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Responding to global stimulant use: challenges and opportunities

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Abstract

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Contributors

MF, ES, LD, RM, and RA drafted the initial outline of the paper.

NKM, AB, JAC, LD, and MF conceived the modelling. AB and JAC did the modelling with supervision from NKM. ES, LTT, RM, JR, LD, ES, and MF reviewed the literature and drafted specific sections of the paper.

ES, RM, LD, MF, MT, and RA contributed specific inputs into drafts of the panels. SS provided critical input to the drafting of the section on interventions and the interpretation of this evidence. MF led the writing of the full draft of the paper. All authors provided substantial critical review of the manuscript and approved the final manuscript.

Declaration of interests

MF and LD have received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma, and Seqirus. RA has received untied educational grants from Reckitt Benckiser/Indivior and Mundipharma for studies of opioid substitution and agonist medication treatments in Australia. NKM has received unrestricted research grants to her university from Gilead and Merck unrelated to this work. MT has received educational grants in Spain from Gilead, Merck Sharp & Dohme, Servier, and Lundbeck unrelated to this work. JR has received educational grants from Lundbeck GmbH. SS has received clinical supplies from Alkermes and Medicinova for randomised trials outside of the submitted work. ES, AB, JAC, LTT, and RM report no competing interests.

We did a global review to synthesise data on the prevalence, harms, and interventions for stimulant use, focusing specifically on the use of cocaine and amphetamines. Modelling estimated the effect of cocaine and amphetamine use on mortality, suicidality, and blood borne virus incidence. The estimated global prevalence of cocaine use was 0·4% and amphetamine use was 0·7%, with dependence affecting 16% of people who used cocaine and 11% of those who used amphetamine. Stimulant use was associated with elevated mortality, increased incidence of HIV and hepatitis C infection, poor mental health (suicidality, psychosis, depression, and violence), and increased risk of cardiovascular events. No effective pharmacotherapies are available that reduce stimulant use, and the available psychosocial interventions (except for contingency management) had a weak overall effect. Generic approaches can address mental health and blood borne virus infection risk if better tailored to mitigate the harms associated with stimulant use. Substantial and sustained investment is needed to develop more effective interventions to reduce stimulant use.

Background

Stimulant drugs are used globally to produce euphoria, increase confidence, sociability, energy, and wakefulness, and reduce hunger. These drugs include a broad spectrum of natural and synthetic compounds (appendix p 4), but cocaine and amphetamines (particularly methamphetamine) have been a focus of attention because of the global scale of their extramedical use and the serious harms related to their use.

Cocaine is a natural product of coca leaves (*Erythroxylum coca* Lam leaves) extracted as a hydrochloride salt or free base (so-called crack cocaine). Amphetamine and methamphetamine are synthetic substances, which are part of the phenethylamine family (N,α-methylphenethylamine)—referred to as amphetamines. Amphetamines and cocaine increase noradrenaline and dopamine neurotransmitter activity and sympathetic arousal. They can be ingested, snorted in powder form, injected, and (when in the form of crack cocaine and crystalline methamphetamine) smoked. Other synthetic stimulants that are used extramedically are discussed by Peacock and colleagues.[1]

This Series paper synthesises evidence on the extent of extramedical use and dependence on cocaine and amphetamines, the associated harms, and the effect of interventions to address these harms. We estimate the excess fraction of deaths associated with stimulant dependence globally and use epidemiological modelling to explore the contribution of stimulant use to harms in people who inject drugs, men who have sex with men (MSM), and transgender (trans) women.

Medicinal uses of stimulants

Cocaine and amphetamine have potential medicinal uses. Amphetamines are prescription medications used to treat narcolepsy, obesity, and attention-deficit hyperactivity disorder along with less potent stimulants (eg, methylphenidate).[2] Prescriptions of stimulants have risen over the past two decades largely for attention-deficit hyperactivity disorder.[2] The medicinal use of cocaine as a local anaesthetic was common in the 19th century,[3] but it has been superseded by drugs with lower dependence liability (appendix p 6).[4]

Epidemiology of extramedical stimulant use and dependence

Substantial variations exist in the global distribution and use of illicitly produced cocaine and amphetamines. The production of cocaine is mainly done in Latin American countries that grow the coca plant, such as Bolivia, Columbia, and Peru. In 2016, global cocaine output reached 1410 metric tonnes, the highest ever estimated (appendix p 7).[5] Cocaine is trafficked from these source countries through transit countries to markets in North America and Europe. Amphetamines (primarily methamphetamine) are manufactured using precursor chemicals in laboratories, so their production is geographically wider. Methamphetamine can be efficiently synthesised from pharmaceutical ephedrine and pseudoephedrine with readily available chemical reagents. Its ease of manufacture has created lucrative burgeoning markets for amphetamines in lower-income countries that have weak regulations on precursor chemicals.[6]

Prevalence of extramedical cocaine and amphetamine use

Cocaine and amphetamines are two of the most widely used illicit drugs worldwide.[7] The 2018 UN Office on Drugs and Crime World Drug report estimated that 18·2 million people (range 13·9–22·9; 0·4% [range 0·3–0·5] of the global population) aged 15–64 years used cocaine and 34·2 million (13·4–55·2; 0·7 [0·3–1·1] of the global population) people aged 15–64 years used amphetamines (appendix p 8).[5] The overlap between these two stimulant-using populations is restricted by geographic disparities in drug availability.

The highest proportion of cocaine use was in North America (1·9% of the population; range 1·86–2·0), South America (0·95% of the population; 0·8–1·0), Oceania (1·7%; no range), and western and central Europe (1·2% of the population; 1·1–1·2; figure 1A). The highest proportion of amphetamine use (including methamphetamine and prescription stimulants eg, dexamphetamine) was in North America (2·0%; 1·7–2·3) followed by Oceania (1·3%; no range; figure 1B). Prevalence estimates are only available for a few countries in southeast and west Asia, but methamphetamine is believed to be one of the most commonly used illicit drugs in these regions.

Analysis by the UN Office on Drugs and Crime[5] of the global changes in drug manufacture and production suggests that cocaine and amphetamine supply and use might be increasing globally. Global cocaine manufacture rose by 56% between 2013 and 2016 (increasing by 25% in 2015–16 alone), and some reports suggest an increase in cocaine consumption in North and South America.[5] The number of global seizures of amphetamine-type stimulants are at their highest ever, increasing by 20% between 2015 (205 tonnes) and 2016 (247 tonnes).[5]

Several specific populations—including MSM, people who inject drugs, sex workers, and people who use stimulants for occupational reasons—have a higher proportion of people that use stimulants than others (appendix p 11).

Prevalence of cocaine and amphetamine dependence

Dependence on the use of stimulants is a major problem for public health. The Global Burden of Disease (GBD) study estimated the prevalence of cocaine and amphetamine dependence at country, regional, and global levels (figure 1C,D; appendix p 12).[8]

Globally, the age-standardised prevalence of amphetamine dependence was 96 per 100 000 population (95% uncertainty interval (UI) 70–128; 7·4 million people [5·4–9·8 million]). For cocaine, it was 64 per 100 000 population (UI 57–71; 5·0 million people [4·5–5·6 million]). The highest estimates of the prevalence of amphetamine dependence were in Australasia and high-income North American countries; cocaine dependence was most prevalent in high-income North American countries.

Polydrug use

People who use stimulants typically use a range of drug types. Cannabis use is very common, as is the use of other stimulants (eg, ecstasy), particularly in recreational settings. Heavy consumption of alcohol is common, which when used with stimulants increases the risk of cardiotoxicity[9] and violent behaviour.[10] The combined use of stimulants and opioids places pressure on the cardiovascular and respiratory systems, and CNS, with unpredictable health outcomes. In the USA, the coinjection of cocaine and heroin (so-called speedballs) and methamphetamine and heroin (so-called goofballs) is common, with 11% of a sample of people who inject drugs recruited in 2011–13 from San Francisco, CA, USA, reporting a goofball injection in the past 30 days.[11] In 2015, the injection of both methamphetamine and heroin over the previous 12 month period (either co-injection or injection on separate occasions) was reported by 50% of a cohort of people who inject drugs in Colorado, USA. This practice of injecting both methamphetamine and heroin was associated was associated with a 2·8 (95% CI 1·7–4·5) times higher risk of overdose in the past 12 months than heroin injection alone.[12]

The combined injection of stimulants and opioids increases exposure to blood borne viruses because it is associated with multiple injections per day and the reuse of syringes.[12] Concern is also increasing about interactions between cocaine, methamphetamine, and fentanyl use because of a rapid increase in fentanyl-related mortality in the USA[13] and Canada.[14] These changing drug use patterns present challenges for harm reduction and treatment, as outlined by Degenhardt and colleagues.[15]

Evidence on the potential effects of stimulants on a range of health harms

Fatal harms

Systematic reviews showed that overall mortality is substantially elevated in people who use amphetamines and cocaine, with an all-cause standardised mortality ratio of 6·83 (95% CI 5·27–8·84) for amphetamines[16] and 6·13 for cocaine (4·15–9·05 [Peacock A, University of New South Wales Sydney, personal communication]; table 1; appendix p 15).

Suicide and overdose are substantial causes of mortality for people that use amphetamines[17] and cocaine.[18,19] Consistent evidence also suggests that stimulant use increases

cardiovascular pathology and mortality, resulting in deaths from acute (eg, acute coronary syndrome, myocardial infarction, aortic dissection, and cardiac arrhythmias) and chronic (eg, coronary artery disease and cardiomyopathy) cardiovascular pathology.[20] Other important causes of mortality in people that use amphetamines and cocaine include accidental injuries (predominantly motor vehicle accidents)[21] and homicide.[22] All these causes of death are highly elevated in people that use cocaine or amphetamines compared with the general population (table 1).

Quantifying effect of stimulant dependence on fatalities

We used the estimates of elevations in mortality risk (table 1) and GBD estimates of the prevalence of amphetamine and cocaine dependence (figures 1C,D), to estimate the excess global and regional burden of deaths associated with stimulant dependence.[23,24] We estimated the fraction of deaths and total number of deaths associated with amphetamine and cocaine dependence in 2017 by region (appendix p 27).

Globally, an estimated 0·58% (95% UI 0·41–0·80) of all-cause deaths were associated with amphetamine dependence and 0·32% (0·21–0·45) with cocaine. This estimate equated to 326 000 (UI 228 000–449 000) excess all-cause deaths associated with amphetamine dependence and 178 000 (119 000–252 000) excess all-cause deaths associated with cocaine dependence in 2017. These estimates do not account for any overlap between stimulant-dependent populations, but more than half of the excess amphetamine dependence deaths occurred in east and southeast Asia where deaths related to cocaine dependence were low (appendix p 29).

The fraction of all-cause deaths associated with amphetamine and cocaine dependence vary from region to region (figure 2; appendix pp 28–30). Amphetamine dependence was associated with a substantially higher proportion of excess mortality in Australasia than other regions. The highest number of excess all-cause deaths associated with amphetamine dependence was in east Asia, high-income North American countries, east and southeast Asia, and western Europe (comprising 74% of all amphetamine-associated deaths, appendix p 29). By contrast, the highest associated fraction and the most excess all-cause deaths associated with cocaine use was in high-income North American countries. 69% of all cocaine-associated deaths occurred in high-income North American countries, western Europe, and Brazil and Paraguay.

Globally, stimulant dependence accounted for an important number of suicides, accidental injuries, cardiovascular disease, and homicide deaths (appendix p 28). Cocaine dependence was associated with 0·65% (95% UI 0·44–0·90) of suicide deaths, 0·24% (0·16–0·33) of accidental injury deaths, 0·14% (0·02–0·35) of cardiovascular deaths, and 0·47% (0·06–1·31) of homicide deaths in 2017. Amphetamine dependence was associated with 1·23% (UI 0·32–3·08) of suicide deaths, 0·59% (0·25–1·14) of accidental injury deaths, 0·48% (0·32–0·69) of cardiovascular deaths, and 1·23% (0·71–1·96) of homicide deaths in 2017.

Non-fatal harms

We assessed the reviews of evidence on the effect of stimulant use on non-fatal health harms (table 2), separately for amphetamines and cocaine (appendix p 109). The evidence on

whether amphetamine or cocaine are linked to injuries and diseases varied by outcome. Some causal relationships were plausible (eg, stroke or myocardial infarction), but no pooled estimate of the magnitude exists.[30] Some of the evidence is difficult to summarise, for example, some studies of injecting risks compare people who inject cocaine or amphetamines with people who inject other drugs, whereas other studies compare people who inject cocaine or amphetamines with the general population. For this reason, the comparisons of health outcomes for amphetamines and cocaine need to be interpreted with caution.

Many of the non-fatal harms of stimulant use (table 2), are acute problems that might result in contact with emergency health-care services and law enforcement, placing substantial burdens on these frontline services.

Dependence upon stimulants is a common non-fatal harm. For example, the lifetime probability of dependence in the USA has been estimated in people who have used either drug as 11% for amphetamines[25] and 16%[26] for cocaine (appendix p 109).

Other harms include elevated risks of stroke, myocardial infarction,[30,31] and respiratory disease.[18,32] People who use stimulants are also at elevated risk of road injury,[21] and those who are intoxicated with stimulants might have altered somatic and risk perception and have a higher risk of being assaulted.[43]

The use of amphetamines[28] and cocaine[18] is associated with double the odds of depression (table 2; appendix p 109). Depressive symptoms are common in people seeking treatment for stimulant dependence.[44] Withdrawal from heavy stimulant use can also precipitate or worsen depression.[45] The mood-elevating effects of stimulant intoxication can lead to a vicious cycle of stimulant self-medication of depressive symptoms. Evidence for an association between cocaine[18] use with anxiety is not compelling and is poor for amphetamines,[28] although panic can occur during acute intoxication.

An association between stimulant use and violent behaviour exists, particularly interpersonal and intimate partner violence.[18,28] These behaviours are biologically plausible because acute CNS stimulants increase sympathetic arousal, which can augment aggression.[46] Chronic exposure to cocaine and amphetamines can also increase the risk of aggression by impairing mood regulation[47] and impulse inhibition.[48] However, the association is complex, the results are inconsistent, and the role of the illicit drug market is debated.[18]

Psychotic symptoms occur in a subset of people who use stimulants. These symptoms are typically transient, occur after chronic heavy use, and feature paranoia (intense suspiciousness) and auditory or visual hallucinations. In systematic reviews people who use amphetamines have double the odds of psychotic symptoms.[28] Estimates of their prevalence in people dependent on cocaine vary considerably, from 7% to 75%.[29] In a systematic review, published in 2018, the most consistent correlates of psychosis in people using methamphetamine were frequency and quantity of use and severity of dependence and polydrug use.[49]

Symptoms of psychosis associated with stimulant use usually abate after the person reduces or stops use.[50] In a minority of people, symptoms persist or recur, suggesting a chronic psychosis. People who have developed psychotic symptoms have been suggested to be more likely to develop psychotic symptoms at reduced drug use if they return to use—so-called sensitisation.[50] Stimulants can exacerbate and precipitate psychotic episodes in people with a diagnosis of schizophrenia.[51]

People who use stimulants have an elevated risk of HIV infection through sexual risk (particularly in MSM[52] and sex workers,[18] although sexual risk might play some role in people who inject drugs) and injecting risk.[35] The potential role of methamphetamine use in facilitating sexual risk in MSM has attracted attention,[52] as has the use of crack cocaine and its association with injecting and sexual risk.[18,35]

People who inject stimulants also have elevated hepatitis C (HCV) prevalence and so do those who use drugs through non-injection routes (probably by sharing other equipment).[53] Both amphetamines and cocaine have been associated with higher risks of sexually transmitted infections.[18,52]

Modelling the effect of stimulant use on non-fatal harms

Given the higher prevalence of stimulant use and associated harms in people who inject drugs[54] and MSM, we undertook mathematical modelling to quantify select health harms associated with stimulant use in these populations. In people who inject drugs (panel 1), we investigated the excess risk of HIV and HCV in people who inject stimulants in three illustrative scenarios (Bangkok, Thailand; Montreal, Canada; and St Petersburg, Russia) with varying patterns of stimulant use, using risk associations (appendix p 109). We found that a disproportionate number of incident HIV and HCV cases in all settings occurred in people who inject stimulants and that stimulant injection was associated with an important fraction of new HIV and HCV cases among people who inject drugs in the next year. For each 10% of the population who inject stimulants, a median of 11–15% of HIV and HCV infections occurred in this group. A median of 5–10% of new HIV and 3–7% of new HCV infections in the next year could be attributed to each 10% increase in the prevalence of stimulant injection.

A separate modelling exercise (panel 2) quantified the excess risk of HIV and suicide in MSM and trans women who use stimulants. Lima, Peru, was used as a test case because stimulant use characteristics in MSM in the city are similar to global estimates (ie, 10% prevalence of recent stimulant use), finding that stimulant-using MSM and trans women shoulder a disproportionate burden of HIV, with more than a third of all suicides in MSM and trans women occuring in this group (panel 2).

Interventions to address stimulant use and related harms

The interventions designed to reduce stimulant use (table 3) and the interventions to reduce harms associated with stimulant use (table 4) have varying effects (appendix p 111).

Psychosocial treatment to reduce stimulant use

The current standard of care for stimulant dependence is primarily psychosocial interventions combined with case management. However, the majority of evidence does not support their effectiveness when compared with treatment as usual. Cognitive behaviour therapy is commonly used to help people reduce their stimulant use, but Cochrane reviews conclude it is no more effective in reducing use than treatment as usual.[74] The same is true of other forms of counselling and interpersonal therapies,[72,74] motivational interviewing,[72] screening and brief intervention,[71] and relapse prevention (table 3).[74] Other psychosocial interventions that have been evaluated (meditation, 12step, supportive psychodynamic expressive therapy, and therapeutic communities) have consistently produced outcomes that do not differ substantially from usual care.[74]

Meta-analytic reviews indicate that contingency management leads to a statistically significantly reduction in stimulant use.[74] Contingency management involves providing non-financial or financial incentives in exchange for evidence (eg, clean urine tests) of abstinence from stimulant use. Nonetheless, contingency management has not been applied in routine care because of substantial opposition from service planners, clinicians, and communities to contingency management. A notable exception is the US Department of Veterans Affairs, which has used contingency management to treat cocaine use disorder with promising outcomes.[112]

Some evidence suggests that adding a community reinforcement approach or cognitive behavioural therapy to contingency management is more effective than contingency management alone.[52] Future work might investigate whether other combinations of psychosocial interventions with contingency management and pharmacotherapy improve outcomes.[113] Residential rehabilitation and inpatient treatment help for those who do not engage with community-based outpatient treatment might complement psychosocial interventions. However, benefits seen following residential rehabilitation are often not sustained,[114] and few patients receive the ongoing support needed to prevent relapse.[115]

Pharmacotherapy and medication to reduce stimulant use

No medications have been approved to treat either cocaine or amphetamine (or methamphetamine) dependence, whether in managing withdrawal, maintaining abstinence, or preventing relapse (table 4). Other psychostimulants (eg, bupropion, modafinil, dexamphetamine, lisdexamfetamine, methylphenidate, mazindol, methamphetamine, mixed amphetamine salts, and selegiline) can produce a small temporary increase in abstinence from cocaine use, but the quality of evidence was classified as very low.[77] These drugs do not reduce the frequency of use in those who continue to use cocaine or improve retention in treatment.[77] Dopamine agonists (amantadine, bromocriptine, L-dopa) also do not reduce cocaine use.[78]

Fewer drugs have been trialled for methamphetamine or amphetamine dependence. Dexamphetamine, bupropion, methylphenidate, and modafinil do not reduce use, craving, or increase abstinence, or retention in treatment.[116] These conclusions are not definitive because of the poor quality of the evidence, including high attrition in trials.[116]

Treatments under investigation include long-acting stimulant medications,[117,118] combination pharmacotherapies,[119] compounds that target brain systems involved in reward learning, and proantioxidant compounds with neuroprotective properties (eg, ibudilast[120] and N-acetyl-cysteine).[121] A trial is exploring the promising early results with the antidepressant mirtazapine.[122,123] Novel compounds like ibudilast and N-acetyl-cysteine bring putative benefits, including lowered risk of toxicity, a low abuse potential and, in some cases, a generic action across different drug classes. This research is in its infancy, with insufficient evidence to support the clinical use of these medications. More trials are also needed to determine if the opioid antagonist, naltrexone, is useful in treating stimulant problems (table 3).[124–126]

Incarceration, compulsory detention, and law enforcement responses

Imprisonment is an added risk for people who use stimulants in most countries. Far too often people with stimulant problems are detained in prisons, or, in some Asian countries, in compulsory drug detention centres.[127] More than 235 000 people who use drugs are said to be detained in more than 1000 centres in several Asian countries.[128] No evidence exists to suggest that compulsory drug detention centres reduce drug use,[82] drug risk behaviours,[83,109,110] or related harms (tables 3, 4). Major infringements of human rights occur within these settings; the number of relapses and reincarcerations are very high after release. Prisons and jails increase risky injecting behaviours and blood borne virus exposure in people who use stimulants.[111] People with a history of incarceration face major challenges in social and vocational integration.

Drug courts are often seen as an alternative to prison and a bridge between the criminal justice and the health-care systems. Drug court evaluations might reduce the number of reimprisonments, but studies are often confounded by participant selection bias. Initial enthusiasm for so-called Swift and Certain Justice Courts (Project HOPE) has been tempered by trials reporting less compelling evidence for effects.[129–131] Police diversion before court has been suggested to avert substantial criminal justice costs and reduce drug use and reoffending, but the evidence supporting this theory is weak.[132] Pathways from the criminal justice system to treatment need to be better evaluated.

Prevention and treatment of blood borne viruses and sexually transmitted infections

Well established, effective interventions exist to reduce blood borne viruses and sexually transmitted infections in people who use drugs generally rather than in people who use stimulants specifically (although globally a third of people who use stimulants primarily administer the drugs through an injection).[54] The evidence on interventions to reduce sexual risks mainly applies to people who are heterosexual and MSM and not those who use stimulants (table 4).

Effective approaches include the provision of sterile injecting equipment through needle and syringe programmes, which reduces injecting risk,[89,90] HIV,[91] and potentially HCV transmission;[40] provision of materials for safer inhalation of drugs, which might reduce

injecting risk behaviour;[95,96] and professionally supervised drug consumption rooms.[94] Testing and treatment of HIV and HCV infections might reduce injecting risk and incidence in people who inject drugs.[103,105]

We examined the potential effect of needle and syringe programmes on HIV and HCV infection in people who inject stimulants (panel 1), finding needle and syringe programmes could ameliorate, but not eliminate, excess injecting-related HIV and HCV transmission in this group. Our results were consistent with empirical findings of insufficient needle and syringe programme coverage for people who inject drugs transitioning to stimulant (methamphetamine) injection.[133] The findings reinforce the urgent need to scale-up needle and syringe programmes for people who inject stimulants and to develop effective novel interventions to reduce risk in this group.

Provision of condoms[85] and pre-exposure prophylaxis (PrEP) for both HIV[101] and sexually transmitted infections[102] reduce sexual risk behaviours, and the transmission of HIV, HCV, and sexually transmitted infections in people who inject drugs and MSM, rather than specifically in people who use stimulants (table 4). Condoms and treatment for infectious diseases will probably prevent blood borne viruses and sexually transmitted infections in people who use stimulants, but who do not inject them as these interventions do in the general population. However, there is a poor understanding of blood borne virus and sexually transmitted infection risk in this context (eg, via pipe sharing and sexual risk behaviour), and of the effectiveness of interventions to mitigate these risks.

Our modelling of people from Lima (panel 2) indicates that prioritising HIV PrEP in MSM and trans women who use stimulants could enhance PrEP prioritisation that is based on sexual behaviour only, or sexual orientation and gender identity. The addition of stimulant use as a criterion guiding PrEP prescription or implementing substance use campaigns might be warranted in MSM and trans women, as has occurred in some settings in Australia and the USA.[134] These contacts might be used to provide brief mental health and suicide prevention advice about the risks of heavy stimulant use.

Interventions to improve the mental health of people who use stimulants

Developing effective responses around comorbid mental health issues is essential because of the high prevalence of the comorbidity and the strong associations between stimulant use and mental health problems. Multiple effective interventions are available (appendix p 139). The use of the interventions is complicated in people who use stimulants because mental health problems can be both premorbid and induced or exacerbated by stimulant use. The implementation and evaluation of the interventions is an essential area for further research because very few mental health interventions have been evaluated in people with stimulant dependence.

Acute psychoses can be treated effectively with antipsychotics, but there is only a small amount of evidence regarding the effectiveness of antipsychotics in managing acute stimulant psychosis.[135] No evidence is available regarding whether antipsychotic prophylaxis is safe and effective in people who use stimulants who have recurrent episodes

of psychosis. These patients are often excluded from mainstream services for psychotic disorders because of their comorbid stimulant dependence.

Managing agitation and violence in stimulant-induced psychoses is a substantial challenge for frontline emergency medical and police services. This risk of violent behaviour has an immediate, but unquantified adverse effect on family and peers. More research is needed on the effectiveness of protocols to reduce agitation related to stimulant intoxication and to manage violence risk more generally.[136] Punitive responses to aggressive or violent behaviour within clinical services can exclude people who use stimulants from treatment and perpetuate their engagement with the criminal justice system. Therefore, treatment needs to be delivered in ways to reduce the risk of violent behaviour.

Evidence-based strategies to reduce depression include psychological therapies (cognitive behavioural therapy, contingency management, acceptance and commitment therapy, and meditation-based therapies; appendix p 133). Cognitive behavioural therapy can also reduce suicide risk in people who use drugs[137] and it is effective for depression.[138] Antidepressant drug therapy reduces depression in people who use cocaine,[79] but it does not reduce stimulant use and some antidepressants are contraindicated for methamphetamine dependence.[139] Substitution therapies (including dopamine agonists) do not relieve depression in people who are dependent on stimulants.[77,78,80]

Interventions to prevent and treat overdose, injuries, and other harms

Harm reduction approaches to reducing risky stimulant use and the harms of acute intoxication are not well evaluated (table 4). Common strategies include providing information and education about avoiding rapid-onset routes of administration (such as smoking and injecting), limiting the quantity and frequency of stimulant use, identifying early signs of stimulant psychosis (eg, illusions and persecutory ideation), general advice on risk assessment (eg, drug driving), and tips on general health (eg, sleep hygiene, diet, and dental health).

Overdose prevention approaches to stimulants emphasise awareness of drug strength and avoiding high-dose toxicity complications, such as seizures, by reducing dose. No substantial attention has been given to reducing accidents and injuries, nor to reducing cardiovascular risk in this population (appendix p 139).

Challenges and future considerations

Responses to the growing global problems related to the illicit use of stimulants have often been modelled on services for problem opioid use. These provide a poor basis for responding to stimulants whose consumers can be difficult to engage and when many services are not equipped to manage acute stimulant problems. The development of evidence-based forms of care is urgently needed.

The absence of an effective policy response to the scale and severity of harms related to stimulant use, combined with the fear and stigmatisation of so-called problem users, has restricted the allocation of resources to reduce stimulant-related harms. Insufficient long-

term investment into the development and implementation of evidence-based treatment strategies have been made, with an over-reliance on law enforcement. Globally, and particularly in the Asia-Pacific region, policy has been dominated by incarceration, with an estimated 235 000 people detained in compulsory drug detention centres in which major infringements of human rights occur.

A key challenge for policy is the absence of readily implementable effective interventions to reduce long-term stimulant use and dependence. Contingency management is the only treatment with robust evidence of effectiveness, but it has not been widely implemented. A need exists to identify and remove barriers to using this approach and assessing its acceptability and effectiveness in clinical settings.

Effective pharmacotherapies are needed. Trials designed to overcome high attrition and poor adherence are needed to develop a better evidence base. Study inclusion criteria need to be more pragmatic and researchers should engage with people who use stimulants to ensure that trial methods are feasible and outcome measures are relevant and realistic.

Replacement psychostimulant therapies have a small benefit in treating cocaine dependence, but the quality of evidence for this approach is very low so substantial caution is warranted before its widespread application.

Most people who use stimulants have little contact with treatment services, and these services do not always provide respectful, tailored, and specific treatment (panel 3). Major barriers to seeking help include stigma, low perceived need to reduce use, self-medication of poor mental health, and concerns about confidentiality. The design of treatment and other health services should respond to the needs and experiences of people who use stimulant drugs (eg, by being available in acute care settings where people who use stimulants are over-represented).

Effective ways to reduce some of the harms of heavy or dependent stimulant use, such as psychosis, depression, suicide, and blood borne virus risks, do exist. Effective ways for mainstream approaches to mitigate stimulant-related harms are urgently needed. A greater focus on the prevention and treatment of these harms might improve the overall outcome for stimulant problems. Our modelling studies emphasise the need for an integrated response to reduce HIV and HCV infection in people who inject drugs, and HIV infection and suicide in MSM. In these populations, needle and syringe programmes, HIV antiretroviral treatment and PrEP, HCV treatment, and mental health care are needed to reduce the full range of harms. This integrated strategy is well suited for people who use stimulants because they can often require interventions from a range of specialties, such as behavioural science, infectious diseases, primary care, psychiatry, and social work.

A community approach requires a broader ambulatory care system of services that provide screening, early intervention, primary care, community interventions, criminal justice programmes to divert people into treatment, and prison-based treatment programmes. Community-based day programmes are essential before and after residential treatment to maximise residential treatment capacity and effectiveness. Overall, service users derive benefits from residential treatment, but its effects are often hard to sustain over time.

Engagement with people who use stimulants needs to be improved (including people who inject drugs) to deliver effective harm reduction interventions. More innovative approaches and evaluations are needed to produce better ways for justice and health services to work together. These approaches need the strong engagement of people who use drugs, family, and community engagement if they are to be sustainable.

This Series paper has focused on stimulants; many people who take stimulants use multiple substances, including alcohol. An overlap exists between people who use opioids and those who use stimulants, particularly in people who inject drugs. We need to better understand how stimulant use (administered through injection and non-injection pathways) in combination with opioid use affects the risk of transmitting blood borne viruses (eg, pipe sharing and skin picking), sexually transmitted infections (eg, increased libido), and endocarditis. Heavy concurrent cannabis use might increase the risk of mental health harms, particularly psychosis, and concurrent use of stimulants with sedatives might alter the effects of intoxication and increase risks of injury or violence.

Research investment needs to be strategically focused on developing cost-effective interventions that can be delivered to scale and in a sustainable way within a community health-care and social-care system. Access and delivery of psychosocial interventions at every stage of the evolution of stimulant drug use needs to be broadened. Existing clinical interventions focus on the importance of self-help and family support. Broader community-based intervention approaches that incorporate primary care and other opportunities for early intervention and that engage communities, peers, families, and other key stakeholders need to be adopted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

- Problems arising from stimulant use continue to grow globally, presenting major challenges to health and justice services in many parts of the world. These problems require sustained and comprehensive strategies to reduce mortality and non-fatal harms (poor mental health, violence, injury, sexually transmitted infection and blood borne virus risk, and harm to the fetus).
- People who use stimulants have a six times higher risk of mortality, accounting for approximately 326 000 excess deaths associated with amphetamine dependence and 178 000 associated with cocaine dependence in 2017.
- Modelling indicates an additional 3–10% of new HIV and Hepatitis C virus infections in people who inject drugs in the next year could be attributable to each 10% increase in the prevalence of stimulant injection. Comprehensive harm reduction approaches are needed to reduce these risks.
- The risks for suicide, psychosis, depression, and violence are significantly elevated. Evidence-based approaches for these mental health harms need to be tailored to, and effectively delivered to, people who use stimulants.
- Psychosocial interventions other than contingency management have weak and non-specific effects on stimulant problems and there are no effective pharmacotherapies. Substantial research investment is needed to develop more effective, innovative, and impactful prevention and treatment.
- The acute disruption caused by the more severe problems associated with stimulant use produces fear and stigma in the community, hindering access to health care for people who use stimulants and reducing capacity to deliver structured and effective responses.
- Many governments rely on punitive responses, such as involuntary detention in drug centres, despite the absence of evidence for their effectiveness and their potential to increase harm.

Panel 1:

Stimulant injection and transmission of HIV and hepatitis C virus (HCV) in people who inject drugs

Given the associations between stimulant injection and HIV and HCV infection (table 2), syringe sharing,[55–59] and sexual risk in people who inject drugs, these associations were used to estimate the contribution of stimulant injection to HIV and HCV transmission in people who inject drugs across different scenarios with varying stimulant injection prevalence and predominant type (cocaine or amphetamine). Our dynamic modelling (appendix p 27) explored the potential contribution of stimulant injection to HIV and HCV epidemics in three illustrative scenarios (Bangkok, Thailand; Montreal, QC, Canada; and St Petersburg, Russia) selected to mimic settings with different stimulants injected and varying prevalence of stimulant injecting in people who inject drugs. All scenarios exhibit a high burden of HCV (73–93% seroprevalence), but varying prevalence of HIV. For these analyses, we simulated increased injecting and sexual risk in people who inject stimulants, calibrating these excess risks to elevated HIV incidence and HCV prevalence in people who inject stimulants by stimulant type obtained from our global review (appendix p 109). The HIV incidence rate ratio for people who inject amphetamine is 3·0 (95% CI 2·2–4·1) and 3·6 (2·8–4·7) for people who inject cocaine; additionally, the HCV odds ratio for people who inject amphetamine is 2·4 (1·3–4·4) and is 2·9 (2·5–3·4) for people who inject cocaine. We note each setting has published associations between stimulant injecting and HIV or HCV, or both, consistent with global estimates.[55,60–63]

Modelling based on these associations suggests that people who inject stimulants shoulder a disproportionate burden of new HIV and HCV infections (for each 10% of people who inject stimulants, a median 11–15% of incident HIV and HCV infections occur in this group in the next year). Additionally, a median additional 5–10% of new HIV and 3–7% of new HCV infections in the next year could be attributable to the excess risks associated with each 10% increase in prevalence of stimulant injection. Overall, across the three illustrative scenarios, stimulant injection risks could be associated with a median 13–32% of new HIV cases and 9–24% of new HCV cases in people who inject drugs in the next year (appendix p 44). These findings were robust to sensitivity analyses with lower HCV prevalence and differing turnover assumptions for stimulant injection (appendix p 27).

Our reviews indicated needle and syringe programmes can protect against HIV and HCV risk (table 4), but modelling from these associations indicates that scaled-up needle and syringe programmes for people who inject stimulants can ameliorate, but not eliminate, excess risks. If high coverage needle and syringe programmes (defined as when people who inject drugs receive one or more sterile syringes for each injection) were increased to a 60% coverage of people who inject stimulants in each of these scenarios, this could reduce overall HIV incidence by 27–69% and HCV incidence by 8–11% in 10 years, but in all scenarios incidence in people who inject stimulants would still exceed that currently observed in people who inject other drugs.

These scenarios emphasise the important role stimulant injection contributes towards HIV and HCV epidemics. Indeed, we could underestimate the effect of stimulant injecting as we neglect potential excess risk associated with polysubstance injection. Additionally, our results emphasise the urgent need for scale-up of harm reduction interventions targeting people who use stimulants and inject drugs, such as needle and syringe programmes, and the development of effective novel interventions to reduce risk in people who inject stimulants.

Panel 2:

HIV and suicide among stimulant using men who have sex with men (MSM) and transgender (trans) women

Stimulant use is more prevalent in MSM and trans women compared with heterosexual and cisgender men (appendix p 11). Stimulant use has been associated with increased frequency of unprotected anal sex and risk of HIV infection[64,65] (table 2), although causality is not well established. Rather, engagement in stimulant use and participation in higher risk sexual behaviours are considered to co-occur within a broader risk environment. In MSM and trans women, stimulant use has also been associated with increased suicide ideation and attempts,[66,67] supporting global findings of increased suicide mortality in people who use stimulants (table 1). On the basis of these findings, we used an epidemic model of HIV transmission and suicide in MSM and trans women in Lima, Peru[68] (differentiating homosexual from heterosexual and bisexual, self-identified MSM, male sex workers, and trans women) to quantify the contribution of MSM and trans women who use stimulants to HIV and suicide incidence and to estimate the effect of prioritising HIV pre-exposure prophylaxis (PrEP) for MSM and trans women who use stimulants (appendix p 27). We chose Peru as a useful case study, given the strong data available on HIV and drug use in MSM and trans women, and also because stimulant use characteristics in Lima are similar to global estimates in MSM. For example, in Lima, 6–24% of MSM and trans women (varying by subgroup) report stimulant use (mostly cocaine) in the past 3 months, similar to other high-income countries (appendix p 47). Like many MSM and trans women populations worldwide, the prevalence of HIV in Lima is high (13% in MSM and 27% in trans women), and, based on the 2011 Peruvian MSM and trans women HIV Surveillance Survey, stimulant use is associated with an increased risk of unprotected sex during the last encounter (rate ratio 1·35 [95% CI 1·17–1·57]). According to the first Peruvian national household LGBTI survey,[69] 24·5% of young people (aged 18–29 years) who are part of the LGBTI community have attempted suicide or had suicide ideations. However, data on suicide mortality in MSM and trans women are scarce, including Peru, so we represented the increased risk of suicide mortality in MSM and trans women who use stimulants based on the global review (standardised mortality ratios 6·26 [2·84–13·80]; table 1).

Modelling based on these associations indicates that despite the fact that MSM and trans women who use stimulants comprise an estimated 9·5% (95% CI 7·8–11·5) of the overall MSM and trans women population in Lima, our model estimated that, in the next year, 11% (2·5–97·5% interval (I): 10–13%) of new HIV infections and 39% (95% I 18–60%) of suicides would occur in MSM and trans women who use stimulants. Scaling up PrEP in all (100%) MSM and trans women who use stimulants in each group would prevent 19% (95% I 11–31%) more HIV infections across 10 years compared with covering the same proportion of MSM and trans women in each group, but without prioritising those who use stimulants. These findings suggest that MSM and trans women who use stimulants experience a disproportionate burden of HIV infection and suicide, and that prioritising PrEP on the basis of stimulant use, in addition to sexual behaviour, or gender identity criteria, could increase its effect. Importantly, as the world moves towards

integration of HIV services, providing comprehensive and integrated substance use, mental health, and HIV care could address the multiple harms in MSM and trans women who use stimulants.[70]

Panel 3:

Perspectives of people who use stimulants

These perspectives were submitted in response to an email, circulated between March and June 2019 on our behalf by researchers and peer-based organisations, inviting input from people from various regions of the world with lived experience of using drugs.

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

"A large proportion of drug use is recreational and not problematic apart from legal issues with illicit drug use", (man, aged 58 years, Australia)

"I liked the rush, and now I do it [use crystal meth] out of need…. Crystal [meth] helps me to re-energise, to feel freer, and able to speak without fear. We are just like them, we deserve the same respect.… It is easy to judge other people but they do not know the problems that each one [person] carries", (man, aged 53 years, Mexico)

What changes have you seen in the types of drugs people are using and how they are using them?

"The popularity of ice (crystal methamphetamine) is something new. There were always Speed Heads, but with the sheer amount of product coming onto the market I guess… [the] scene has changed.… Ice changed everything; it has changed the culture of drug use and how people behave", (man, aged 48 years, Iran)

"Crystal [meth]—sometimes it is stronger and sometimes weaker. Right now it is stronger. It changes colour; white, yellow, dark grey. Right now it is good", (man, aged 36 years, Mexico)

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?

"Huge gaps! Drug treatment facilities are notoriously difficult to access, huge burden of bureaucracy, usually create huge barriers to access services. Services need to value and prioritise peer and lived experience… and total abstinence should not be seen as the only goal", (woman, aged 36 years, Australia)

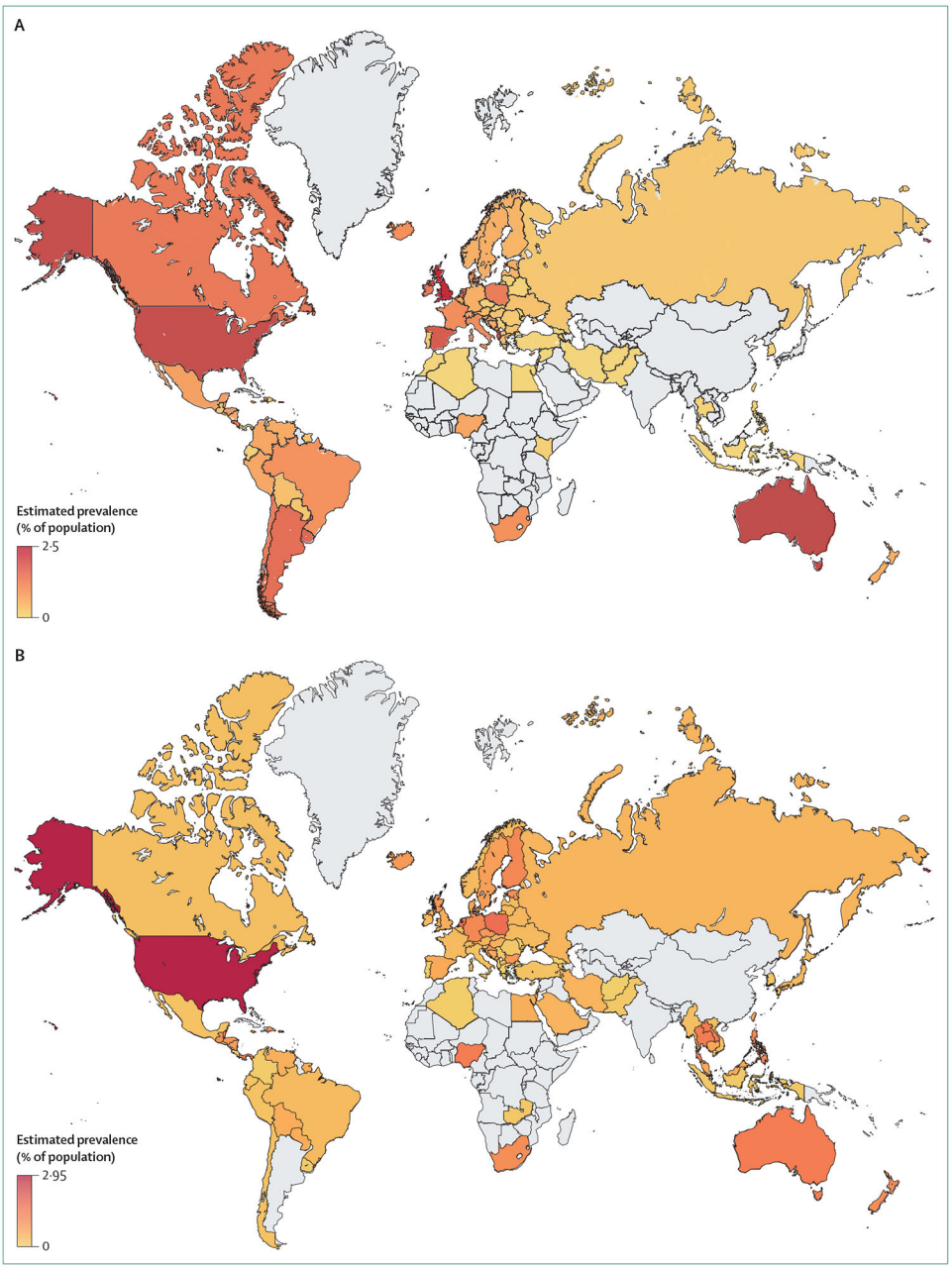
"Despite all the hysteria in the mainstream media… we [society] do not even have any pharmacotherapy programmes for people wanting to stop or reduce their ice usage. Rehabilitation services are hardly comprehensive and many adhere to the tired, old abstinence dogma and a just say no mantra. The gaps in services are massive.

At least for opioid users there is methadone or buprenorphine", (man, aged 60 years, USA) "The major gap is when we stop using. There is no support, no understanding of what we need to get back to society. We are left out, so we get back in the cycle of using and stopping", (man, aged 48 years, Iran)

How can people who use drugs and other stakeholders work together to improve health and harm reduction for people who use drugs?

"Services, governments, and other stakeholders need to work with drug users to more comprehensively assess needs", (woman, aged 52 years, Australia)

"There are many educated people, like doctors, and the way they talk to you, very harshly and without respect, they forget to say please. An educated person must have respect for others regardless of how they look, no matter whether they are wearing a tie or not", (man, aged 53 years, Mexico)



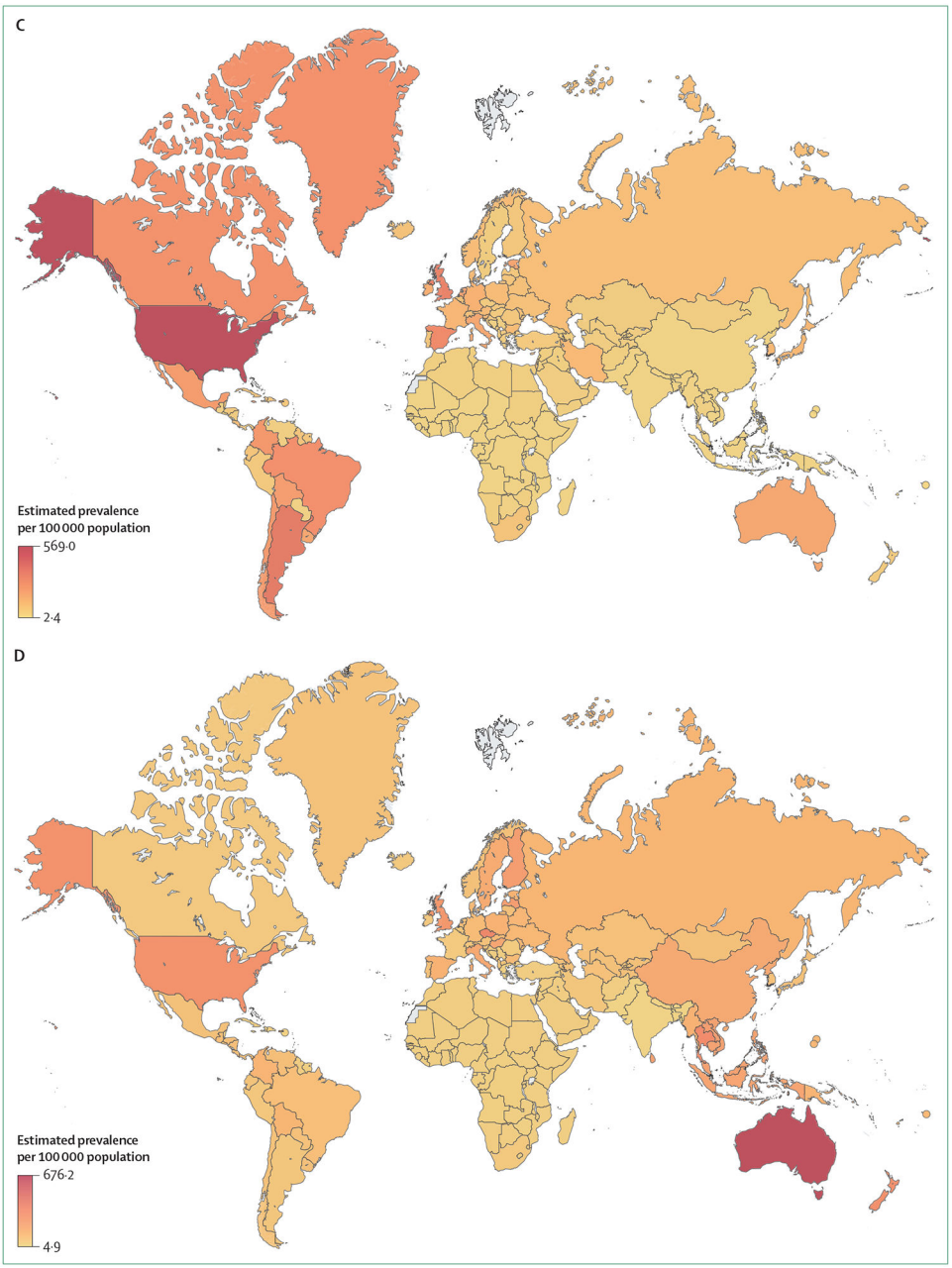


Figure 1: Prevalence of (A) cocaine[6] and (B) amphetamine[6] use and estimated age-standardised prevalence of (C) cocaine[8] and (D) amphetamine[8] dependence per 100 000 population

Drug use data from the UN Office on Drugs and Crime World Drug Report 2018.[6] For methods used to generate these estimates see appendix p 8. Drug dependence data from the Global Burden of Disease study 2017.[8]

For methods used to generate these estimates see appendix p 12. No prevalence estimates have been reported by the UN Office on Drugs and Crime for grey countries. Amphetamines estimates include use of prescription stimulants.

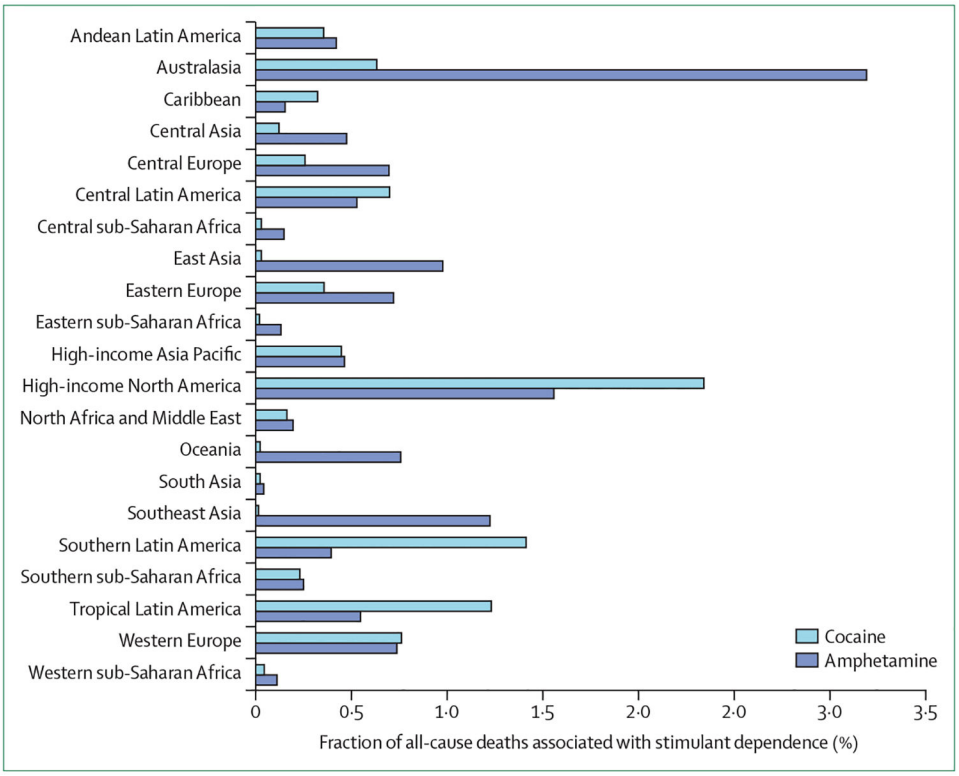


Figure 2: Fraction of regional all-cause deaths associated with cocaine and amphetamine dependence in 2017

For methods used to generate these estimates see appendix p 27.

Table 1:

Summary of causes of mortality summarised across cohorts of people with regular or problematic amphetamine or cocaine use

	Amphetamines[16]		Cocaine*	
	Crude mortality per 100 patient-years	**Standardised mortality ratio**	**Crude mortality per 100 patient-years**	**Standardised mortality ratio**
Suicide	0·20 (0·07–0·55)	12·20 (4·89–30·47)	0·07 (0·04–0·10)	6·26 (2·84–13·80)
Drug poisoning	0·14 (0·06–0·34)	24·70 (16·67–36·58)	0·34 (0·10–1·15)	NA
Accidental injury	0·20 (0·08–0·47)	5·12 (2·88–9·08)	0·09 (0·04–0·22)	6·36 (4·18–9·68)
Cardiovascular	0·13 (0·06–0·29)	5·12 (3·74–7·00)	0·13 (0·07–0·24)	1·83 (0·39–8·57)
Homicide	0·03 (0·02–0·06)	11·90 (7·82–18·12)	0·09 (0·01–0·54)	9·38 (3·45–25·48)
All-cause	1·14 (0·92–1·42)	6·83 (5·27–8·84)	1·24 (0·86–1·78)	6·13 (4·15–9·05)

NA=not applicable.

*Peacock A, University of New South Wales Sydney, personal communication. For details of the search strategies used see appendix p 15.

Table 2:

Evidence for potential causal impacts of amphetamine and cocaine use on a range of non-fatal health harms

	Amphetamines		Cocaine	
	Effect	**Level of evidence**	**Effect**	**Level of evidence**
Substance use				
Dependence	Increase	B[25]	Increase	B[26]
Non-fatal overdose and poisoning	Increase	C[17]	Increase	C[27]
Mental health				
Depression *	Increase	D[28]	Increase	B[18]
Anxiety	Unclear	D[28]	No effect	B[18]
Psychosis	Increase	E[28]	Increase	C[29]
Violence *	Increase	D[28]	Potential increase †	E[18]
Physical Health				
Stroke and myocardial infarction	Increase	C[30]	Increase	C[31]
Respiratory and lung disease	Increase	C[32]	Increase	C[18]
Skin and soft tissue infection	Increase	B[33]	Increase	B[33]
Bloodborne viruses and sexually transmitted infections				
HIV	Increase	B[17,34,35]	Increased ‡	B[18,35]
Hepatitis C virus	Increase §	C[36,37]	Increase	B[18]
Sexually transmitted infections	Unclear	C[8,38–40]	Increase	B[18]
Other harms				
Non-fatal Injury	Increase	B[21]	Potential increase	B[21]
Neonatal outcomes	Increase	B[41]	Increase	B[18]
Parkinson's disease	Increase	C[42]	Unknown	..

Level of evidence: B=findings across cohorts, representative, population-based. C=findings across cohorts of people who use drugs. D=findings across cross-sectional studies, representative population-based, or case-control studies. E=cross-sectional associations among non-representative samples of people who use drugs, case series suggesting outcomes.

* Any use versus no use of amphetamine or methamphetamine.

† Increased for injecting cocaine use; results for other cocaine use not consistent.

‡ Effect in female sex workers and people who inject drugs.

§ Effect in people who inject drugs.

Table 3:

Summary of the evidence of interventions to reduce stimulant use

	Effect	Size of effect	Level of evidence
Screening and brief intervention	No effect	IRR 0·97 (0·77 to 1·22)	B[71]
Motivational enhancement therapy (also known as motivational interviewing)	No effect	RR 1·16 (0·95 to 1·42)	B[72]
Self-help interventions	No effect	Hedges' g 0·13 (−0·05 to 0·31)	A[73]
Self-help interventions involving peers	No effect	OR 0·75 (0·30 to 1·86)	A[74]
Peer-based support groups (12-step programmes, and NA)	Potential decrease	Insufficient evidence	B [*][75]
Cognitive behaviour therapy	No effect	OR 1·17 (0·79 to 1·74)	A[74]
Family interventions, multisystemic therapy	Potential decrease	NE	B[76]
Contingency management	Decrease	OR 2·22 (1·59 to 3·10)	A[74]
Community reinforcement approach	No effect	OR 2·10 (0·67 to 6·59)	A[74]
Acceptance and commitment therapy	No effect	Compared with CBT RR 0·73 (0·26 to 2·07)	B[72]
Meditation-based therapies	No effect	OR 1·37 (0·48 to 3·93)	A[74]
Psychostimulant drugs	Decrease	RR 1·36 (1·05 to 1·77)	A[77]
Dopamine agonists	No effect	OR 1·12 (0·85 to 1·47) [†]	A[78]
Antidepressants	No effect	OR 1·22 (0·99 to 1·51) [†]	A[79]
Antipsychotics	No effect	OR 1·30 (0·72 to 2·33) [†]	A[80]
Therapeutic communities	No effect	RR 1·05 (0·87 to 1·27) [†]	C[81]
Compulsory drug treatment	No effect	Very low-quality evidence; likely to not be effective [†]	C[82]
Compulsory drug detention centres	No effect	Very low-quality evidence; likely to not be effective [*]	C[83]
Other law enforcement interventions (drug courts)	Unclear	OR 1·49 (0·88 to 2·53) [‡]	D[84]
Criminalisation of drug use	..	..	..

IRR=incidence rate ratio. RR=rate ratio. OR=odds ratio. NA=not applicable. CBT=cognitive behavioural therapy. NE=no pooled quantitative estimate reported. Level of evidence: 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 with some inconsistent conclusions from authors; or multiple consistent ecological studies, or cohort studies. D=cross-sectional association, case series suggesting outcome, single cohort study.

[*] Evidence from people with substance use problems not necessarily stimulants.

[†] Evidence specifically for cocaine.

[‡] Evidence specifically for amphetamines.

Table 4:

Summary of the evidence of interventions to reduce stimulant related harms

	Injecting risk behaviours			HIV incidence			HCV incidence			Sexually transmitted infections			Overdose		
	Effect	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**
Condom provision	..	..	..	Decrease	RR 0·29 (0·20–0·43)	A *[85,86]	Unclear	NE	C[87]	Decrease	NE	C †[88]	..	..	..
Provision of sterile injecting equipment	Decrease	aOR 0·52 (0·32–0·83)	A †[89,90]	Decrease	OR, HR, or RR 0·42 (0·22–0·81)	C †[91]	Potential decrease	OR 0·77 (0·38–1·54)	C †[40]	..	..	..	Decrease	NE	D †[92]
Drug consumption rooms	Decrease	RR 0·31 (0·17–0·55)	C †[93]	Unclear	NE	D †[94]	Unclear	NE	D *[94]	..	..	..	Decrease	NE	D †[92]
Use of safe inhalation methods	Decrease	NE	C †[95,96]	..	..	..	..	..	..	..	..	..	..	..	..
HIV testing and informing of serostatus	Decrease	NE	D †[97]	..	..	..	..	..	..	..	..	..	..	..	..
HCV testing and informing of serostatus	No effect	NA	C †[98]	..	..	..	..	..	..	..	..	..	..	..	..
PrEP for HIV for MSM	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
PrEP for HIV for PWID	No effect	NA	B †[99,100]	Decrease	48·9% (9·6–72·2)	B †[101]	..	..	..	No effect	NA	B †[99,100]	..	..	..
PrEP for sexually transmitted infections	..	..	..	..	..	..	..	..	..	Decrease	OR 0·27 (0·09–0·83)	B †[102]	..	..	..
HCV treatment	Decrease	NE	D †[103]	..	..	..	..	..	..	..	..	..	..	..	..
HIV treatment	No effect	aOR 0·78 (0·42–1·45)	D †[104]	Decrease	NE	D †[105]	..	..	..	..	..	..	..	..	..

	Injecting risk behaviours			HIV incidence			HCV incidence			Sexually transmitted infections			Overdose		
	Effect	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**	**Effect**	**Size of effect**	**Level of evidence**
Sexually transmitted infection treatment	..	..	..	..	..	..	..	..	..	Decrease	NE	A*[106–108]			
Compulsory detention centres	Increase	NE	D†[83,109,110]	..	..	..	..	..	..	..	..	..	..	..	..
Criminalisation of drug use	Increase	NE	C†[111]	Increase	NE	C†[111]	..	..	..	..	..	..	..	..	..

Values in parentheses are 95% CI. Levels of evidence: 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 with some inconsistent conclusions from authors; or multiple consistent ecological studies, or cohort studies. D=cross-sectional association, case series suggesting outcome, single cohort study. HCV=hepatitis C virus. RR=rate ratio. NE=no pooled quantitative estimate reported. aOR=adjusted odds ratio. OR=odds ratio. HR=hazard ratio. NA=not available. PrEP=pre-exposure prophylaxis. MSM=men who have sex with men. PWID=people who inject drugs.

*Evidence drawn from people who might or might not have a substance use disorder.

†Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically.