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Mental Disorders and Illicit Drug Use Expert Group

Louisa Degenhardt and Wayne Hall

Illicit drugs as risk factors: some definitions

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1 Introduction

For the Global Burden of Disease (GBD) study, illicit drug use is treated as a risk factor for disease and injury. The GBD defines risks according to the following considerations:

- Risk factors should be potentially modifiable;
- Risks should be assessed irrespective of their place in a causal chain or scientific discipline that has traditionally analysed the risk factor, as long as evidence of causal effect can be established;
- Risks are defined so as not to be too broad (e.g. diet or environment as a whole) or too narrow (e.g. every single fruit and vegetable or every toxicant in tobacco smoke) so as to allow a relatively specific definition of risk factor exposure;
- Protective as well as hazardous factors are considered. However, the absence of a specific intervention should not be assessed as a risk factor, but rather in measurement of intervention coverage and effectiveness; and
- There are sufficient epidemiological data on risk factor exposure and risk-factor disease relationships.

2 Exposure variable for illicit drug use in the GBD

Illicit drug use includes the non-medical use of a variety of drugs that are prohibited by international law, namely: amphetamine-type stimulants,[1] cannabis,[2] cocaine,[3] heroin[4] and other opioids,[5] and MDMA (ecstasy).[6] The use of these legally proscribed psychotropic substances appears to be increasing in many parts of the world but it has been difficult to quantify the rate of increase because this behaviour is often hidden. Estimates of the contribution that illicit drug use makes to the burden of disease need to be made because there is evidence that it produces substantial loss of life and disability[1].

The risk of premature mortality and morbidity from illicit drug use is dependent on dose, frequency and route of administration. Consequently, it is necessary to define what is meant by "use" when defining the exposure variable "illicit drug use". The mortality risks of illicit drug consumption increase with increasing frequency and quantity of consumption [2]. Simple prevalence estimates of the proportion of the population that have *ever* used an illicit drug are likely to be associated with a low average mortality risk since a single occasion of use and infrequent use, the most common patterns of use reported in population surveys, are associated with a small increase in mortality. More accurate estimates of the burden of disease attributable to illicit drugs require estimates of the prevalence of the most hazardous patterns of illicit drug use. These are most commonly found among dependent drug users who typically inject drugs daily or near daily over periods of years. This pattern of use exposes users to the highest chance of fatal overdose [3] and of contracting blood borne viral diseases [4].

The World Health Organization (WHO), following the International Classification of Disease, defines problem drug use as "harmful drug use" and "drug dependence".

[1] Amphetamine-type stimulant (ATS): one of a class of sympathomimetic amines with powerful stimulant action on the central nervous system.

[2] Cannabis: a generic term for preparations (e.g. marijuana, hashish and hash oil) derived from the *cannabis sativa* plant.

[3] Cocaine: an alkaloid central nervous system stimulant drug that is derived from the coca plant.

[4] Heroin: an opioid drug derived from the opium poppy.

[5] Opioids: generic term applied to derivatives from the opium poppy, their synthetic analogues, and compounds synthesized in the body, which act upon the opioid receptors in the brain. They have the capacity to relieve pain and produce a sense of euphoria, as well as cause stupor, coma and respiratory depression.

[6] MDMA: 3,4 methylenedioxymethamphetamine, a synthetic drug that is used as a stimulant.

Harmful drug use is defined by clear evidence that the substance use is responsible for physical (e.g. organ damage) and psychological harm (e.g. drug-induced psychosis). Drug dependence, as defined in ICD-10, requires the presence of three or more indicators of drug dependence [5]. These include: a strong desire to take the substance; impaired control over the use; a withdrawal syndrome on ceasing or reducing use; tolerance to the effects of the drug; requiring larger doses to achieve the desired psychological effect; a disproportionate amount of the user's time is spent obtaining, using and recovering from drug use; and the user continues to take the drugs despite associated problems. The problems should have been experienced at some time during the previous year for at least one month.

The United Nations Office on Drugs and Crime (UNODC) identifies "problem drugs" based on "the extent to which use of a certain drug leads to treatment demand, emergency room visits (often due to overdose), drug-related morbidity (including HIV/AIDS, hepatitis etc.), mortality and other drug-related social ills" [6].

Most prevalence estimates vary with the assumptions made and the methodology employed to estimate prevalence. Data provided by the UNODC[7] do not have the same reliability as large-scale household surveys of the type generally conducted in developed countries. Unfortunately the expense of conducting such surveys makes their use in many developing countries unfeasible. Even if such surveys were feasible in all countries, it is generally accepted that surveys probably underestimate the prevalence of the most harmful patterns of illicit drug use [8].

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has invested considerable resources in developing methods for the collection of data on the prevalence of harmful illicit drug use that are both valid and comparable [9]. Although these standards have been developed for use within the European Union, the global adoption of such standards may greatly improve estimates of drug-related harm. The EMCDDA defines "problem drug use" as **injecting drug use (IDU) or long duration or regular use of opioids, cocaine or amphetamines** [10]. I

In the previous comparative risk assessment exercise, there was no estimation of cannabis use as a risk factor for disease burden [11]. **Regular (weekly+) or dependent cannabis use** will be considered in the estimates made for the CRA exercise for cannabis.

2.1 Illicit drug types not included in the GBD study

Estimating the contribution that MDMA (ecstasy), hallucinogenic substances and inhalants make to premature mortality presents special problems [12]. Although there are case reports of deaths associated with MDMA intoxication [13-15] these appear to be rare, by comparison with overdose deaths due to opioids and cocaine in developed societies with a moderate prevalence of illicit drug use and good mortality data, such as, Australia [16]. There is also continuing controversy about the nature and significance of any MDMA dependence syndrome, and there is no specific MDMA dependence syndrome currently classified in the American Psychiatric Association or the ICD.

The illicit use of licit pharmaceuticals (e.g. benzodiazepines) and anabolic steroids have also been excluded from further analysis because difficulties in measuring (a) the prevalence of their harmful use; and (b) mortality attributable to their use preclude the calculation of relative risks. A review of mortality related to benzodiazepine was undertaken [17] and a separate discussion paper written on the decision to drop this drug class from GBD estimates (both may be downloaded or requested from: www.gbd.unsw.edu.au). Similarly, the failure to include solvents stems largely from a lack of good evidence on the prevalence and extent or harms attributable to such use.

The failure to include these drugs in our estimates of burden of disease attributable to illicit drugs reflects our ignorance; it does not imply that the use of these drugs is without risk to users.

3 Counterfactual exposure distribution

The *theoretical* minimum counterfactual exposure distribution is zero illicit drug use. There may be countries in the world that can truly claim to have zero illicit drug use but there must be few of these now. Even countries that have the policy aim of achieving a drug-free society, such as Sweden, do not have zero illicit drug use. Arguably, once illicit drug use and dependence have appeared in a society, it is unrealistic to expect to be able to return to a zero level of illicit drug use. It may be reasonable to aim to reduce the prevalence of some types of illicit drug use and to minimize the harm that their use causes.

One approach to defining a *plausible* counterfactual exposure would be to use developed countries with the lowest prevalence of illicit drug use as the basis for the estimate. Countries like Finland and Sweden may be suggested as examples. The weakness with this strategy is that illicit drug use trends are dynamic and countries that currently have low rates may show increases in rates of use (as has recently happened in Sweden) as availability of illicit drugs increases and more favourable social attitudes develop towards illicit drug use.

It is also not clear what are feasible minimum counterfactuals. It is not clear whether prevention programmes, such as school-based and other intervention programmes, can prevent problem drug use [18]. These programmes have been most widely implemented and evaluated in the United States. After reviewing this evidence, the United States National Research Council recently concluded that the

> "effectiveness of most of these approaches for reducing substance use is unknown…Some prevention approaches are effective at delaying the initiation or reducing the frequency of tobacco, alcohol and marijuana use [but]…the magnitude of these effects are generally small…[and it] is not clear that preventing or reducing the use of gateway substances translates into a reduced use of cocaine or other illegal drugs" (pp. 233–234).

These conclusions have been supported by a study of the likely impact of the most effective school-based preventive programmes, which concluded that they would have, at best, very modest effects in preventing cocaine use [19].

There is better evidence that some treatment programmes (e.g. opioid agonist maintenance treatment) can substantially reduce illicit opioid use and premature mortality from drug overdose[7] among opioid-dependent persons [3]. In the case of opioid-dependent persons, one could examine the effects that enrolling 10%, 20%, 30%, etc. of persons who were dependent on illicit opioids in opioid maintenance treatment would have on illicit opioid use, overdose deaths and disability produced by illicit opioid dependence. Similar estimates could be made of the expected reduction in HIV/AIDS among injecting drug users from the introduction of needle and syringe exchange and distribution programmes.

[7] Drug overdose: the use of any drug in such an amount that acute adverse physical or mental effects are produced. Overdose in this chapter refers to cases in which death is the outcome.

4 Methods of estimating mortality risk

In this paper, we summarise the methods with which estimates of drug-related mortality and morbidity can be made. We have drawn upon previous work conducted for the earlier CRA exercise[11] and in other related work[20-26].

Methods for estimating mortality attributable to harmful illicit drug use can be direct or indirect. Direct methods count the number of deaths attributed to illicit drug use by applying attributable fractions to ICD classified causes of death in national mortality registers. Indirect methods involve estimating mortality by multiplying measures of mortality risk (e.g. RR) by estimates of the prevalence of exposure to the risk factor in the population.

4.1 Direct methods

In some countries direct measures of mortality are available from mortality registers. This is straightforward in principle for deaths caused by drug overdose, which has an attributable fraction of 1. Aside from individual country mortality registers, other sources of directly measured mortality data include HIV/AIDS surveillance data available from agencies such as UNAIDS and the US Census Bureau.

The difficulties involved in applying this method are exemplified by the case of 'overdose' deaths. This is the only cause of death that is wholly attributable to harmful illicit drug use so all mortality due to this cause must be the result of the risk factor. It is the cause of death that should be the most easily quantified. However, the great many difficulties inherent in assigning any particular case to this cause of death have been well documented [27-29].

In most United Nations member countries, cause of death is classified according to ICD-10 codes, which specify whether the cause of death was intentional poisoning (suicide), unintentional poisoning or dependence. Despite the existence of ICD-10 criteria for classification of cause of death, countries differ in the way that deaths are registered and causes of death are classified [27 28]. For example there is one European

country, in which: *"…it is well known that about 90% of drug related deaths are coded with the code for unknown cause of death"* (p.51) [30].

A report by the UK Home Office was critical of the system for recording drug-related deaths in the United Kingdom [29]. It notes that deaths may not be classified as drug deaths if they are not referred to the coroner (as may happen when a certifying doctor is unaware that the deceased was a drug user) or the death is due to an indirect effect of harmful drug use, such as a viral infection. There also appears to be a great deal of variation between individual coroners in their preparedness to record deaths as drug-related. The report notes that: *"there are coroners working in areas of known high drug prevalence who never certify a death as related to drug misuse"* (p.80).

Other sources for variation identified in the UK report were that neither post-mortem nor toxicological analysis are formally required for suspected drug related deaths; that the verdicts available to the coroner are not mutually exclusive; that coroners do not have the necessary skills to distinguish between the verdicts available to them, most notably "dependence on drugs" and "non-dependent abuse of drugs"; and that there is no requirement of the coroner to identify the drugs involved in overdose deaths [29].

There are also variations between countries in how much information is gathered about the circumstances or cause of death [27 28]. In Australia, for example, autopsy is routinely conducted on all suspected overdose deaths, making forensic and toxicological data the basis for the classification of cause of death. This, however, is a far from universal practice. In the United States, only 20% of drug-related deaths are subject to autopsy [28]. Similarly, the immediate cause of death is recorded in death registers but contributing factors may or may not [27 28]. This can cause large differences in rates of drug-related deaths based on death registers.

For causes other than overdose, where the attributable fraction is less than 1, the difficulties involved in attributing a death to illicit drug use are compounded. In addition to the caveats discussed above, the simple fact that there is a complete absence of such data in the majority of countries in the world necessitates the use of indirect methods to estimate mortality attributable to harmful drug use.

4.2 Indirect methods

Indirect methods of estimating mortality can be used when directly recorded data is unavailable or unreliable. The estimates provided by these methods can be validated against direct methods in countries where reliable mortality data are available. For the vast majority of countries in the world, indirect methods provide the only indicator of the extent of the health consequences of harmful illicit drug use, because of the absence of good quality epidemiological data on drug-related mortality. Three indirect methods can be used to estimate the burden of mortality attributable to illicit drugs.

4.2.1 Attributable fractions

The first method, which requires the greatest amount of data, uses the attributable fraction of mortality attributed to harmful illicit drug use calculated for a population for which direct measures of specific cause mortality are available. This attributable fraction (AF) is then used to extrapolate the mortality attributable to harmful illicit drug use in another population.

This method has the advantage of excluding deaths in those exposed that are *not* due to the risk factor. The most obvious source of mortality data available to use with this method is the All-Cause Mortality Database compiled by the WHO. Attributable fractions for illicit drug use that have been calculated in countries where direct estimates have been made can be applied to these data.

4.2.2 Cohort mortality rates x population of illicit drug users

The simplest method is to multiply mortality rates estimated from cohort studies by estimates of the prevalence of problem illicit drug use in the country. This provides an estimate of deaths caused by illicit drugs, according to the different indications we have considered here.

In terms of estimating risk, as we have described above, the use of annual mortality rates derived from studies of illicit drug users in developed countries may

underestimate mortality in developing countries. By contrast, applying standardised mortality ratios (SMR) from the cohort studies to developed societies may over-estimate the mortality rate of drug users in developing countries (which already have higher mortality rates in general), since it is probable that the higher the general mortality rate in any given country, the lower will be the SMR for illicit drug users in that country [31]. The best approach may be to use both the SMRs and CMRs from cohort studies to produce a range of estimates. This was the approach used in the 2001 CRA estimates.

Other data sources can be used to validate estimates of risk derived from cohort studies in some developed societies. In populations where reliable mortality data are collected the attributable fraction of mortality due to a range of conditions that may be related to problem illicit drug use can be calculated. These fractions can then be applied to estimates of mortality in other countries using the WHO all-cause mortality database. The main weaknesses of this method are: that it does not take into account variations in the prevalence of the risk factor; it assumes homogeneity between the population from which the attributable fraction was derived and the population to which it is being applied; and that cohort studies are representative of the population at risk. It is nonetheless an independent method of calculating mortality that can be used to check estimates of mortality derived by multiplying measures of risk by prevalence estimates.

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