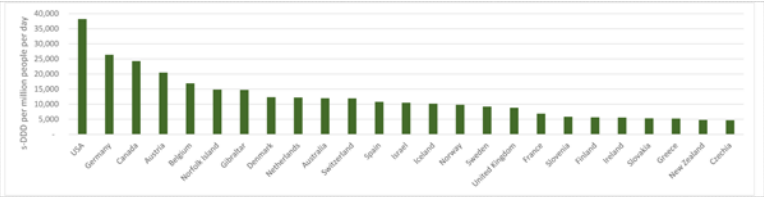

Figure 1a:

Countries with the highest no. standardised defined daily doses (s-DDDs) of opioid analgesics consumed per million people per day, 2016

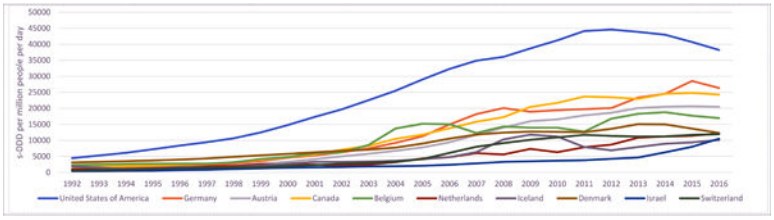

Figure 1b:

Opioid analgesic consumption in highest countries (as at 2016), no. standardised defined daily doses (s-DDDs) of opioid analgesics consumed per million people per day, 1990–2016
Source: Data provided by the International Narcotics Control Board. Used 3-year rolling averages. Opioid analgesics includes codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, morphine, ketobemidone, oxycodone, pethidine, tilidine and trimeperidine.

It is important to note that there are gaps in reporting of data by member states and there may be differences in the quality of data reported across countries. See Appendix C for details on how INCB data are collected from member states and analysed. Please note that these figures report on a subset of opioids used for analgesia and do not include the full list of narcotic drugs the full list of narcotic drugs reported in the INCB's annual reports.

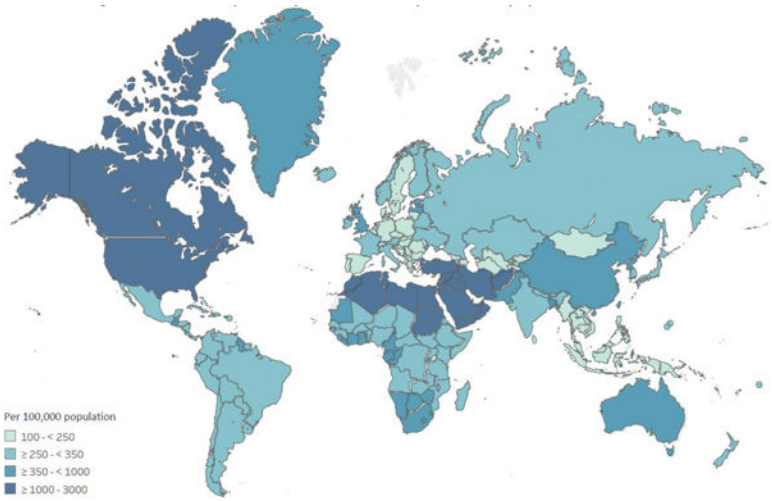

Figure 2:

Estimated prevalence of opioid dependence and opioid overdose mortality, Global Burden of Disease study 2017

2a. Estimated age-standardised opioid dependence cases per 100,000 population

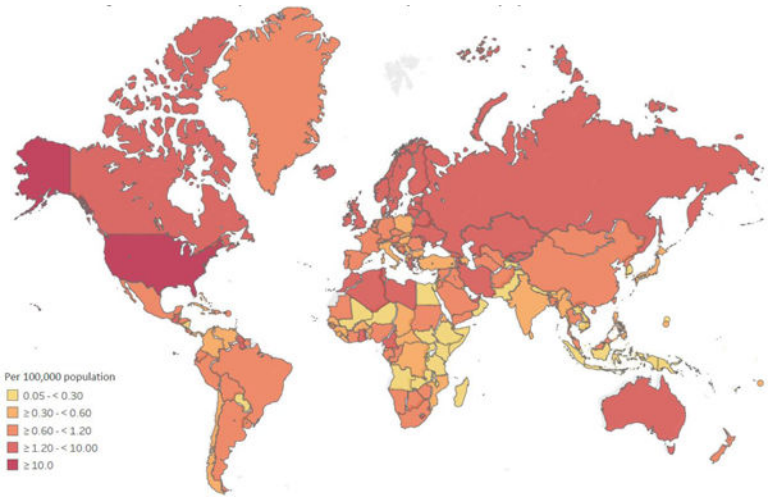

Figure 2b:

Estimated age-standardised opioid overdose deaths per 100,000 population

Source: Global Burden of Disease 2017[26,60]. For details on the methods used please see Appendix E.

Table 1:

Existing evidence for adverse outcomes among people who are opioid dependent

	People dependent on illicit opioids				People prescribed pharmaceutical opioids			
	Effect		**Level of evidence**	**Sources**	**Effect**		**Level of evidence**	**Sources**
Non-Fatal outcomes								
Receptive syringe sharing (past year)	↑	25.5% (16.7, 34.3%) [PWID]	C	[85]		NA		
HIV incidence	↑	0.8–10.7 per 100 PY [PWID]	*C*	[107]		NA		
HIV prevalence	↑	17.8% (10.8, 24.8%) [PWID]	C	[85]		No review level quantitative evidence		[88]
HCV incidence	↑	5.9–42.0 per 100 PY [PWID]	C	[108]		NA		
HCV prevalence (HCV antibody)	↑	52.3% (42.4, 62.1%) [PWID]	C	[85]		No review level quantitative evidence		[88]
HCV prevalence (HCV RNA)	↑	39.2% (31.6, 47.0%) [PWID]	C	[163]		No review level quantitative evidence		[88]
Skin and soft tissue infections…								
…current	↑	6.1–32.0% [PWID]	C	[86]		No review level quantitative evidence		[88]
…past 6–12 months	↑	6.9–37.3% [PWID]	C	[86]		No review level quantitative evidence		[88]
…ever	↑	6.2–68.6% [PWID]	C	[86]		No review level quantitative evidence		[88]
Infective endocarditis (ever)	↑	0.5–11.8% [PWID]	C	[86]		No review level quantitative evidence		[88]
Quality of life	↓	No review level quantitative evidence	C	[87]		No review level quantitative evidence		[88]
Mental health (depression, anxiety)	↑	No review level quantitative evidence			↑	No review level quantitative evidence		[88]
Criminal activity	↑	RaRa 5.84 (1.36, 10.32) [SYNTH]	C	[89]		NA		
Contact with criminal justice system	↑	RaRa 2.97 (1.43, 4.51) [SYNTH]	C	[89]		NA		
Non-fatal overdose (ever)	↑	41.5% (34.6–48.4%)[PWID]	C	[164]	↑	No review level quantitative evidence	C	[164]
Poor neonatal outcomes…								

	People dependent on illicit opioids				People prescribed pharmaceutical opioids			
	Effect		**Level of evidence**	**Sources**	**Effect**		**Level of evidence**	**Sources**
…low birth weight	↑	RR 4.61 (2.78–7.65)	C	[165]	?	RR 1.36 (0.83–2.22) [METH]	C	[165]
…neonatal abstinence syndrome	↑	50–95%	C	[166]	↑	47–57%	B	[167]
…pre-term birth	↑	TBC		[168]	↑	7–19%	B	[167]
Fatal outcomes								
Overdose	↑	SMR 58.43 (38.09–89.64)	C	[100]	↑	CMR 0.63 per 1000PY (0.18–2.23)	C	[101]
Other accidental injuries	↑	SMR 6.85 (4.41–10.64)	C	[100]		No data	C	[101]
Suicide	↑	SMR 8.52 (6.00–12.10)	C	[100]		No data	C	[101]
Cancer	↑	SMR 2.69 (1.84–3.92)	C	[100]		No data	C	[101]
AIDS-related	↑	SMR 18.50 (8.15–41.99)	C	[100]		No data	C	[101]
Viral hepatitis	↑	SMR 35.94 (16.06–80.42)	C	[100]		No data	C	[101]
Overall mortality	↑	SMR 9.90 (7.52–13.05)	C	[100]	↑	CMR 23.84 per 1000PY (9.21–61.75)	C	[101]

Note: For details of the search strategies used please see Appendix H **and** Appendix I. PWID – based on studies of people who inject drugs, not necessarily opioids specifically. SYNTH – authors did not pool estimates, but we did for this review. METH – studies examining women on methadone versus controls. RR – relative risk. RaRa – rate ratio. SMR – standardised mortality ratio. NA – reviews of pharmaceutical opioid dependent people specifically were not located. ND – reviews indicated that no estimates could be found for this outcome.

A Consistent conclusions across meta-analyses, high quality systematic reviews, or multiple randomised controlled trials

B Evidence from one or two randomised controlled trials only

C High quality systematic reviews of cohort, case-control or cross-sectional studies

D Systematic reviews with inconsistent conclusions from authors or of cross-sectional studies; OR multiple consistent ecological studies

E Cross-sectional association, case series suggesting outcome, single cohort study

Table 2:

Existing evidence for impacts* of opioid agonist treatment with methadone or buprenorphine

	Effect		Level of evidence	Sources
OAT vs. no treatment in the community				
Opioid use	↓	RR 0.48 (0.41, 0.55) SYNTH	A	106
Injecting frequency	↓	SMD −0.59 (−0.91, −0.26) SYNTH	A	106
Injecting risk (sharing needles/syringes)	↓	RR 0.53 (0.4, 0.7) SYNTH	A	106
HIV linkage to care and treatment	↑	HR 1.87 (1.50, 2.33)	C	109
HIV treatment adherence	↑	OR 2.14 (1.41, 3.26)	C	109
HIV treatment attrition/discontinuation	↓	OR 0.77 (0.63, 0.95)	C	109
HIV viral suppression	↑	OR 1.45 (1.21, 1.73)	C	109
HIV incidence	↓	RR 0.46 (0.32, 0.67)	C	107
HCV testing	↑	OR 1.73 (1.19, 2.51)	C	169
HCV linkage to care and treatment	↑	OR 1.40 (0.90, 2.17)	C	169
HCV treatment sustained virological response	×	OR 0.75 (0.45, 1.25)	C	169
HCV incidence	↓	RR 0.50 (0.40, 0.63)	C	108
Skin and soft tissue infections	*?*	NE	*D*	86
Mental health problems	↓	SMD 0.49 (0.35, 0.63)	C	170
Quality of life (social – WHOQOL-BREF)	↑	SMD 0.29 (0.16, 0.42)	C	170
Criminal activity	↓	SMD −0.57 (−1.00, −0.13)		110
Contact with the criminal justice system	×	RR 0.75 (0.46, 1.23)	C	171
Overdose mortality	↓	RaRa 0.25 (0.18, 0.36) SYNTH	C	111
Suicide mortality	↓	RaRa 0.48 (0.39, 0.59)	E	112
Other injury mortality	↓	RaRa 0.40 (0.34, 0.46)	E	112
All-cause mortality	↓	RaRa 0.33 (0.28, 0.39) SYNTH	C	111
OAT vs. no treatment in prison				
Unsanctioned opioid use	↓	NE	B	172
Injecting frequency	↓	NE	B	172
Injecting risk behaviour	↓	NE	B	172
HIV incidence	?	NE	B	172
HCV incidence	?	NE	B	172
Prison infractions	↓	NE	E	172
Criminal activity (post-release)	?	NE	B	172
Reincarceration	?	NE	C	172
OAT engagement (post-release)	↑	NE	B	173,174
HIV treatment adherence (post-release)		NR		
HIV viral suppression (post-release)		NR		
Overdose/suicide/injury mortality (in prison)	↓	aHR 0.13 (0.05, 0.35)	E	175

	Effect		Level of evidence	Sources
All-cause mortality (in prison)	↓	aHR 0.26 (0.13, 0.50)	E	175
All-cause mortality (4 weeks post-release)	↓	aHR 0.25 (0.14, 0.45)	E	114,115
Buprenorphine vs. methadone (ref)				
Retention in treatment	↓	RR 0.83 (0.72, 0.95)	A	117
Mortality during induction (4 weeks)	↓	RaRa 0.28 (0.08, 0.95) SYNTH	C	111,118
Mortality remainder in treatment	ND	RaRa 0.68 (0.44, 1.04) SYNTH	C	111,118
Mortality following cessation (4 weeks)	ND	RaRa 0.62 (0.16, 2.42) SYNTH	C	111,118
Neonatal outcomes…				
…Head circumference	↑	RCT WMD 0.91cm (0.14 1.66)	B	119
…Low birth weight	↓	RCT WMD 324g (32, 617)	B	119
…Preterm birth	↓	RR 0.40 (0.18, 0.91)	B	119

For details of the search strategies used please see Appendix J.

* Please note that the comparator groups used vary across outcomes; they can include a placebo or active control or an out-of-treatment comparator.

SYNTH – we pooled estimates for this review. NR – no quantification located. NE – no quantitative synthesis reported. ND – no difference between methadone and buprenorphine detected. RR – relative risk. RaRa – rate ratio. RCT – randomised controlled trial. WMD – weighted mean difference. SMD – standardised mean difference. HR – hazard ratio. OR – odds ratio.

Presence or absence of effect

× OAT does not appear to have a significant effect upon the outcome

↑ This outcome may be increased by OAT

↓ This outcome is decreased by OAT

? Unclear if OAT has an impact on this outcome

Level of evidence

A Consistent conclusions across meta-analyses, high quality systematic reviews, or multiple RCTs

B Evidence from one or two randomised controlled trials only

C High quality systematic reviews of cohort, case-control or cross-sectional studies

D Systematic reviews with inconsistent conclusions from authors; OR multiple consistent ecological studies

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Table 3:

Current evidence for effects of interventions to address key outcomes and behaviours among people who use opioids extra-medically

	Injecting risk behaviours				Extra-medical opioid use				HIV incidence				HCV incidence				Skin and soft tissue infections				Quality of life			
Intervention	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**
Provision of sterile injecting equipment	↓	aOR 0.52 (0.32, 0.83)	A[PWID]	131	-	-	-	-	↓	OR/HR/RR 0.42 (0.22, 0.81)	C[PWID]	132	↓?	RR 0.77 (0.38, 1.54)	C	108	?	-	D	86	-	-	-	-
Condom provision	-	-	-	-	-	-	-	-	↓	RR 0.29, (0.20, 0.43)	A[GEN]	179	?	-	C	180	-	-	-	-	-	-	-	-
Naloxone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Drug consumption rooms	↓	RR 0.31 (0.17, 0.55)	C[PWID]	181	-	-	-	-	?	-	D	182	?	-	D	182	↓	OR 0.47 (0.23, 0.94)	E	86	-	-	-	-
Peer-based self-help groups	-	-	-	-	↓?	-	B[ALC]	139	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosocial interventions	↓	SMD −0.43 (−0.69, −0.18)	A	183	↓	WMES −0.18 (−0.30, −0.06)	A	184	?	-	D	182	?	-	D	182	?	-	E	185	-	-	-	-
Opioid detoxification alone					×																			
Oral opioid antagonists	×	NE	A	186	×	RR 1.39 (0.61, 3.17)	A	127	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Extended-release opioid antagonists	↓	NE	A	128	↓	NE	A	128,187	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Opioid agonist treatment	↓	RR 0.53 (0.4,	A	106	↓	RR 0.48 (0.41,	A	106	↓	RR 0.46 (0.32, 0.67)	C	107	↓	RR 0.50 (0.40, 0.63)	C	108	?	-	D	86	↑	SMD 0.29	C	170

	Injecting risk behaviours				Extra-medical opioid use				HIV incidence				HCV incidence				Skin and soft tissue infections				Quality of life			
Intervention	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**
		0.7) SYNTH				0.55) SYNTH																(0.16, 0.42)		
Residential rehabilitation	↓	NE	C	188	↓	NE	C	188	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV testing + informing of serostatus	↓	NE	D[PWID]	135	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV testing + informing of serostatus	×	aOR 0.97 (0.94, 1.00)	C[PWID]	189	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV treatment	×	aOR 0.78 (0.42–1.45)	D	190	-	-	-	-	↓	-	D	134	-	-	-	-	-	-	-	-	-	-	-	-
HCV treatment	↓	NE	D[PWID]	133	↓	NE	D[PWID]	133	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STI treatment	-	-	-	-	-	-	-	-	↓		A[GEN]	191–193	-	-	-	-	-	-	-	-	-	-	-	-
Suicide prevention strategies	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Opioid prescribing limits	-	-	-	-	↓?	NE	D[GEN]	194	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Abuse-deterrent opioid formulations	↓	NE	D	144,195	?	NE	D	144	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prescription opioid monitoring programs	-	-	-	-	↓?	NE	D[GEN]	194,196	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Compulsory drug treatment/ drug detention centres	↑	NE	C*	143,197	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Criminalisation of drug use	↑	NE	C[PWID]	147					↑	NE	C[PWID]	147												

	Overdose				Suicide				Other injuries				Overall mortality			
Intervention	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**	**Effect**	**Size of effect**	**Level**	**Sources**
Provision of sterile injecting equipment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Condom provision	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Naloxone	↓	-	D	198	-	-	-	-	-	-	-	-	-	-	-	-
Drug consumption rooms	↓	-	D	199	-	-	-	-	-	-	-	-	-	-	-	-
Peer-based self-help groups	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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Opioid detoxification alone																
Oral opioid antagonists	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Extended-release opioid antagonists	↓?	-	A	128	-	-	-	-	-	-	-	-	?	-	A	128,187
Opioid agonist treatment	↓	RaRa 0.25 (0.18, 0.36) SYNTH	C	111	↓		E	112	↓		E	112	↓	RaRa 0.33 (0.28, 0.39) SYNTH	C	111
Residential rehabilitation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV testing + informing of serostatus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV testing + informing of serostatus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV treatment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV treatment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STI treatment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medication for suicide prevention	-	-	-	-	?	-	A GEN	200	-	-	-	-	-	-	-	-
Opioid prescribing limits	↓?	-	D GEN	194	-	-	-	-	-	-	-	-	-	-	-	-
Abuse-deterrent opioid formulations	?	-	D GEN	144	-	-	-	-	-	-	-	-	?	-	D	144
Prescription opioid monitoring programmes	?	-	D GEN	145,196	-	-	-	-	-	-	-	-	?	-	D	145
Compulsory drug treatment/drug detention centres	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Criminalisation of drug use	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Notes on codes used in this table

Presence or absence of effect

× This intervention does not appear to have a significant effect upon the outcome

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? unclear evidence on impact of this intervention on the outcome

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D Systematic reviews with inconsistent conclusions from authors or cross-sectional; OR multiple consistent ecological studies

E Cross-sectional association, case series suggesting outcome, single cohort study

GEN Evidence drawn from people who may not specifically use any drugs (including opioids)

PWID People who inject drugs that may not include opioids

ALC Note that this evidence pertains to people attending alcoholics anonymous

NE no pooled quantitative estimate reported

UN**otes on codes used in this table**

Presence or absence of effect

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