# Benefits and risks of pharmaceutical opioids: Essential treatment and diverted medication

## A global review of availability, extra-medical use, injection and the association with HIV

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# Foreword

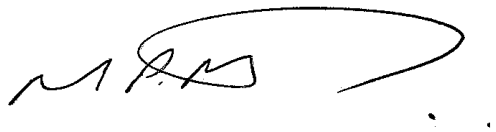
Opioids are the *drug of choice* for many people who inject drugs. Frequently, this opioid is heroin, which is produced, distributed, purchased and consumed illegally. However, a significant number of people inject opioids manufactured by pharmaceutical companies. These are intended for medical use, but at some point in the chain between production and prescribed consumption, they are diverted for what is termed *extra-medical use*.

Important efforts to reduce drug use and its consequent burden can too easily ignore the greater context in which drug use occurs. This paper describes the factors that make addressing extra-medical use and injection of pharmaceutical opioids a complex problem.

On the one hand, there is the need to regulate opioid availability to prevent extra-medical use and injection, and on the other, to ensure that opioids are available for appropriate medical use. This balance is critical, yet, as detailed in this paper, difficult to achieve.

Regulation, availability and consumption differ geographically. Opioids have an essential role in medical practice yet, alarmingly, many people who need them, especially those in low and middle income countries, do not have access. The harm caused by **not** providing them must be considered when restricting access to reduce the harm of extra-medical use.

As Director of the Secretariat of the Reference Group to the United Nations on HIV and injecting drug use, it is my pleasure to present this report, which is the second in a series of thematic papers produced on behalf of the Reference Group in 2007. The thematic papers address issues of current concern relating to injecting drug use and HIV, and supplement the two annual reports of Reference Group that examine the global epidemiology of injecting drug use and HIV prevention and care services.



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# Abbreviations

| | |
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| ART | antiretroviral treatment |
| ARVs | antiretrovirals |
| BBVI | blood borne viral infection |
| CNS | central nervous system |
| HAART | highly active antiretroviral therapy |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| ICD-10 | International Classification of Diseases, 10th revision |
| IDU | injecting drug use |
| IDUs | injecting drug users |
| INCB | International Narcotics Control Board |
| MMT | methadone maintenance treatment |
| NDARC | National Drug and Alcohol Research Centre |
| NGO | non-government organisation |
| NSP | needle and syringe programme |
| OST | opioid substitution treatment |
| PIEDs | performance and image enhancing drugs |
| SSRIs | Selective Serotonin Reuptake Inhibitors |
| STI | sexually transmitted infection |
| UN | United Nations |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| UNDP | United Nations Development Programme |
| UNODC | United Nations Office on Drugs and Crime |
| UNSW | University of New South Wales |
| WHO | World Health Organization |

# Executive Summary

## 1.1. Introduction

Psychoactive pharmaceuticals have an important, legitimate role in medical practice, and can make an enormously positive contribution to the health and wellbeing of many patients. Not all pharmaceuticals are used in accordance with doctors' prescriptions. In some countries the extra-medical injection of some of these drugs is being noted and is the focus of increasing attention worldwide. Here, we review the literature on the extra-medical use and injection of opioid pharmaceuticals and associated harms across the globe. We finish with a brief review of interventions to address misuse and harm.

'Opioid' is a general term which includes drugs containing natural opiates derived from the opium poppy and a range of synthetic and semi-synthetic substances, which have effects upon the opioid receptors in the brain. The immediate effects of all opioids include analgesia (relief from pain) and euphoria (feeling of wellbeing). A large number of pharmaceutical opioids have been developed for medical use; those used most commonly in the management of acute and chronic pain include morphine, oxycodone, hydromorphone, dextropropoxyphene, fentanyl, pethidine and codeine. Methadone and buprenorphine are the most commonly used opioids for the management of opioid dependence.

Adverse consequences are associated with opioid use, even when used in accordance with medical directions. Some side effects from normal doses may include nausea, vomiting, respiratory depression, constipation, drowsiness and confusion. Inappropriately high doses can produce respiratory depression and circulatory failure.

When medications are used outside the guidelines for safe and effective use, adverse effects are more likely, particularly those due to overdosing. Additional risks of injection include risks of blood borne viral infections (BBVIs) if injection equipment is shared; harms related to injection of non-sterile preparations not intended for injection; risks of polydrug use; and harm related to pre-existing conditions for which opioids may be contra-indicated. Because of the dependence liability of opioids, the risk of developing dependent use may also be particularly great if used outside, or without, medical supervision.

## 1.2. Terminology

This report uses a number of different terms to describe the problems associated with pharmaceutical use outside the bounds of a medical professional's prescriptions. **'Diversion'** describes the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended. It does **not** refer to use of medications by a patient outside the doctor's recommended treatment regime.

**'Misuse'** refers to the use of pharmaceuticals for purposes not in line with either medical or legal guidelines. Misuse, **'non-medical use'** and '**extra-medical use'** are often used interchangeably in practice. The term 'extra-medical use' makes clear that use is without a prescription, but does not exclude the possibility that the user may have medically driven reasons for using the drug.

**'Harmful use'** refers to a pattern of drug use that is causing negative impacts upon health and may have negative social consequences. The term **'abuse'** is **not** used in this report because of its ambiguity and negative connotations.

## 1.3. Scope of this report

The focus in this report is on pharmaceutical opioids. Opioid dependence is a problem of

considerable concern, and dependence through use of prescription opioids has increased in low and middle income countries as well as high income countries.

Injection of other pharmaceutical drugs is also worthy of investigation and future work might examine in detail the epidemiology of injection and harm related to these drugs. Injection of pharmaceutical drugs such as performance and image enhancing drugs (PIEDs) is likely to be concentrated among specific subpopulations in high income countries and, to our knowledge, has not been noted as an issue in low and middle income countries. Although injection of benzodiazepines is associated with significant harm, it is thought to be typically concentrated among persons who are primarily opioid dependent.

The risks of *extra-medical* opioid use and diversion are acknowledged by multiple international organisations, including those which monitor pharmaceutical opioid availability, and those which address injecting drug use (IDU), Human immunodeficiency Virus (HIV) and the treatment of pain. All of these agencies also emphasise the importance of providing medical treatment for those who need it and are unanimous in assertions that pharmaceutical opioids must be made available for this purpose.

The 1961 Single Convention stipulates that although the provision of designated drugs (including morphine-like opioids) is restricted to prevent recreational use, their availability and supply should meet medical and scientific need. The International Narcotics Control Board (INCB) is required to report on the adequacy of availability of drugs covered under the 1961 Convention. This report summarises published data from the INCB Annual reports on the kinds of opioids available, and the *extent* of their availability adjusted for population size. There are massive inequities in the availability of pharmaceutical opioids for medical and scientific purposes across countries and regions, inequities that do not preclude misuse and injection occurring in many regions of the world.

There is a complex interplay of factors that appear to be linked to the extent of pharmaceutical opioid misuse and injection, and associations with HIV. This report attempts to highlight several that seem core: the extent of opioid availability – heroin and opium as well as pharmaceutical opioids; regulation of pharmaceutical opioids and their availability; the existence of established populations of injecting drug users (IDUs), and of dependent opioid users; and the prevalence of HIV in different locations and within certain populations. Once illicit opioid use of any sort is established, and injecting occurs among some users, the extent to which HIV harm reduction interventions are in place – particularly needle and syringe programmes (NSPs) and opioid substitution treatment (OST) – may modify both the extent of injection of pharmaceutical opioids and of incident HIV cases.

This report provides an overview of the availability of pharmaceutical opioids and the evidence on the extent of misuse, diversion, injection and associated HIV. It is intended to stimulate further research into the many complexities surrounding this issue. There are huge gaps in our understanding of the extent of misuse, injection and attributable HIV transmission. Literature on the mechanisms and comparative risks of diversion, misuse and injection is also very limited.

## 1.4. Findings

## 1.5. The use of pharmaceutical opioids outside of prescribed bounds

There are numerous motivations for the extra-medical use, diversion and/or injection of pharmaceuticals. Not all extra-medical use is via injection. Some people use pharmaceuticals for extra-medical purposes and take them orally and irregularly; these groups do not attract the

attention of authorities and little is known about this use. Few population studies have been conducted looking at motivations for the extra-medical use of pharmaceuticals; most have examined motivations among IDUs. Different responses will be required depending upon the reason for initiation and maintenance of use; not all misuse is occurring for the same reasons.

Various types of opioids differ in the extent to which they are likely to be misused. In large part this is because of their varying potency which is a key determinant of **dependence potential**. In the case of misuse or diversion for *injection*, different opioids will also vary in the likelihood of misuse depending upon how easily they can be injected (e.g. whether in injectable, tablet or patch form), and degree to which adverse effects occur following injection.

Availability plays an obvious role. It is affected by the extent to which clinicians can and do prescribe different opioids, and how easy they are to obtain from a health professional. Misuse and diversion will also depend upon the availability of illicit drugs, particularly heroin and opium.

Regular use of opioids (even in therapeutic applications) can lead to dependence, and this is one of the reasons that clinicians are hesitant to prescribe opioids for pain over extended periods of time. Dependence is more likely with higher doses consumed for longer durations. There is considerable debate about the frequency of dependence developing under usual clinical conditions.

## 1.6. Mechanisms of diversion

As with all psychoactive medications, opioid substitution and pain medications carry a risk of diversion. Diversion can occur anywhere along the wholesale to consumer chain. Few studies have attempted to estimate the relative contributions of different diversion sources to the pool of diverted medication; many discussions refer to long lists of potential mechanisms without attempting to prioritise their importance; others make strong claims about which are the most important sources of diversion without providing the data upon which such claims are made.

Although limits to the supply of opioids may include the costs of these drugs and other structural factors, it is clear that fears of diversion drive many countries' policies on pharmaceutical opioids: a default position of limiting or precluding supply of prescription opioids for medical conditions appears to be the norm. This can have the serious consequence of depriving patients in need of access to essential medications that would be highly effective in treating them.

Such an approach also appears unsuccessful in avoiding diversion and injection. Even in countries where legitimate access is currently limited, epidemics of pharmaceutical opioid injecting and HIV transmission have been documented; this has occurred in a number of South Asian countries. When opioid injection of any kind is established, and HIV is prevalent, there is an additional public health imperative to introduce OST which has been demonstrated as an effective strategy in the prevention of HIV transmission.

More sophisticated and coordinated policy approaches can and have been developed. Key organisations affiliated with the World Health Organization (WHO) have been working successfully with several countries to ensure a more balanced approach towards supply and control of these medications.

## 1.7. Clinical use of pharmaceutical opioids

There are two broad clinical indications for the use of pharmaceutical opioids: 1) management of pain that is often dichotomised as either acute or chronic, and as cancer or non-cancer related; and 2) OST in the management of opioid dependence.

As outlined above, it is likely that some diversion of pharmaceuticals occurs at the level of importation or production, particularly in countries where there is only limited capacity to monitor this. In many countries, however, it seems reasonable to assume that the bulk of opioids that are diverted, or used extra-medically, are acquired from health professionals and patients. There are good reasons to assume, however, that the risk of diversion and misuse is not the same for all patient groups.

## 1.8. Harms associated with pharmaceutical opioid injecting

When medications are used outside the guidelines for safe and effective use, adverse effects are more likely, particularly those due to overdosing. Additional risks are associated with the concomitant use of other substances, particularly sedative drugs, and in the presence of pre-existing conditions for which opioid use may be contra-indicated. The injection of pharmaceutical opioids also carries risks such as the potential transmission of BBVIs if injecting equipment is shared as well as harms related to injection of a non-sterile medication that is intended for consumption by other routes. The risk of developing opioid dependence (see below) may also be greater if used outside of or without medical supervision.

The literature on the magnitude of risk for HIV transmission among IDUs injecting pharmaceutical opioids is limited but there is reason for concern. We were unable to locate specific studies examining the relative risk of HIV *transmission* among IDUs injecting pharmaceutical opioids, but it seems reasonable to assume that in countries where most IDU is occurring with pharmaceutical opioids, and where HIV transmission also occurs, that unsafe injection of these drugs is driving the epidemic.

Globally, between 5-10% of HIV infections result from IDU, but in some countries in Asia and Europe, over 70% of HIV infections are attributed to IDU; in many countries in these regions, pharmaceutical opioids are commonly injected drugs. Of particular concern here is South Asia. Unsafe injecting drug use – including dextropropoxyphene and buprenorphine injection – is a significant issue in some countries in this region, and is also a significant cause of the spread of HIV. From such high-risk groups the virus is now reportedly spreading to non-injecting populations through sexual transmission.

## 1.9. Pharmaceutical opioid availability, extra-medical use, injection, and HIV

This report summarises pharmaceutical opioids available for the treatment of pain and for OST, from peer reviewed and grey literature, and using the INCB's consumption estimates. INCB data are the only data collected internationally on pharmaceutical opioid availability. There is a range of issues that make it difficult to comprehensively evaluate adequate coverage of required medical needs or estimate the scale of misuse/diversion across different countries.

Data from extensive searches are presented on misuse, injection, and HIV among injectors of these drugs. In many countries there seems to be a reluctance to provide opioids for the treatment of pain and to a greater extent for OST. To provide insufficient pharmaceutical opioid coverage (for pain *and* illicit opioid dependence) is against the recommendations of international health and regulatory bodies. Such an approach also clearly fails to preclude misuse, diversion and injection.

### • Eastern Europe and Central Asia

In almost every country in the region, large populations of injecting heroin users have become firmly established, and HIV has become prevalent among these IDUs. Opioid substitution treatment is available in some but not all countries; in many places OST programmes that are available are limited in size and therefore entry to these programs is

difficult. Access to opioids for the management of pain appears to be limited in a number of countries in the region which would limit the availability of these drugs for extra-medical use. In some countries, there is evidence of injection of pharmaceutical opioids among already established populations of heroin dependent IDUs; in some cases this extra-medical use is occurring despite less than adequate provision of opioids for medical purposes.

In **Belarus**, the injection of methadone is becoming increasingly common; however, OST is not available in this country. Methadone is rarely diverted in the **Czech Republic,** but buprenorphine is frequently diverted, and in some locations is more commonly injected than heroin. Both drugs are available for OST, but buprenorphine can be prescribed by any general practitioner (GP) regardless of training, whereas methadone is only available in specialist settings. In **Georgia**, methadone is available as OST but buprenorphine is not; the injection of buprenorphine, believed to be diverted from nearby countries where it is legally available, has recently been reported as increasingly common among IDUs who perceive it to be a preferable alternative to heroin.

## • South Asia

In some South Asian countries there have been marked problems related to pharmaceutical opioid misuse and increasingly, injection, particularly in **India, Nepal** and **Bangladesh**. Some have suggested that a shift from heroin smoking to pharmaceutical opioid injection may have been related to reduced availability or increased costs of heroin at certain times, the low cost and easy availability of pharmaceuticals, and legal controls introduced in India to address heroin supply. The pharmaceutical opioids being misused in this region are typically lower potency opioids such as codeine, nalbuphine and dextropropoxyphene, in contrast to the pharmaceutical opioids being used by IDUs in other regions around the globe which include oxycodone and morphine, and high dose buprenorphine.

These problems have occurred despite very low levels of licit opioid medication consumption for medical purposes in this region suggesting that misuse has not been avoided simply through having limited supplies of the drug for medical purposes. Consistent reports indicate that prescribing for all types of pain is inadequate in this region; OST is available in some countries but *much* better coverage is needed, particularly since unsafe injecting is driving the HIV epidemic in some countries. HIV and HCV co-infection are common among IDUs in the region.

A recent United Nations Office on Drugs and Crive (UNODC) report concluded that the diversion of pharmaceutical opioids for misuse and trafficking is occurring on a large scale both within and outside the region, primarily because of the limited enforcement of pharmaceutical regulations. It is thought that **India** accounts for significant large-scale diversion both within the country and to other countries in the region, and to countries further afield through illegal online pharmacies based in India.

## • East and South East Asia

In East and South East Asia, pain relief has been noted as "poor" with low availability of opioid medications, but some efforts are being made to increase coverage. Few reports of pharmaceutical opioid diversion or injection were noted, with the exception of **Singapore**. This was in contrast to the prominence of heroin as a drug of dependence in this region: all countries are close to the heroin producing region, the "Golden Triangle". OST availability has traditionally been extremely limited, but concerted efforts have been made to establish and roll out OST in several countries, particularly **China**, **Malaysia**, **Thailand** and **Indonesia**.

**Singapore** previously had widespread and relatively poorly regulated availability of buprenorphine as an OST for heroin dependence, leading to a significant problem with injection of the drug, sometimes by persons who had been initiated to injecting with

this drug. Rather severe restrictions were introduced in 2005 to address this problem, with removal of patients from this form of OST through detoxification. The impact of this has not yet been reported in the literature.

## • Caribbean

Coverage of opioids for medical purposes is clearly inadequate in many countries in this region. Governments are preparing legislation to improve the nature of controls over pharmaceutical substances: this includes **the Bahamas** and **Dominica**. Few data could be located on the extent of pharmaceutical opioid misuse, injection or diversion. Given the low levels of consumption, it seems likely that the extent of pharmaceutical opioid misuse and diversion is not great, but there is a need for much better coverage of opioid medications for the treatment of pain and for OST.

This is particularly the case in **Puerto Rico**, where injecting drug use is a major cause of HIV transmission and heroin injection is the most commonly injected drug. The general population prevalence of HCV in San Juan is 6.3%, with estimates of 39% for heroin injectors. HIV incidence rates are much higher among IDUs in Puerto Rico than in New York, whereas methadone and HIV treatment coverage is much worse, although methadone has been piloted in prison settings.

## • Latin America

The availability of pharmaceutical drugs in general is poor in many countries of Latin America. In response to the high cost of drugs, some countries in the region have developed methods for encouraging generic brands of these medications and ensure swift registration.

Access to opioids for pain and drug dependence is inadequate; few mentions of pharmaceutical drug misuse in this region could be found, with most of the focus upon cocaine production, trafficking and use. Access to opioid medication is very low. A meeting of cancer pain physicians, researchers and government representatives over a decade ago considered the use of opioid medication in Latin America and concluded that opioids were severely under-utilised for the treatment of cancer pain in all countries in the region because of cost, bureaucratic requirements that dissuaded physicians from prescribing stronger opioids, a clinical orientation to short-term mild opioids for acute pain only, and limited training leading to fear of prescribing by doctors and failure to stock medications by pharmacists. Efforts have been made in some countries to improve inadequate standards of care for dependent drug users.

Use and injection of opioids in general (including heroin) is thought to be low in this region. The exception is **Mexico**, which has an established population of heroin users (and injectors), and is one of the heroin producing countries of the world. Heroin is the most common drug used by Mexican IDUs and increased poppy cultivation, greater security at the United States border, and reduced prices may be related to the establishment of significant heroin use in the country. Risky practices among IDUs are reportedly high and risk perception is low; there are some indications that HIV prevalence may be increasing among this group, with estimates of 4% prevalence in 2003. OST treatment has been available in **Mexico** since 2001. No reports of pharmaceutical opioid diversion were located from studies of treatment or out-of-treatment drug users.

## • Oceania and the Pacific

Pharmaceutical opioid misuse was not noted as an issue in most countries in this region. This is almost certainly because of very minimal availability of these drugs for medical use. Most countries in this region have minimal levels of opioid consumption reported to the INCB. Two exceptions are **Australia** and **New Zealand**. These countries have comparatively high opioid consumption, including comparatively good levels of coverage for pain treatment.

In **Australia**, OST for the treatment of illicit opioid dependence is long established and there is a high level of coverage of the opioid

dependent population. OST is highly regulated and there is highly regulated availability of other opioid medications. OST is considered a "low threshold" treatment, in accordance with a policy designed to minimise harms associated with illicit opioid use. Markets for diverted opioids in Australia have been described as "small scale" and "disorganised" and diversion seems typically to occur sporadically among established heroin injectors, and is probably related to the availability of their preferred opioid (heroin).

In **New Zealand**, misuse and injection of prescription opioids has been a more long-standing issue among established IDUs, related in part to the poor availability of heroin for many years as a result of the disruption of a major heroin trafficking ring in the 1970s. In 1990, 81% of opioid users presenting to a drug treatment clinic for treatment of their opioid dependence reported the injection of buprenorphine within the past month, and 68% had injected morphine. Following the introduction of buprenorphine-naloxone in 1991, among clients presenting for treatment, 57% were injecting buprenorphine-naloxone, with patients reportedly having learnt to inject buprenorphine-naloxone at doses and frequencies that would allow them to avoid withdrawal.

- **Canada, United States and Western Europe**

In terms of extra-medical use, injection and diversion, the **United States** appears to have the largest per capita problem in the world. Even the INCB voiced significant concern about the extent of problems in the country. It accounted for half (49%) of the world's estimated morphine consumption in 2005, despite only comprising 4.7% of the world's population. Controlled-release oxycodone is widely misused, and the country accounts for 99% of the world's consumption of this opioid. It was estimated that prescription opioid misuse cost US$8.5 billion in 2009; given that problems seem to be increasing, the figure is likely to be much larger today. Dependence, and the number of both non-fatal and fatal overdoses related to pharmaceutical opioid misuse continue to increase across the country, particularly oxycodone misuse. Methadone is increasingly being used for pain management, and the number of dosage units of the tablets used for pain increased by 277% between 2000 and 2005, as compared to a 163% increase in diskettes used both for pain and opioid treatment, and a 99% increase in liquid used in opioid treatment. Between 1999 and 2004, the number of poisoning deaths mentioning methadone increased 390%, while the number of deaths mentioning other opiates such as oxycodone and hydrocodone increased 90%.

Multiple formulations of varied opioids are available, and many appear easily obtained from GPs for diffuse, non-specified pain conditions. It seems to be this feature of the US policy context that is in part related to the extent of the problem with oxycodone, but other important aspects have played a part. The pharmaceutical company that manufactures the most popular of these products, OxyContin® (Purdue Pharma), aggressively marketed the drug as a treatment for both cancer and chronic non-cancer pain to oncologists, palliative care physicians and pain specialists, claiming it had a low dependence liability. In May 2007, the company agreed to pay $600 million in fines and other payments to resolve the criminal charge of "misbranding" its product; further lawsuits are currently underway.

In **Canada**, there has been sustained research and community attention upon the misuse and injection of pharmaceutical opioids among regular illicit opioid users, with evidence of increasing use and injection of pharmaceutical opioids, probably related to inconsistent heroin supply in most areas of the country. Despite this, population level data on illicit opioid use (including heroin) are limited. Data suggest that OST coverage in the country is around 23%, representing a very substantial increase relative to the poor availability of OST until a decade ago. There is no national monitoring system in place to track the diversion and extra-medical use of prescription drugs, although district-level systems are in place.

In Western Europe, there is certainly less population-level consumption of these drugs compared to Canada and the United States, and it is not related to OST coverage; in many countries (e.g. France) OST coverage is decidedly superior. Some countries had notably low levels of pharmaceutical opioid consumption, such as **Albania**, **Andorra**, **Serbia**, and **Montenegro**, and no data could be located on the existence or extent of misuse or diversion in these countries. However, there is a need for better coverage of OST in some of these areas, given evidence of heroin dependence and HIV prevalence among these populations.

Misuse and diversion is occurring in Western Europe. Although very good monitoring occurs through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), routine reporting does not appear to stress differentiation between heroin and pharmaceutical opioids. As a result, it is not clear in some countries to what extent problems related to these pharmaceuticals are a concern. Future monitoring might separate heroin from other opioids.

In **Finland**, there have been high levels of diversion of buprenorphine from OST for some years. In 2005, buprenorphine was the most frequently injected drug among IDUs attending an NSP (73%) and was reportedly commonly used to avoid withdrawal. Some evidence has suggested that it might be a more common problem among younger drug users. Since the introduction of buprenorphine-naloxone, many IDUs said that they had injected the drug (68%) but 80% of these users reported a negative experience; the street price of this formulation was also reportedly half that of buprenorphine. Overdose deaths are likely to involve buprenorphine but overdose rates are low.

In **France**, a similar problem has been reported in relation to buprenorphine, but much of the misuse appears to be among users enrolled in OST, which is widely available and dispensed through pharmacies. A 1997 study found some evidence of a younger cohort of IDUs who *only* injected buprenorphine (not heroin or cocaine); compared to an older group who also injected these other drugs, they injected drugs more frequently and were more likely to be enrolled in buprenorphine treatment. There is evidence of doctor shopping and prescription fraud among OST clients – one study found two profiles for forged prescriptions: males under 45 years, presenting with stolen prescription forms and requesting opioids; and women aged over 45 years presenting with altered prescriptions for benzodiazepines or opioids.

- **Middle East and Northern Africa**

Medication for severe pain is inadequate in supply in many countries in the region. According to the INCB, pharmaceutical preparations containing controlled substances are easily obtained on unregulated markets in this region, with considerable unregulated sale of pharmaceuticals over the counter without prescriptions occurring. Misuse of these preparations is reported to be taking place but no data were available to quantify this. Drug control legislation prohibiting such practices is in place in most countries, but it is often not adequately implemented and enforced. Due to insufficient funds, there is apparently a shortage of trained pharmacists and pharmacy inspectors in many African countries, which is often exacerbated by a lack of funds to fill vacancies. The INCB recently voiced concern about controlled drugs being sold via illegally operating internet pharmacies in larger cities. Data on the extent of this possible problem are seriously lacking.

- **Sub-Saharan Africa**

Provision of pharmaceutical opioids for the management of severe pain is severely limited in this region and repeated calls are being made for dramatic changes to availability and use. There are significant structural barriers to the provision of medication in some countries, and doubtless fear of limited capacity to control diversion adds to difficulties in achieving change.

An added issue is the fact that many African countries now serve as routes for the trafficking

of illegal drugs, including heroin, through to the richer markets of Europe. It is likely that countries such as **India** may account for significant and/or increasing supply of diverted pharmaceutical opioids to this region; this needs to be addressed. The development of noticeable drug problems has been noted in multiple transit countries in Sub-Saharan Africa, with many countries lacking national policy frameworks to address these issues. Policies are being introduced across the continent to address illegal drug use and related harm. The development of populations of dependent heroin users is an issue of significant concern, given the very high population prevalence of HIV existing in the country. OST should be introduced as a matter of priority in countries where heroin injection has become an issue.

## 1.10. Discussion

Pharmaceutical opioids have an important role in the treatment of a range of medical and psychological conditions, but globally, they are inadequately prescribed for the conditions for which it is known they are highly effective. Patients (particularly those who are terminally ill) should be given relief from severe pain; and OST should be introduced to help dependent users and avoid the significant risks of HIV transmission and other harm.

Diversion and injection of pharmaceutical opioids is occurring in many countries, but it is important to consider this within the context and the manner of licit availability. Considering the level of concern about its occurrence, there is comparatively little data with which to understand the extent and nature of extra-medical use in each country, but it seems reasonable to expect some level of diversion will occur. Monitoring of trends in South Asia and South East Asia is important – these countries are likely to account for the majority of users injecting pharmaceutical opioids. The evidence on associated harms of pharmaceutical injection is dominated by research in high income countries where use and diversion of pharmaceutical opioids probably differs from low and middle income countries.

On the basis of the current evidence, extra-medical use, diversion and injection of pharmaceutical opioids appears to be a significant problem for the United States, South Asia, South East Asia, and some Eastern European countries. The nature of the populations injecting these pharmaceuticals seems very different across countries. For example, in India, populations of IDUs appear to be developing dependent, injecting use of these drugs; in Australia, injection may be more common among IDUs whose preference is heroin and for whom injection is less frequent; in the United States, a generalised epidemic of pharmaceutical opioid use appears to have been driven by overly liberal prescription for non-specific pain states, leading to a new cohort of dependent opioid users who may switch to injecting.

Different opioids have different dependence potential, and the types available may also affect the likelihood of misuse and diversion for injection. There needs to be much more routine monitoring work conducted to provide data on the extent of the problem (or otherwise). There appears to be a general tendency for those opioids that are more available to be those which are more likely to be misused. If a range of pharmaceuticals is available, those which are more potent appear to be more sought after and misused. In countries where strong opioids are not available (e.g. India), other less potent opioids are still used and injected. Where pharmaceutical opioids (even less potent ones) are introduced without sufficient regulation, it seems that there is a risk of misuse and diversion (e.g. the United States and Singapore). The challenge is ensuring that such problems are addressed without implementing policy that is overly restrictive and ensuring that patients are not deprived of appropriate treatment.

In terms of injecting risk, the evidence on this topic is limited. Some studies have suggested increased injecting risk among pharmaceutical opioid injectors compared to other IDUs, others

have not. The context of opioid use – whether it is among IDUs in contexts where OST is currently available, or whether pharmaceuticals are largely used by otherwise naïve IDUs – may be related to this. The prevalence of HIV and HCV among this group of IDUs is poorly documented in almost every country, except where these drugs are the major drugs of injection. The evidence on the magnitude of HIV risk associated with pharmaceutical opioid injecting – relative to other opioids such as heroin – is limited, although it may be lower if injection occurs less frequently.

Responses to misuse, diversion and injection should *not* further discourage what we know are inadequate levels of medical use of opioids for the treatment of pain. Unfortunately, there has been little research examining the relative benefits of different policy interventions, a gap that would benefit from systematic research examining different contexts and policy responses across countries. There seem to be few cases where national policies spanning palliative care, HIV and AIDS, OST and other pain management have been produced. There is much that is not known about how, why, where and how much diversion is occurring.

For users who have developed dependence on opioids, treatment should be provided: it has positive impacts upon illicit drug use, physical and mental health, and public amenity. OST is an effective HIV prevention strategy that should be considered for implementation as a treatment for IDUs with opioid dependence in communities at risk of HIV epidemics.

## 1.11. Regulatory responses

"Optimally-designed" drug diversion control programmes have three goals: a) limit access to only those with a legitimate need for the drug; b) track and identify cases where control over this access is compromised; and c) minimise the effect of these controls upon legitimate medical practice. These general principles must be used to produce a mix of strategies to apply to the context of a given country. The question is: how does a country balance the needs and risks?

International bodies can and do play an important role in determining pharmaceutical opioid availability. The INCB in particular can place pressure upon countries to increase or further regulate pharmaceutical opioid availability. It has urged many countries to make opioids more available for the effective management of pain –an important change that must be made.

The INCB can also play an important part in ensuring the availability of opioids for OST where illicit opioid dependence has developed as an issue. Given the documented benefits of widespread OST implementation – reduced HIV transmission, reduced opioid overdose, improved wellbeing for patients and improved public amenity – there is a clear public health imperative for international agencies to assist countries to make OST available where it is required.

In many countries, it may be appropriate to register a greater number of opioid medications for use. As the tables in this report show, many countries not only have highly inadequate opioid supply, but also do not stock the medicines listed by WHO as essential in the treatment of acute and chronic pain. Fewer still stock the model medicines for treatment of illicit opioid dependence.

Pharmaceutical companies can play an important role in opioid pharmaceutical use and misuse. The US example of oxycodone highlights the very significant risk that unbalanced depictions of dependence risk, and overly generalised marketing to health professionals may pose for populations that are predisposed to taking up medications for a variety of health conditions. One way in which availability needs to be regulated therefore includes monitoring of drug company promotion of pharmaceutical opioids to the medical profession and the broader community to ensure that appropriate use occurs.

## 1.12. Drug preparations and formulations

The pharmacological formulation of different pharmaceuticals may impact on their potential for misuse and/or injection. Approaches can include the addition of naloxone to deter injection, less injectable formulations, or formulations which prevent drug tampering. This avenue of research should be continued as a matter of priority for obvious public health reasons.

Not all people who inject drugs will cease injecting, even if pharmaceucitcal opioids are less amenable to injection. Some IDUs will inject formulations or preparations that are designed not to be injected. For IDUs who have not responded to standard oral OST and repeatedly struggle to remain in treatment, provision of injectable formulations such as morphine or heroin may represent an alternative treatment option and warrants further research.

## 1.13. Harm reduction

As described earlier in this report, OST reduces the level of HIV risks and HIV transmission and allows for stabilisation of persons who have already contracted HIV. OST can therefore be seen as an HIV harm-reduction measure in addition to an intervention to reduce demand for diverted pharmaceutical opioids.

NSPs have been shown to reduce HIV transmission and injecting risk behaviour. Injecting equipment must be made available as a matter of priority in regions where access is currently limited, yet pharmaceutical opioid injection is still occurring and HIV risk behaviours are common, such as South Asia.

Another issue is whether equipment that facilitates the injection of pharmaceutical preparations (e.g. pill filters, large barrels/needles and vein infusion kits) should be made available. Some have recommended *reducing* the availability of equipment for injection of formulations not designed for injection, such as methadone syrup. However, not all IDUs will cease injecting. In one study in Australia, among those IDUs who continued to inject methadone syrup after large-barrelled syringes and winged infusion sets (or 'butterflies') stopped being distributed by NSPs, there was greater re-use of injecting equipment; it was recommended that additional policy initiatives were required to further address this issue.

There is a tension between providing equipment that facilitates injection of these non-injectable drugs, and reducing overall injection at the expense of those who choose to continue doing so. It has been suggested that more comprehensive responses (e.g. including dilution of methadone syrup) were required, since removing access to equipment for injecting methadone syrup clearly has not led to a complete cessation of injecting for some IDUs.

Particularly in countries where pharmaceutical opioid injection is occurring, attempts should be made to provide factual information to IDUs about the risks of injecting these medications, and ways in which harm can be reduced.

## 1.14. HIV treatment

Interventions to address HIV among those who inject pharmaceutical opioids should be consistent with the UNAIDS essential package for HIV prevention and care for IDUs. This package includes:

- NSPs;
- OST;
- HIV counselling and testing; and
- Antiretroviral therapy.

Those actively using drugs should be offered treatment for HIV, but clinicians should provide good support to assist clients with adhering to medication. Part of good clinical practice involves assessment for potential non-adherence and this should be conducted

carefully. Adherence counselling should be a component of treatment.

## 1.15. Future research

There is an imperative for good research on this topic. Concerns about inappropriate responses to evidence of diversion and injection should not preclude research into this issue. Lack of data on the topic will only serve to maintain the status quo, which appears to be a tendency to limit availability of pharmaceutical opioids for medical and scientific purposes. Some areas of research include, but are not limited to:

- systematic collection of detailed data on pharmaceutical opioid availability for medical purposes;
- regular collection of data on the extent and nature of extra-medical use of pharmaceutical opioids, including injection;
- studies examining the relationship between pharmaceutical opioid injection among IDUs and the availability of other illicit drugs;
- studies examining the reasons for pharmaceutical opioid extra-medical use and injection among users from different country contexts and different subpopulations of users within countries;
- studies examining the factors that maximise attractiveness of OST while minimising diversion risk;
- research documenting the prevalence of HIV and HCV among those who inject pharmaceutical opioids;
- research into formulations of pharmaceutical opioids that reduce the risk of injection;
- research into formulations of pharmaceutical opioids that pose less risk of harmful use;
- evaluation of national policies for regulation of pharmaceutical opioids in low and middle income countries;
- research to examine the feasibility and cost effectiveness of injectable forms of OST for those clients who have not succeeded in standard forms of OST;
- further research into the ways in which opioids can be used for chronic pain: which patients benefit from this form of therapy, and in what circumstances;
- research examining the influence of policy in both facilitating and restricting health promotion and harm reduction among those who inject pharmaceutical opioids; and
- review of current national and international legislation through which pharmaceutical companies can be held accountable for policies and procedures that facilitate large-scale diversion of their products.

## 1.16. Conclusions

There are understandable reasons why clinicians and policymakers are concerned about overly liberal access to opioid medications that might place users at risk of developing dependence upon these drugs. It is abundantly clear, however, that the number of people who are not receiving effective medication for their pain (e.g. perhaps 10 million out of 20 million new cases of cancer each year) is far larger than the population of persons with illicit opioid dependence. This means that a huge number of people are being denied effective treatment that has been described as "absolutely essential" by the WHO.

Some diversion should be expected to occur when opioids are made available for medical purposes. That is not sufficient grounds for *a priori* refusal of treatment to all patients who would receive relief from pain. It is imperative for many countries to design effective systems for access to opioids for those who need them, ensuring that prescriptions are provided by those providing good clinical care, and without placing patients at undue risk of developing dependent use of these drugs. Further research must be conducted into the many complexities surrounding this issue. There are huge gaps in our understanding of the extent of misuse, injection, and attributable HIV. We need to know more about why misuse occurs,

particularly in countries where it has begun among previously opioid naïve users. The literature on the mechanisms of diversion and comparative risks of diversion, misuse and injection is also very limited. Until further data are produced, fear of diversion will probably continue to dominate policy decisions, efforts to control diversion will be misdirected and lead to overly restrictive control of supply, and prescriptions for legitimate medical conditions will continue to be inadequate. Yet diversion will continue.

# 2. Introduction

Psychoactive pharmaceuticals have a vital role in medical practice, and make an enormously positive contribution to the health and wellbeing of many patients. However, not all pharmaceuticals are used in accordance with the directions of health professionals. In a number of countries, the injection of some of these drugs outside therapeutic instruction is being reported and is the focus of increasing attention.

Worldwide, 10% of Human Immunodeficiency Virus (HIV) incident cases are attributed to injecting drug use (IDU)[1]. In Eastern Europe and Central Asia, two-thirds (67%) of prevalent HIV infections in 2005 were due to IDU[2-3]. Possible associations between unsafe pharmaceutical injecting and HIV therefore warrant careful consideration, particularly since they have concerned clinicians and health authorities in multiple countries where HIV infections are also of concern[4-5].

## 2.1. Scope of this report

This paper reviews the existing peer reviewed and "grey" literature[i] on the injection of opioid pharmaceuticals and associated harm, including associations with HIV, and considers the context of the availability of pharmaceutical opioid medications for the medical indications for which they are recommended. The paper finishes with a brief review of interventions to address misuse, injection and harm.

Numerous pharmaceutical drugs have the potential for misuse. These include benzodiazepines (e.g. diazepam, temazepam); performance and image enhancing drugs (PIEDs, e.g. anabolic-androgenic steroids); antidepressants (e.g. tricyclics and selective serotonin reuptake inhibitors); and prescription stimulants (e.g. dexamphetamine).

The focus of this report is on pharmaceutical opioids for several reasons: 1) opioid dependence is a problem of considerable concern, and opioid dependence through use of prescription opioids has increased in low and middle income countries[5-7] as well as high income countries[8]; 2) injection of pharmaceutical drugs such as PIEDs is likely to be concentrated among specific subpopulations in high income countries[9] and to our knowledge, has not been noted as an issue in low and middle income countries; and 3) although injection of benzodiazepines is associated with significant harm[10-11], it is thought to be typically concentrated among persons who are primarily opioid dependent[12]. Injection of other pharmaceutical drugs is also worthy of investigation, however, and future work might examine in detail the epidemiology of injection and harm related to these drugs.

The risks of *extra-medical* opioid use and diversion are acknowledged by multiple international agencies, including those which monitor pharmaceutical opioid availability, and those which address injecting drug use, HIV and pain conditions. All of these agencies also emphasise the importance of providing medical treatment for those who need it, and are unanimous in assertions that pharmaceutical opioids must be made available.

The 1961 Single Convention stipulates that although the provision of designated drugs (including morphine-like opioids) is restricted for recreational purposes, their availability and supply should meet medical and scientific needs. The International Narcotics Control Board (INCB) is required to report on the adequacy of availability of drugs covered under the 1961 Convention. This report summarises – as

[i] The methods with which we searched the literature and data are summarised in Appendix A.

part of the review of the "availability" of pharmaceutical opioids – the published data from the INCB Annual reports on the kinds of opioids available, and the *extent* of their availability adjusted for population size (Section 5). As will become clear, there are massive inequities in the availability of pharmaceutical opioids for medical and scientific purposes across countries and regions, inequities that nonetheless do not preclude misuse and injection occurring in many regions of the world.

There is a complex interplay of factors that appears to be linked to the extent of pharmaceutical opioid misuse and injection, and associations with HIV. This report attempts to highlight several factors that seem core: the extent of opioid availability – heroin and opium as well as pharmaceutical opioids; regulation of pharmaceutical opioids and the manner in which they are made available; the existence of established populations of injecting drug users (IDUs), and of dependent opioid users; the background prevalence of HIV, and the extent to which HIV harm-reduction interventions are in place – particularly needle syringe programmes (NSPs) and opioid substitution treatment (OST).

As might be imagined, this report provides an overview of these issues as covered in the literature. It is intended to act as a paper that might be used to stimulate further research into the many complexities surrounding this issue. As will become clear, not only are there huge gaps in our understanding of the extent of misuse, injection, and attributable HIV, but the literature on the mechanisms of diversion and comparative risks of diversion, misuse and injection is also very limited.

## 2.2. Terminology

This report uses a number of different terms to describe the problems associated with pharmaceutical use outside the bounds of a medical professional's prescription. Our use of these terms is in line with both the World Health Organization's (WHO) *Lexicon of Alcohol and Drug Terms* (2007)[13] and the international literature. Some terms used in this report (and those we avoid) are presented below for clarity.

**Misuse**, **non-medical use** and **extra-medical use** are often used interchangeably. The term 'extra-medical use' makes clear that use is without a doctor's prescription but does not exclude the possibility that the user may have medically driven reasons for using the drug (see Table 4 below). 'Misuse' refers to the use of pharmaceuticals for purposes not in line with either medical or legal guidelines[13]. We prefer this term to "abuse", in agreement with others, because it is less judgmental[13].

**Harmful use** refers to a pattern of drug use that is causing negative impacts upon health and which may have social consequences accompanying them[13].

**Abuse** is not used in this report because of the ambiguity and negative connotations of this term. "Abuse" is variously used to refer to a drug use disorder[13], and as a term denoting use that is disapproved of (e.g. in the *World Drug Report*[14]). The WHO does not use the term abuse. In accordance with WHO, this report refers to "harmful patterns of use" or "harmful use" to refer to use that may cause harm.

**Diversion** is used in this report to describe the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended[15-16]. It does **not** refer to use of medications by a patient outside the doctor's recommended treatment regime.

## 2.3. Pharmaceutical opioids

'**Opioid**' is a general term which includes drugs containing natural opiates derived from the opium poppy, and a range of synthetic and semi-synthetic substances which have morphine-like effects[17].

Opioids act primarily on the opioid receptors of the brain. The immediate effects of all opioids relate to analgesia (relief from pain) and euphoria (feeling of wellbeing)[17]. A large number of pharmaceutical opioids have been developed for medical use. We list some of the more common types in Table 1; a full list of pharmaceutical drugs and their availability on a country-by-country basis can be found in the annual reports of the INCB[18-19].

**Table 1: Common pharmaceutical opioids**

- Buprenorphine
- Codeine
- Dextropropoxyhene
- Fentanyl
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Pethidine
- Propoxyphene

Opioids used most commonly in the management of pain (both acute and chronic) include **morphine**, **oxycodone**, **hydromorphone**, **propoxyphene**, **fentanyl**, **pethidine**, **codeine** and less commonly, **methadone** and low dose **buprenorphine**. Methadone and buprenorphine are the most commonly used opioids for the management of opioid dependence.

**Methadone** is a synthetic opioid with full agonist actions at the opioid μ-receptor[20]. It is typically administered orally as a liquid, although it does come in tablet form, and tablets may be more commonly prescribed in the treatment of pain. Methadone is the most common substitution therapy for opioid dependence and was included in 2005 on the WHO's *Model List of Medicines*[21] as an OST for illicit opioid dependence.

**Buprenorphine** is a partial opioid μ-receptor agonist and *k*-receptor antagonist[22], with weaker opioid activity than methadone[22]. It is not well-absorbed when taken orally, so the usual route of administration is sublingual. Because the effects plateau at increasing doses, buprenorphine carries a lower overdose risk than methadone, even if taken with other opioids[23], although it may cause respiratory depression[24]. Buprenorphine dissociates from opioid receptor binding sites very slowly, possibly explaining the limited withdrawal syndrome[25-26]. Like methadone, buprenorphine has applications in both the management of pain and the treatment of opioid dependence. It is increasingly used as an OST, and was also included in 2005 on the WHO's *Model List of Medicines*[21] for this indication.

**Morphine** and **codeine** are both derived from opium. Both are listed as essential medicines on the WHO's *Model List of Medicines*[21] for the treatment of analgesia, and chronic, severe cancer pain. Codeine has about one-sixth of the potency of morphine; it is often combined with other drugs such as paracetamol in low doses for mild to moderate pain. Morphine is also listed as a model analgesic medicine for preoperative pain treatment[21].

**Pethidine** is a synthetic opioid with similar actions to morphine. It is typically used for pre- and post-operative pain; it is neurotoxic, and use is not recommended for more than 36 hours[17]. **Fentanyl** is a potent synthetic opioid with similar properties to morphine, but has a much faster onset and shorter duration of action compared to morphine[17]. It is typically used as a short acting analgesic for acute pain management.

**Dextropropoxyphene** is a synthetic opioid, structurally similar to methadone, with a potency around two-thirds that of codeine[17]. It is used for mild to moderate pain.

**Oxycodone** is a semi-synthetic opioid used for moderate to severe pain. It is superior to morphine in oral absorption and bioavailability, and similar in terms of protein-binding and lipid-solubility[27]. The controlled-release formulation (as opposed to the immediate-release formulation) is considered to be similar to morphine in dependence potential[27]. The pharmacokinetics of oxycodone are altered by age and reduced by renal and hepatic function[27].

Side effects associated with opioid use, even under medical supervision, include nausea, vomiting, respiratory depression, constipation, drowsiness and confusion. Higher doses can produce severe respiratory depression, circulatory failure, coma and death[28].

When medications are used outside the guidelines for safe and effective use, adverse effects are more likely, particularly those due to overdosing. Additional risks are associated with the concomitant use of other substances, particularly sedative drugs, and in the presence of pre-existing conditions for which opioid use may be contra-indicated[17]. The injection of pharmaceutical opioids also carries risks such as the potential transmission of blood borne viral infection (BBVI) if injecting equipment is shared as well as harms related to injection of a non-sterile medication that is intended for consumption by other routes (see Section 4). The risk of developing opioid dependence (see below) may also be greater if used outside of or without medical supervision. In short, extra-medical opioid use matters.

## 2.4. Dependence

Regular use of opioids (even in therapeutic applications) can lead to dependence[29-32], and this is one of the reasons that clinicians are hesitant to prescribe opioids for pain over extended periods of time. Dependence is more likely with higher doses consumed for longer durations. There is considerable debate about the frequency of dependence developing under usual clinical conditions. Organisations such as the United States Academy of Pain Medicine are working to establish guidelines to establish ways to appropriately prescribe and manage iatrogenic dependence. It is important to note that for some cases such as very severe or palliative pain management, dependence is expected to occur and is not considered a concern if the guidelines are followed. The features of opioid dependence are presented in Table 2.

Tolerance can develop following a period of therapeutic opioid use, as well as among those who are using opioids for non-medical purposes[30]. Opioid tolerance is a predictable pharmacological adaptation and patients may require increasing amounts of the drug to maintain the same pharmacological effects[30-31]. Tolerance develops to the analgesic, euphoric, sedative, respiratory depressant and nauseating effects of opioids, but not to their effects on miosis (constriction of the pupils) and constipation[30].

If use ceases after tolerance has developed, withdrawal can and does occur. Common withdrawal symptoms include body aches, diarrhoea, gooseflesh, loss of appetite, nervousness, restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, insomnia, increased sweating, lethargy, tachycardia and fever[28, 30]. With appropriate medical supervision and gradual withdrawal, these symptoms are usually mild. When opioid use is stopped abruptly, however, these symptoms are more severe.

Opioid dependence develops after a sustained period of regular use, and depends upon the amount, frequency, and route of administration. It is likely that individual factors predispose some users to greater

risk of developing dependence than others. Dependence is a complex health condition, with multiple risk factors across individual, social and biological domains[29].

Illicit opioid dependence causes a significant burden to the user, his/her family, and the broader community. It can be a chronic disorder, with users struggling to control their use over years or even decades. Opioid dependence can result in significant costs to society through unemployment, homelessness, family disruption, loss of economic productivity, social instability, criminal activity, or ill health[29, 34-35]. Major health consequences of illicit opioid dependence include increased risk of BBVI such as HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV) through injection[29], and highly elevated risks of premature mortality[36-37].

Where opioid dependence develops in the context of treating chronic non-malignant pain, most of the time its management is not difficult. A proportion of these patients can be very difficult to manage, however, demanding increasing doses, usually of their own preferred opioid, often attending multiple doctors, sometimes fraudulently. Problems are more common and more severe with certain preparations (especially pethidine) and certain routes of administration (especially intra-muscular injections). This first situation is not relevant to HIV except where such patients might begin injecting their own medication. The second situation is where prescription opioids are diverted to street drug users who often inject the prescription opioids; this is of greater concern in terms of the spread of HIV.

### 2.4.1. The concept of "dependence liability"

Drugs differ in their liability to problematic use[8, 38-39]. The WHO defines dependence liability as "the extent to which a substance, as a consequence of its pharmacological effects on physiological or psychological functions, gives rise to dependence on that substance. It is determined by the intrinsic pharmacological properties that can be measured in animal and human drug testing procedures"[17].

There are various factors that have been identified in the literature that influence the degree to which a drug may be associated with harmful patterns of use[8, 12, 17, 26-27, 39-47]. This includes the rate at which the drug enters the brain and exerts an effect (the "rate of onset") and the duration of the drug effect (the "half-life")[17].

In general, drugs that are most highly reinforcing are associated with more harmful patterns of use. These drugs have characteristics that enable rapid entry of a substance into the brain, including rapid absorption, rapid onset of action, rapid entry into the central nervous system (CNS), a high potency, a brief duration of action (short half-life), high purity, water solubility (for injectable use) and/or high volatility (ability to vaporise if smoked)[12, 17, 26, 48-49].

The half-life and speed of onset of a drug are determined by its pharmacokinetic properties (absorption, metabolism, distribution and elimination) and its lipid solubility (because drugs that are lipid-soluble cross the blood-brain barrier more rapidly)[17, 48]. Table 3, developed by Quinn et al[26], summarises some of the specific pharmacokinetic factors associated with how frequently a drug is self-administered, the development of dependence, and the emergence of withdrawal symptoms.

**Table 2: Criteria for past year ICD-10 drug dependence**

Three or more of the following have been present together at some time during the previous year:

- a strong desire or sense of compulsion to take the substance;
- difficulties in controlling drug use in terms of its onset, termination, or levels of use;
- a physiological withdrawal state when substance use has ceased or has been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
- evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses;
- progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects; and
- continued use despite clear evidence of overtly harmful consequences.

Source: World Health Organization[33]

**Table 3: Pharmacokinetic characteristics predictive of dependence potential**

**Persistent self-administration**

- Rapid absorption/high bioavailability
- Rapid delivery of drug to the CNS (specific areas of the brain such as the nucleus accumbens may be particularly important)
- Low protein and peripheral tissue binding
- Small volume of distribution
- Short half-life
- High drug-free clearance

**Dependence**

- Long half-life
- Low drug-free clearance
- Sufficient drug exposure to allow development of tolerance (high enough concentrations, long enough at site of action)

**Withdrawal**

- Short half-life
- High drug-free clearance
- Rapid efflux from the CNS

Reproduced from Quinn, Wodak and Day[26] (p. 46)

# 3. The use of pharmaceuticals outside of prescribed bounds – "extra-medical" use

## 3.1. Why does extra-medical use occur?

There are numerous motivations for the extra-medical use, diversion and/or injection of pharmaceuticals. Not all extra-medical use is via injection. Some use pharmaceuticals for extra-medical purposes and take them orally and irregularly; these groups do not attract the attention of authorities and little is known about this use[50]. Few population studies have been conducted looking at motivations for the extra-medical use of pharmaceuticals; most have examined motivations among IDUs. Table 4 lists some motivations behind this drug use. The multitude of possible motivations behind a user's misuse of pharmaceuticals should be taken into account. Different responses will be required depending upon the reason for initiation and maintenance of use; not all misuse is occurring for the same reasons.

## 3.2. Do all opioids carry the same risk of extra-medical use and diversion?

The various opioids differ in the extent to which they are likely to be misused. In large part this is because of their varying potency as opioid drugs – their varying **dependence potential**. In the case of misuse or diversion for *injection*, different opioids will also vary in the likelihood of misuse depending upon how easily they can be injected (e.g. whether in injectable, tablet or patch form), and degree to which adverse effects occur following injection (e.g. precipitated withdrawal in a heavily dependent heroin user who injects a large dose of buprenorphine or buprenorphine-naloxone[51]).

Availability plays an obvious role. It is affected by the extent to which GPs can and do prescribe different opioids, and how easy they are to obtain from a doctor or purchase from the black market. Misuse and diversion will also depend upon the availability of illicit drugs, particularly heroin and opium and probably also on the availability and attractiveness of treatment for drug users.

Only a limited number of investigations into the importance of these varied factors have been conducted, and all in high income countries. A recent US study came to a rather common sense conclusion: the extent of extra-medical use and related problems for different pharmaceutical opioids in the United States was relatively simple to gauge, and was a function of their relative potency and their ease of availability[60].

In an examination of why some opioids are more attractive for misuse than others, Butler et al developed an "Opioid Attractiveness Scale"[61]. In ranking "attractiveness", questions were asked about features reflecting dependence liability, characteristics of medication and preparation that were *unattractive* (e.g. combined with an antagonist or not meant for injection), and external factors such as costs and the drug's availability and that of alternatives[ii]. There were clear preferences for illicit drug users in the United States to rank different opioids as more or less attractive[61], and it is likely that brand recognition also plays a part in determining their attractiveness. A Canadian study found that fentanyl was the most attractive pharmaceuctical opioid for illicit opioid users[62].

ii It should be noted that this study received unspecified support from Janssen Pharmaceutica Inc., the company involved in the production of Durogesic®.

The "street" value of diverted prescription medications is a relatively good indicator of their attractiveness to users. Compared with generic formulations, trade-name prescriptions may be worth as much as twice as much per tablet when they are sold on the street because they are recognisable[12, 49]. Buprenorphine-naloxone, a mixed partial agonist-antagonist, has been found to have half the street value of buprenorphine[63]. Long-acting opioids have a lower price than shorter-acting ones[64], and injectable preparations have a higher price than tablets[65].

In recognition that some pharmaceutical opioids are more likely to be misused than others, there are growing efforts by pharmaceutical companies to develop formulations that are less prone to being misused and, in particular, injected. Examples of these are slow-release formulations, mixed agonist-antagonist formulations[66], and tablet formulations that are more difficult to inject. This response to diversion and injection is considered in Section 6.

**Table 4: Reasons for extra-medical use of prescription drugs**

| | |
|---|---|
| **Experimental use** | Among young people, non-medical use of pharmaceuticals may reflect wider patterns of experimental drug use[52] |
| **Euphoria** | Prescription opioids may be used to "get high" |
| **Self-treatment of pain** | Opioids may be used to self-medicate chronic pain[53] |
| **Self-treatment of drug dependence** | Pharmaceutical opioids may be used to self-treat withdrawal symptoms, particularly among opioid-dependent persons who perceive treatment services as being unavailable or undesirable[54-55] |
| **Iatrogenic dependence** | Patients may have become dependent on a medication they were being prescribed through their treatment of a medical problem[17] |
| **Drug substitution** | Substitute for other drugs when availability is irregular or low[54, 56-57] |
| **Polydrug use** | Individuals who are entrenched in the illicit drug market may also use diverted pharmaceuticals if they are available[55] |
| **Drug culture** | Influence of peers and exposure to particular patterns of drug use[52] |
| **Preference for injecting over other routes** | Injection may be preferred for its faster onset of action, avoidance of withdrawal, or enjoyment of the ritual of injecting. There is debate about the concept of **needle fixation**. The term has limited usefulness and describes multiple attitudes and practices[58-59] |
| **"Safer" alternative** | A perception that these drugs are "safer" than illicit drugs[17] |
| **Fear of sanction** | There may be a perception of reduced legal risk in supplying and possessing psychoactive pharmaceuticals compared to illicit drugs[50] |
| **Suicidality** | To facilitate an intentional overdose |

**Table 5: Ways in which pharmaceutical drugs may be diverted**

- Cross-border smuggling by traffickers and tourists
- Wholesale and retail shipments via the internet[71-72]
- Robberies or thefts from manufacturers, distributors, pharmacies[73]
- Illegal sale of prescriptions by physicians, pharmacists, nurses or other health professionals[16]
- Residential burglaries[73]
- Thefts of prescription pads and drug supplies
- Theft, forgery or alteration of prescriptions by patients[57, 74-76]
- "Doctor shopping", or multiple visits to numerous doctors by the same patient[57, 74-75, 77]
- Acquisitions from family and friends[52, 78] or other users[57, 74-75]
- Medicine cabinet thefts by housekeepers[78]

Note: List derived from Inciardi et al[16]

## 3.3. How does "diversion" occur?

As with all psychoactive medications, opioid substitution and pain medications carry a risk of diversion[29]. Diversion[iii] can occur anywhere along the wholesale to consumer chain[16] (see Table 5). Few studies have attempted to estimate the relative contributions of different diversion sources to the pool of diverted medication; many discussions refer to long lists without attempting to prioritise them; others make strong claims about which are the most important sources of diversion without providing the data upon which such claims are based.

Fears of diversion appear to drive many countries' policies on pharmaceutical opioids: in many low and middle income countries, a default position of limiting or precluding supply of prescription opioids for medical conditions appears to be the norm (see Section 5). This overly restrictive attempt to avoid pharmaceutical opioid diversion deprives patients in real need of medications that would be highly effective in treating them and which have been described as essential elements of treatment[67-69].

Such an approach is also unsuccessful in avoiding diversion and injection. Even in countries where legitimate access is currently limited, epidemics of pharmaceutical opioid injecting and HIV transmission have been documented, particularly in South Asia (Section 5). When opioid injection of any kind is established, and HIV is prevalent, there is an additional public health imperative to introduce OST. In Section 5 we review the population-adjusted supply of pharmaceutical opioids for all United Nation (UN) member states as reported by the INCB.

More sophisticated and coordinated policy approaches can be developed[67]. This will be mentioned repeatedly through this report, because these are crucial to address both HIV and misuse of pharmaceutical opioids. Key organisations affiliated with the WHO have been working successfully with

[iii] As noted above, we refer to "diversion" as the channelling of regulated pharmaceuticals from legal sources to the illicit (unintended) marketplace, either for personal use or for profit.

several countries to ensure a more balanced approach towards supply and control of these medications[70].

The numerous ways in which diversion might occur may seem overwhelming. It is highly likely, though, that the bulk of diverted opioids are sourced through several primary means, which probably vary across countries and regions.

Supply control factors such as the extent to which diversion is policed, and the ease with which large-scale importation or diversion of medications is possible, will have an impact. Difficulty in controlling supply may be more significant in countries with limited resources to police and regulate these markets, and has been noted as an issue in South Asia. Geography will also affect diversion risk to the extent that it is related to the availability of other preferred opioids (particularly heroin), drug-using cultures, and the availability of OST for those who are already opioid dependent[65, 74, 79]. We are unaware of any studies that have mapped the relationship between all of these factors and the mechanisms of diversion.

There is disagreement, even within countries, about the extent to which different sources of diversion are important. The United States' Drug Enforcement Agency (DEA) announced that physicians' and pharmacists' "diversion" accounted for the majority of pharmaceutical opioids diverted to the black market in the United States[78]. Authors of one US paper voiced concerns about diversion of pharmaceuticals over the internet[8]. Another documented diversion by healthcare providers in one US state with nurses and medical assistants most commonly involved and typically occurring from hospitals[16]. By contrast, US police and regulatory agents perceive that the major source of diversion in the United States is doctor shopping and pharmacy theft or forgery[73]. Although theft and fraud of prescriptions from ill and deceased elderly persons has been suggested as a possible source of diversion, a careful analysis of Canadian records found that the was highly uncommon and when it did occur was unlikely to involve prescriptions for opioid medications[76].

Many extra-medical users in high income countries such as the United States typically obtain medications from family, friends, and peers who often "swap" drugs or sell them on a small scale to fund the use of other drugs[50, 52, 57, 65, 74-75, 78, 80-81].

Notably, in the United States, GPs have been encouraged in recent times to prescribe opioids (particularly oxycodone) for moderate to severe chronic pain conditions. There has been a repeated finding that in such a context, some IDUs who inject pharmaceutical opioids present to doctors for diffuse medical conditions consistent with those for which opioids might be appropriate treatment[50, 52, 57, 65, 74-75, 78, 80-81]. In some cases, these conditions may be authentic, but some will present with feigned symptoms[57, 65, 74-75, 77].

Some sources may be unduly emphasised. The internet is mentioned frequently as a source of diversion[8], but there are views that the contribution of the internet to diversion may be overstated[57, 73-75]. Even in the United States, where internet access is extremely high, only 4% of the general population had *ever* used it to fill a prescription and most sites required a doctor's prescription[73]. It is also unclear to what extent diversion by highly disadvantaged dependent users would occur through this means (given the need for a credit card, computer and internet access, and a fixed address for shipping). The problems related to pharmaceutical opioids in the United States appear to be much greater than those for other countries; it could well be the case that the new cohort of dependent opioid users in that country (see Section 6) is driving substantial demand for opioids, with users seeking new ways to source their medications, including illegal internet pharmacies[19].

There is inadvertent collateral damage from supply control. For example, the system of "triple prescriptions" has been introduced in a number of countries to reduce diversion to the black market and this has been shown to reduce prescribing to patients with severe chronic pain (see Section 6).

Unfortunately, little is known about the mechanisms and extent of diversion of pharmaceutical opioids across countries. As long as fear of diversion exists, and no examination of the situation is made, it is likely that efforts to control diversion will be misdirected and lead to overly restrictive control of supply, and yet diversion will continue.

# 4. Clinical use of pharmaceutical opioids

There are two broad clinical indications for the use of pharmaceutical opioids: 1) management of pain that is either acute or chronic and either cancer or non-cancer related; 2) OST in the management of opioid dependence.

As outlined above, it is likely that some diversion of pharmaceuticals occurs at the level of importation or production, particularly in countries which have only a limited capacity to monitor this. In most countries, however, it seems reasonable to assume that the bulk of opioids that are diverted, or used extra-medically, are acquired from health professionals and patients. The fear of diversion from these sources seems to be an important factor in limiting the adequate provision of opioids for clinical use in many countries. There are good reasons to assume, however, that the risk of diversion and misuse is not the same for all patient groups.

## 4.1. Treatment of acute pain

Opioids are highly effective in the treatment of pain and have a long history of use for pain relief[31]. They are routinely used in hospital settings, particulary in surgery for pre- and post-operative pain management. This involves short-term use to treat acute pain as opposed to the more chronic use that may occur for severe cancer pain, or for chronic non-cancer pain.

### 4.1.1. Risks for misuse and diversion

Because of the short duration of treatment and the acute and normally quite severe nature of the pain to be treated, it is probably unlikely that patients account for much of the diversion of opioids intended for this clinical indication.

The greater risk in this instance is probably from those involved in administering these medications, namely doctors, nurses, and other medical professionals. There is some evidence that medical professionals are at risk of misusing such medications themselves[82]. There is also some evidence (e.g. from the United States) that nurses and doctors may be involved in diversion to the illicit market[78, 82]. The highly regulated nature of opioid medications in hospital and other settings probably reduces the size of this source of diversion, and/or increases the likelihood of detection when it occurs[16], but few studies have estimated the magnitude of this diversion source. Having said that, there are many sources other than health professionals: in the United States alone, there are as many as one million registered manufacturers, distributors, pharmacies, hospitals, nursing homes and physicians[78].

## 4.2. Treatment of cancer pain

It has been estimated that there are 10 million incident cases of cancer each year, and six million deaths. Twenty years from now, 70% of the 20 million incident cancer cases worldwide are likely to be in low and middle income countries[83].

Pain specialists recognise pharmaceutical opioids to be central in the management of severe cancer pain[68, 84-86]. The WHO stated that morphine and codeine were "*absolutely necessary*" for the management of severe cancer pain (p.7)[67]. The WHO recommended that health professionals and

governments use a three-step "Analgesic Ladder"[iv] to treat cancer pain. This entirely depends on the availability of drugs which are effective in relieving severe pain, such as morphine or other strong opioids (including fentanyl, hydromorphone, methadone and oxycodone)[68-69].

Global morphine consumption has increased since 1986 but has been concentrated in a small number of high income countries: Australia, Canada, Denmark, France, Germany, Japan, Spain, Sweden, the United Kingdom, and the United States[68]. The remaining countries, representing approximately 85% of the world's population, consumed only 13% of the morphine in 1999[68]. A WHO survey of countries concluded that 60% were not following the Analgesic Ladder because of inadequate availability of opioid medication[68].

In some countries, the lack of palliative care and opioids for pain management is particularly serious because, by the time most patients are diagnosed, they have late-stage cancer that is often accompanied by pain[68]. As many as 50% of cancer patients worldwide may suffer from pain that goes unrelieved[69, 83]. In many instances this may be due to a lack of knowledge and experience in delivering this form of treatment in the countries concerned. Despite being urged by the UN's INCB to provide adequate pharmaceutical opioid coverage for pain management[87], in many countries, the prescription of opioids for cancer pain management is considered highly inadequate[5, 44, 85, 87-90]; in some cases, it is non-existent (see Section 5).

### 4.2.1. Risks for misuse and diversion

It seems plausible that patients with severe cancer pain are at comparatively low risk of diverting their own medication. Even in relatively resource-limited countries, outpatient, long-term opioid medication can be provided to those suffering from cancer pain, with a relatively low incidence of diversion or apparent misuse. This has been well illustrated in India, where an outpatient pain clinic was established to address very poor levels of opioid prescription particularly for cancer patients[5]. A two-year trial of oral morphine for severe cancer pain at a Pain and Palliative Care Clinic in Kerala, India[91] involved the assessment of 1,723 patients, treatment plans, and careful monitoring by medical staff trained in pain medicine; no diversion occurred during the entire trial[91]. The authors recommended that palliative care programmes talk to concerned governmental authorities to make them aware of the medical need for opioids, and communicate with local news media to increase awareness of palliative care and the use of these analgesics[91].

Doctors might be concerned about the possibility that relatives or others close to the patient might divert medication. However, the relatively high level of patient-doctor contact in the treatment of chronic cancer pain along with good clinical skills and training may ensure good monitoring and hence help reduce risk.

There is a need for better coverage of cancer pain with opioid medication[70] and better education needs to be provided both to doctors and patients about the benefits of medication and the relatively low risk of diversion or misuse for this group[68, 70]. Countries need to implement policies that do not overly restrict access for this group because of concerns about diversion by others (those with chronic non-cancer pain, and those who are opioid dependent). The WHO has published guidelines for developing more balanced policies to ensure appropriate treatment of pain for this condition[67].

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[iv] The analgesic ladder involves three steps:
**Step 1**: Aspirin or paracetamol.
**Step 2**: Codeine or dihydrocodeine, with or without non-steroidal or anti-inflammatory drugs such as ibuprofen.
**Step 3**: Morphine, with or without co-analgesia, with or without steroid anti-inflammatory drugs. Other strong opioid analgesics include pethidine and fentanyl.

## 4.3. Palliative care for HIV/AIDS

For patients suffering from AIDS, uncontrolled pain and other symptoms can be severe. This is particularly true in the late stages of the illness[92]. The need for pain relief for AIDS has been recognised by the WHO as a crucial component of palliative care for this patient group[92], yet in many countries where HIV is highly prevalent, opioid treatment will be limited or non-existent[92]. In many of these same countries, there is also inadequate access to HIV medications.

### 4.3.1. Risks for misuse and diversion

The nature and extent of risks for misuse and diversion are probably similar to those for cancer pain, but no research on this issue was found for this review.

## 4.4. Treatment of chronic non-cancer pain

Chronic pain is a common complaint. In one survey of 16 European countries, between 10% and 30% of participants in each country reported "chronic pain", one-third (35%) of whom said that they experienced pain every day, and 16% that some days the pain made them "want to die"[85]. One-quarter reported that it had impacted upon their careers[85]. Between 30% and 50% of those with chronic pain in these general population samples felt that their pain was not "adequately controlled"[85].

Chronic pain is caused by many factors, including trauma; the varied aetiology probably impacts upon the effectiveness of treatment[31]. Physical and psychological factors such as depression and anxiety, a history of psychological trauma, and sleep problems moderate the pain experience[31]. Context is also important: relationships, occupational setting and culture all impact upon the experience and expression of pain[31].

Effective behavioural treatments and non-opioid pharmacotherapy exist for chronic pain[31], but even when a combination of interventions is used, some patients continue to suffer. Controlled trials have evaluated pharmaceutical opioids in the treatment of a range of chronic non-cancer pain conditions and have demonstrated modest attenuation of pain[93]. An open label US study of long-term treatment (three years) with controlled released oxycodone[v] among chronic non-cancer pain patients (n=219), found that treatment was well tolerated, most had stable or decreased doses over time, and pain ratings often remained unchanged or decreased[94]. Investigators reported six cases (3%) of possible drug misuse, but no new cases of dependence were observed[94].

A recent cross-sectional study in Denmark examined chronic non-cancer pain among a representative population sample, and contrasted opioid users and non-users, adjusting for age, gender, concomitant use of anxiolytics and antidepressants, and pain intensity[95]. Opioid usage was associated with more severe pain, poorer self-rated health, unemployment, higher health care service use, and poorer quality of life. Acknowledging that the cross-sectional nature of the study limited the capacity to consider the reasons for this association, the authors nonetheless commented that "it is remarkable that opioid treatment of long-term/chronic non-cancer pain does not seem to fulfil any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity" (p.172)[95].

Such a statement is of concern because it does imply causality. It ignores the possibility that persons with chronic pain who use opioids may have fared even worse before starting use, and that they may have

[v] This study received funding from, and one of the authors was employed at, Purdue Pharma Inc., which markets Oxycontin®

failed to respond to other treatments for their pain; it further assumes that the treatment regimens of the treating physicians were in line with recommended best practice (prescription of opioids for chronic pain in Denmark is apparently "liberal"[96]).

There are clear statements from peak pain organisations supporting some use of opioids in the treatment of chronic non-cancer pain[85, 97]. Debate continues about how, when, and in what manner opioids should be prescribed for this diverse patient group[31, 95-96, 98-101]. Consensus statements have recommended that prescription of opioids for chronic pain is only recommended after following these steps: a thorough assessment of the patient's pain problem and history, development of a treatment plan, consultation with a pain specialist if necessary, and regular reviews of patient progress[85, 97]. It is unclear how many physicians in routine clinical practice follow such guidelines. It is highly likely that in the United States, where rapid increases in prescribing of opioids for these conditions has occurred (with increases in dependence, injecting and overdoses across the country), that many GPs may not have conducted sufficient assessment of conditions, nor gone through the recommended steps to ensure that alternative treatments were considered and that progress was carefully monitored.

### 4.4.1. Risks for misuse and diversion

The situation for those suffering from chronic non-cancer pain is more complicated. The therapeutic role for long-term opioid medication in such cases is less than well established, the aetiology of these problems is varied, and its expression is highly moderated by the cultural context of the patient. This patient group is likely to have comorbid conditions that place the patients at risk of problematic drug use. Some physicians are also concerned about the risk of respiratory depression that may be seen early in treatment, as well as the need for escalating doses due to the development of tolerance.

Some patients will be at greater risk of misusing medication prescribed for chronic non-cancer pain. For example, in a US routine pain care setting, 9% of clients misused opioid medication (4% doctor shopping, and 5% diverting in "trafficable" quantities)[102]. Misuse or diversion was more likely among those who were younger, who had a pain condition as a result of a motor vehicle accident, had more extensive pain, and a history of illicit drug use[102].

This highlights the comorbidity that tends to occur between chronic pain conditions and drug dependence[53, 103-106]. US research suggests that chronic pain patients with comorbid mental health and drug use problems are much more likely to be those at risk of misusing their medication or developing a problem with use[106-108].

Without careful assessment and monitoring, problematic use may develop. In countries such as the United States, where there has been extremely aggressive marketing of some pharmaceutical opioids to a wide range of specialist and non-specialist physicians, where medication is a prominent feature of treatment, and where GPs without training in pain management can prescribe opioids for such patients, there may be an over-reliance on medication. This has led to a significant problem in the United States with many patients developing iatrogenic dependence, and easier access for others who are actively seeking opioids.

The extent of the problem with oxycodone is instructive with respect to policy. The pharmaceutical company (Purdue Pharma) that manufactures the most popular of these medications, OxyContin®, a sustained release formulation of oxycodone, aggressively marketed the drug in the United States as a treatment for both cancer and chronic non-cancer pain to oncologists, palliative care physicians and pain specialists, claiming it had a low dependence liability[109]. The drug was also heavily promoted to primary care and family practitioners, who were encouraged to prescribe it liberally[110]. There was a major campaign to market the drug to patients; in this campaign, the risks of dependence were

minimised[110-112]. Those liable to misuse the drug were probably alerted to its misuse potential by the product information material which said patients should *not* crush or dissolve the tablets because this released a large dose of the drug[110]. In the United States, problems related to pharmaceutical opioid misuse have been increasing across the country, particularly for oxycodone[44, 47, 60, 113-118]. We return to this example in the section on epidemiology (Section 6).

As will become clear, it seems most likely that it is among this relatively diverse population of patients, with diffuse symptoms and high comorbidity, in which misuse may occur. Fears of misuse or diversion among this group are warranted, but it should not mean that this patient group is not given the opportunity for pain relief through opioid medication[85, 97]. A balanced approach that ensures appropriate access while minimising diversion and misuse is essential. Good clinical practice should involve careful assessment of need and risk, and careful monitoring of patient progress.

## 4.5. Treatment of illicit opioid dependence

Some people become dependent on opioids, whether upon illicit heroin or opium, or diverted pharmaceutical opioids. Some people become dependent upon prescribed opioids because of inadequate monitoring (by prescribers and/or the patient themselves) of doses and usage levels. It is estimated that less than 0.5% of the world's population is dependent on opioids, and it is likely that far fewer would be dependent upon prescription opioids[119-120].

Nonetheless, dependence is a disabling disorder which causes significant harm to the user, his/her family and the community at large. Research with prospective cohort studies of dependent opioid users spanning decades in the United Kingdom and the United States indicates that many dependent heroin users, who seek treatment or come to attention through the legal system, continue to use heroin for decades[121-122]. In this population, daily heroin use is punctuated by periods of abstinence, drug treatment and imprisonment. In the year after any episode of drug treatment, the majority of users relapse to heroin use[123]. When periods of voluntary and involuntary abstinence during treatment or imprisonment are included, it has been estimated that dependent heroin users use heroin daily for 40-60% of their 20-year use careers[124-125]. In the most recent 2000 WHO Global Burden of Disease estimates, it was thought that illicit drug use caused around 200,000 deaths worldwide, of which opioid overdose was estimated to account for around 70,000 (around 35%), and AIDS around 105,000 (around 53%)[36].

Pharmaceutical opioids have important applications in the treatment of opioid dependence. OST involves the medically supervised administration of an opioid and can be used either to help manage withdrawal, or to maintain a patient on a safe dose as opposed to the more hazardous use of illicit drugs[29]. There is strong evidence that OST is effective in reducing the spread of HIV, reducing drug use, improving physical and mental health and social functioning, and reducing criminality[20, 22-23, 29, 126-132]. Methadone is also associated with a low level of side effects and positive health outcomes[20]. Higher doses and longer durations of methadone are generally associated with greater reductions in heroin use[20, 29] and HIV risk behaviours[133-134]. Demand for treatment, however, typically far exceeds the number of treatment places[22].

Untreated illicit opioid dependence increases the risk of HIV transmission: some research has found that IDUs who do not enter OST are up to six times more likely to become infected with HIV than injectors who enter and remain in treatment[29, 135]. OST is not only an HIV prevention measure, but will allow those who are already HIV positive to stabilise their underlying condition[136-140]. In multiple countries worldwide where IDU is an important vector for HIV transmission, the expansion of OST provision is believed to underlie the reductions in HIV incidence seen in these countires[140].

Longitudinal studies examining changes in HIV risk behaviour for patients currently in treatment have found that longer retention in drug treatment, as well as completion of treatment, are correlated with reduction in HIV risk behaviours related to drug taking or an increase in protective behaviours[29].

OST drugs typically have a longer duration of action than the drug they are replacing, to delay onset of withdrawal symptoms and reduce the frequency of administration[29], although there is continued debate about the role of shorter-acting opioids for patients who have not responded to first line OST such as methadone and buprenorphine[141] (see Section 6). Whereas illicitly used opioids are usually injected or inhaled, prescribed opioids are typically meant for oral administration as tablets or in a solution to reduce the risk of infections associated with injections, and to encourage behavioural change (from injecting)[29]. Some exceptions to this are injectable heroin and morphine for OST in the United Kingdom[142-144], and injectable heroin in Switzerland[145] and the Netherlands.

### 3.5.1 Risks for misuse and diversion

Persons in OST for treatment of illicit opioid dependence may also misuse or divert these medications. Indeed, most research on misuse and diversion has been conducted with IDUs in treatment for drug use problems, probably reflecting the greater likelihood of misuse. The manner in which OST is provided probably has an impact upon the extent of misuse and diversion for injection. This may include instances where treatment is provided without good patient monitoring, where large amounts of OST are provided in takeaway doses, and where unstable or disadvantaged patients are also not provided with psychosocial support. Many other factors might also play a role in changing the likelihood of misuse, diversion and injection, including cost of the drugs, the availability of other illicit drugs (particularly heroin) and varied cultural factors (e.g. whether injecting is an established route of administration among the population). Economic factors are likely to be important. If demand for OST far outstrips supply, then the black market price of OST medications will be high. If OST patients are poor, as they usually are, then it is inevitable that income generation may take place on a considerable scale.

One prescription database study in France estimated that "doctor shopping" (patients approaching multiple doctors to obtain greater a quantity of drugs) accounted for 19% of the entire "delivered" quantity of buprenorphine for OST ("delivered" takes account of the fact that patients could see more than one physician)[146]. This occurred among a minority of patients and was extremely concentrated: 87 out of the total 3,259 patients accounted for 45% of all doctor-shopped buprenorphine[146]. In France, e.g. there has been a policy of "low threshold" entry into buprenorphine, which has led to large numbers in OST, reduced overdose rates related to opioids at a population level, and low HIV prevalence among IDUs. An even greater problem with bupreorphine diversion has been noted in Finland[147-148].

Misuse or diversion of OST may occur for many reasons, including:

1. heroin availability may be low or fluctuating in price and/or purity;
2. treatment may not be sufficient to maintain the person in a stable maintenance pattern, through inadequate doses or dissatisfaction with the treatment medication's effects;
3. users may wish to switch between different opioids (e.g. sometimes selling OST doses in order to buy heroin or another opioid);
4. users may have a strong preference for injection despite high doses of OST;
5. there may be insufficient treatment places available, so patients assist other users not able to enter treatment; and
6. theft or "standovers" may occur.

The policy implications for these various motivations differ. Evidence strongly suggests that higher OST doses are more effective in retaining patients in treatment, and reducing misuse, diversion and other opioid use. There is continued debate about the need for varied OST to assist different patients (e.g.

heroin, morphine) who may not be adequately held in standard OST such as methadone and buprenorphine. Debate continues about the need for injectable forms for some patients who have repeatedly found other OST difficult to continue. Finally, diversion to assist other users obviously indicates a need for more treatment places of sufficient attractiveness to retain more users in treatment.

## 4.6. Summary of medical and extra-medical pharmaceutical opioid use

There are understandable reasons why clinicians and policymakers are concerned about overly liberal access to opioid medications that might place users at risk of developing dependence upon these drugs. It is abundantly clear, however, that the number of people who are not receiving effective medication for their pain (e.g. perhaps 10 million out of 20 million new cases of cancer each year) is far larger than the population of persons with illicit opioid dependence. This means that a huge number of people are being denied effective treatment that has been described as "absolutely essential" by the WHO[69] and a "human right" by the International Society for the Study of Pain[149]. There is a great imperative for many countries to design effective systems for access to opioids for those who need it, ensuring that prescriptions are provided by those providing good clinical care, and without placing patients at undue risk of developing dependent use of these drugs.

# 5. Harms associated with pharmaceutical opioid injecting

## 5.1. Association with HIV

The literature on the magnitude of risk for HIV transmission among IDUs injecting pharmaceutical opioids is limited but there is reason for concern. We were unable to locate specific studies examining the relative risk of HIV *transmission* among IDUs injecting pharmaceutical opioids, but it seems reasonable to assume that in countries where most IDU is occurring with pharmaceutical opioids, and where HIV transmission is occurring, that unsafe injection of these drugs is driving the epidemic.

Globally, between 5% and- 10% of HIV infections result from IDU, but in some countries in Asia and Europe, over 70% of HIV infections are attributed to IDU; in many countries in these regions, pharmaceutical opioids are commonly injected drugs[29]. Of particular concern here is South Asia[150]. Injecting drug use – including dextropropoxyphene and buprenorphine injection – is a significant issue in some countries in the region, and is also the primary cause of the spread of HIV among communities of IDUs (see Section 4)[151-153].

From such high-risk groups, the virus is now reportedly spreading to the non-injecting populations through sexual transmission[151-152]. The first convincing evidence of HIV transmission from HIV positive IDUs to their female regular sex partners (wives) who had never injected drug in South Asia came from Manipur, one of the north-eastern states of India bordering Myanmar[154]. The explosive spread of HIV epidemic among IDUs of Manipur took place in 1990 and 45% of the wives of HIV positive IDUs were found to be HIV infected within seven years of this outbreak. The drugs injected in Manipur and other north-eastern states included heroin (white sugar) and dextropropoxyphene[154].

## 5.2. Injecting risk behaviours

Research on persons injecting pharmaceutical opioids is largely confined to a few high income countries. In these contexts, injection of pharmaceutical opioids has mainly been studied among groups of entrenched IDUs with extensive histories of heroin and other drug injecting. Conclusions drawn about associations of risks in these populations may not be directly comparable to low and middle income countries.

One exception is research on IDUs in South Asia, which indicates that the epidemic of injecting occurring in that region typically involves diverted pain medication, with infrequent injection of other drugs[151-153]. Although behavioural surveillance data in some countries such as Bangladesh suggest that knowledge of injecting risk is quite good among persons who inject drugs, and that they are typically aged in their 20s and 30s, other populations of younger and less knowledgeable IDUs in South Asia exist and are likely to be taking risks without understanding the harms that may result.

In high income countries with established IDU and heroin injecting populations, and relatively good OST coverage, the context of pharmaceutical opioid injection differs. Injection of methadone syrup (prescribed as an OST) has been associated with higher levels of injection-risk behaviour[155-156]. Among an Australian sample of heroin users, methadone injectors reported poorer general health, more injection-related problems and were also more likely to report having passed on used injecting equipment[156-157]. Other studies have examined the injection-related HIV risk behaviours associated with injection of OST, such as methadone and buprenorphine[155-160], with mixed findings.

In France, however, buprenorphine injectors have been found to display *fewer* injection-related HIV risk behaviours than other groups of illicit drug users[160-161]. One study surveyed IDUs and found that 34% were polydrug users who occasionally injected buprenorphine in addition to heroin and/or cocaine,

while 24% had only injected buprenorphine in the previous six months. IDUs in this latter group were significantly younger, injected more frequently, and were more frequently on buprenorphine substitution therapy, but they were less likely to be HIV-infected and to report HIV-related risky injecting behaviours[160]. Injection-risk behaviours appeared more likely among those who were primarily using *diverted* buprenorphine (as opposed to injection of one's own medication); these users were also more likely to be unemployed and to be polydrug users[162-163].

In South Asia, attempts to compare IDUs who are "only buprenorphine or dextropropoxyphene" injectors and "only heroin" injectors, in cities where both licit and illicit opioids are available, has led to a situation fraught with difficulty[152]. The division has proved artificial because opioids injected by IDUs in these settings are mostly guided by the availability of the substances in the market and their cost rather than by individual choices. In fact, all of the 208 heroin injectors in a study from Chennai had also injected buprenorphine at some point in time of their injecting career[152]. Ninety percent of those who had reported ever using heroin had used it first through smoking and the rest had injected heroin when they were using it for the first time. Only 18 IDUs were exclusive buprenorphine injectors in this study.

## 5.3. Injection among those living with HIV

### 5.3.1. Effects of opioids and impact of injecting drug use

Some pharmaceutical opioids – e.g. oxycodone – are metabolised by the cytochrome isoenzyme CYP2D6[27], an enzyme that is severely impaired by liver dysfunction[27]. Harmful patterns of opioid use may mask symptoms associated with HIV, and dependent users may delay seeking testing or treatment for HIV infection[164].

### 5.3.2. Non-adherence to HIV treatment

Harmful patterns of psychoactive pharmaceutical use may interfere with adherence to HIV treatment regimens and lead to the development of viral resistance[165-166]. In these cases, it is important that treatment for drug use is initiated to support adherence to antiretroviral treatment and medical follow-up[29]. It has been shown that stopping drug injecting slows the progression of HIV disease in infected subjects[29]. Interventions could be developed to improve treatment adherence among HIV positive patients in antiretroviral therapy[167].

### 5.3.3. Interactions between opioids and HIV medication

The occurrence of HIV and HCV co-infection is common among IDUs, many of whom are opioid dependent. It is important to understand the adverse drug to drug interactions that may occur between antiretroviral therapeutic agents, unsanctioned psychoactive pharmaceuticals and the medications used in OST. For a detailed review of the drug interactions between antiretroviral drugs and co-medicated agents, see previous reviews[168-169]. The following summary outlines some of the main drug-drug interactions that have been identified.

Methadone has been the most widely used treatment for OST. Methadone has significant, adverse drug-drug interactions with Efavirenz and Nevirapine, which can contribute to non-adherence and poor clinical outcomes in this high-risk population[170]. For opioid-dependent IDUs who are HIV positive, methadone therapy may facilitate adherence to complex highly active antiretroviral therapy (HAART) regimens. Current HAART regimens include one or more nucleoside analogues. One study examined the effects of methadone on the pharmacokinetics of the tablet formulation of didanosine (ddI) and of stavudine (d4T). The results suggest that larger doses of the tablet formulation or an alternate formulation may be needed when didanosine is given to study subjects treated with methadone[171]. Pharmacokinetic studies have demonstrated that non-nucleoside reverse transcriptase inhibitors and some protease inhibitors may interfere with the metabolism of methadone, which in turn may lead to withdrawal symptoms[165, 172-174].

The extent to which these interactions may impact on adherence with HAART and illicit drug use has only received limited research attention. One US study found that diverted methadone was not

associated with HIV status or treatment, and was used among older heroin users to treat signs of withdrawal[55]. The absence of a higher rate of diverted methadone use among HIV-positive IDUs does not suggest that antiretroviral/methadone interactions are a primary determinant of use outside of treatment settings[55].

Buprenorphine is a more recent OST and as the number of persons receiving buprenorphine treatment and antiretroviral therapy continues to grow, so too does the existence and clinical impact of drug interactions between buprenorphine and HIV medications. The evidence to date suggests that buprenorphine may have fewer adverse interactions with antiretroviral agents[165, 170]. Buprenorphine has a significant kinetic interaction with Efavirenz but no dynamic interaction; therefore, simultaneous administration of these drugs is not associated with opioid withdrawal, as has been observed with methadone[170].

## 5.4. Viral hepatitis

Injecting drug use is now the dominant mode of transmission of HCV worldwide. Infection with HCV results in chronic infection in 50-85% of cases; approximately 7-15% of chronically infected persons progress to liver cirrhosis within 20 years, and of these, a proportion will subsequently develop liver cancer[29].

Compared to active heroin injectors, the risks of HCV transmission among prescription opioid injectors may be lower if the frequency of injection is less (as might reasonably be expected for those such as bupnreorphine, which have a longer duration of action). Evidence on the extent of HCV infection risk is, however, limited. In countries where pharmaceutical opioids are the predominant drug injected (e.g. some countries in Asia) most of the incident HCV cases among this group will be related to pharmaceutical injection[175-179].

## 5.5. Other injection-related problems

Injection-related problems can result from a number of different scenarios, such as non-sterile preparation of an injected substance, non-sterile injection sites, and repeated puncturing of major vessels. All of these situations can lead to a range of infective and non-infective complications[180], even where the pharmaceutical is a formulation specifically developed to be injected (e.g. some formulations of morphine). The injection of drug formulations that have been developed as oral, sublingual tablets or transdermal patches can lead to further complications. The availability of specific injecting equipment (e.g. availability of needles/syringes, winged vein infusion kits, pill filters, etc.) may also impact on the experience of harms.

As mentioned above, methadone injecting has been independently associated with higher levels of injection-related heath problems[158, 181]. The literature examining harms associated with pharmaceutical injecting focuses mainly on buprenorphine and methadone, and less is known about the injecting behaviour and harms associated with injection of other pharmaceutical opioids[156-157, 159, 182].

A case of paralysis of the long thoracic nerve of Bale resulting in winging of scapula has been recorded[183]. This was observed in a buprenorphine injector on the streets of Kolkata from a larger sample of street-based injectors; his arm muscles were atrophied due to neuralgic amyotrophy following repeated injecting of buprenorphine in the deltoid. Most of the injectors reported injecting buprenorphine alone or in a cocktail with injectable chlorpheniramine or promethazine[183]. One-third of the IDUs reported injecting drugs through intravenous route and an equal proportion took it intramuscularly, the rest switched intermittently between these two routes of injecting.

### 5.5.1. Consequences of injecting drugs formulated for oral use

Some opioid injectors produce solutions from formulations intended for oral or sublingual administration so they can inject these preparations (e.g. methadone, buprenorphine, morphine tablets)[26, 184]. The

viscous consistency of oral liquids such as methadone make it unsuitable for injection and increase the likelihood of vein damage[182]. In one study of methadone clinic attendees who injected methadone, it was found that 58% had difficulty accessing veins and 30% had experienced vein problems as a result of injecting methadone[185].

Adding non-sterile water to methadone syrup or sublingual buprenorphine tablets carries the additional risk of infection/contamination. The crushing and dissolution of tablets (such as morphine, oxycodone, etc.) intended for oral administration also carries further risks. For example, the additives and particulate matter in tablets developed for oral ingestion can cause vein damage. Further, tablets are not produced in sterile environments and are bulked out with insoluble particulates[186-187], which add to the risks of injection-related problems.

The most common injury associated with injection of oral or sublingual drug formulations is vascular and soft tissue damage, which can lead to a range of secondary complications[180, 188-189]. The injection of oral and sublingual formulations of pharmaceutical opioids (such as methadone, buprenorphine and oxycodone) has been associated with thrombosis[180, 190]; limb ischaemia (in some cases leading to amputation)[180, 190-191]; nerve damage[191]; tissue necrosis[188, 192]; rhabdomyolysis[190], pulmonary granuloma[192], and ocular candidiasis[193].

When buprenorphine is injected by an opioid-dependent individual, it can precipitate an uncomfortable withdrawal syndrome. This may last several hours or, if used in large quantities, may last as long as three to four days[51, 190], and may be even more exacerbated if buprenorphine-naloxone is injected[42, 63, 194].

Examples of serious physical consequences of injecting drugs formulated for oral use in South Asia came from Mizoram, one of the north-eastern Indian States bordering Myanmar[195-196]. Stringent laws and enforcement activity against heroin trafficking and peddling in the early 1990s in Mizoram, and the early 2000s in Manipur, resulted in a shift among local youths towards injecting dextropropoxyphene. The synthetic powder emptied from the capsules (containing dextropropoxyphene, diazepam and paracetamol), obtained from peddlers or procured over the counter, is injected after dissolving it in water by heating up the solution in easily available containers such as a spoon or the metal caps of beverage bottles[196]. A surgical ward dedicated to deal *only* with physical consequences of dextropropoxyphene injecting (non-healing ulcers, cases requiring skin grafting, osteomyelitis, amputation etc.) had to be established in one of the prime hospitals of Aizwal, the capital city of Mizoram. It is capable of catering for only 15 people at a time and is reportedly adequate for only one-third of demand at any given point in time[195].

## 5.5.2. Consequences of injecting transdermal patches

Transdermal patches were developed as a non-intrusive system for delivering a time-released dose of a medication through the skin. They are commonly used in nicotine replacement therapy ("nicotine patches"). Opioid transdermal patches (e.g. transdermal fentanyl patches) have been associated with harmful patterns of use and injection. When aspirated with a syringe, the content of fentanyl patches can be injected; this practice has been associated with fatalities[197-199], probably related to the very high potency of the drug.

## 5.5.3. Infective complications

Injection of a non-sterile preparation of a pharmaceutical (that is itself not produced in a sterile environment) carries the risk of contamination with bacteria, fungi and other microbes that can cause infection and disease. Contamination may occur through contact with skin flora, re-use/sharing of injecting equipment, contact with non-sterile surfaces, removal of a supervised dose from the mouth (for injecting at a later time), and repeated puncturing of veins (leaving injecting sites vulnerable to infection).

The injection of methadone has been associated with abscesses and infections at injecting sites[156, 200]. The injection of buprenorphine has been associated with abscesses, cellulitis, endocarditis, myositis/pyomyositis, and multiple reports of candida endophthalmitis[180, 191, 193, 201-204]. Candida endophthalamitis has been reported from injecting buprenorphine prepared with lemon juice containing

fungus (*C albicans*) or contaminated with fungi from an oral infection (in the case of removal of a supervised dose)[180]. In India, one-third of street-based IDUs in Kolkata had had an abscess within the last six months, with 12% having had maggots growing in them, reflecting neglect of health among street recruited IDUs in this region[183].

## 5.6. Polydrug use and interactions

Alcohol, opioids and benzodiazepines all have sedative effects, and the interactions between these drugs increase the risk of toxicity and adverse effects. The combination of opioids with other sedative drugs places users at increased risks of polydrug dependence, overdose and perhaps more severe withdrawal. There is good evidence of high rates of comorbid benzodiazepine and opioid use in particular[57, 74-75, 158, 205-213].

Opioid potentiation of the sedative response to benzodiazepines has been observed in the anaesthetic setting as well as among individuals who co-ingest these drugs[12, 26, 214]. Among a cohort of methadone patients in Italy, those with comorbid benzodiazepine use problems were more likely to have experienced significant social and drug use problems during follow-up[214]. A recent UK study also found that dependence upon benzodiazepines worsened the withdrawal syndrome for opioids[215].

The clinical picture for IDUs with comorbid opioid and other drug dependence also tends to be much more complex. There is evidence that those with comorbid benzodiazepine use problems are more disadvantaged, engage in higher levels of risk behaviours (both injecting and other), and that they are likely to have comorbid mental health problems[158, 208, 214, 216-218].

## 5.7. Non-fatal overdose

Non-fatal overdose causes considerable morbidity among IDUs[219]. Among heroin users, non-fatal overdose is a significant risk, particularly for those injecting the drug[219]. The magnitude of risks for pharmaceutical opioid users and injectors is less well studied, but there are good reasons to expect that the magnitude of risk might be less than for heroin because of the slower onset of effects, or the partial agonist effects[220-221].

There are risks nonetheless. The injection of methadone carries risks due to its unique pharmacological characteristics: it builds slowly to peak blood levels and has a long half-life, leading to an accumulation in the body that can result in toxicity and increased likelihood of mortality[17, 26, 158, 222]. Buprenorphine carries virtually no risk of non-fatal opioid overdose (respiratory depression, and CNS depression)[24, 223-224] if the drug is taken on its own without any other CNS depressants. Risks are greater when polydrug use occurs: a number of studies have found that the toxicity of methadone and buprenorphine are increased when used in conjunction with other opiates, benzodiazepines and/or alcohol[206, 220-221] .

A recent study found that among persons who had used both buprenorphine and methadone, symptoms of opioid toxicity were more likely for methadone and non-fatal overdose on methadone was 10 times more likely[206]. Injection of the medication was more strongly related to buprenorphine toxicity, whereas methadone toxicity was likely to have accompanied co-administration of heroin; the consumption of benzodiazepines was common in both cases[206].

## 5.8. Mortality

Compared to heroin, the risk of death – both for overdose and other causes – for many pharmaceutical opioid drugs is likely to be significantly lower, regardless of whether the user is in maintenance treatment or not. The reason for this lower risk is related to the slower onset of action, the impact of sustained release preparations[225], and in the case of partial agonist drugs such as buprenorphine, the ceiling effect for the agonist component of the formulation.

One exception is fentanyl, a very potent and short-acting opioid[197]. Harmful use of transdermal fentanyl patches have been associated with deaths in the United States[226-227], Canada[199], Europe[198] and Australia[228]. Deaths have also been associated with clandestinely produced fentanyl[229].

Buprenorphine has a smaller risk of fatal overdoses than heroin or other full-agonist opioids[221, 230-231]. Factors associated with fatalities include intravenous administration, high-dose buprenorphine and especially concomitant use of benzodiazepines, neuroleptics and/or alcohol[232-237]. One study has noted that the introduction of high-dose buprenorphine in France coincided with a substantial *decrease* in opioid poisoning mortality[221]. Similar reductions in overdose mortality have been noted in the United Kingdom following treatment expansion[238].

A number of international studies have examined deaths associated with methadone[221, 233, 239-243]. These studies have identified that a number of deaths have occurred in IDUs who had recently commenced methadone where high doses were involved[239, 244]; one Australian study concluded that in the first two weeks after treatment induction, the mortality risk was six times that of heroin users *not* in treatment[245]; thereafter, mortality risk decreased markedly below that of non-treated heroin users[245-246].

In most of these cases, individuals had obtained methadone from sources other than the substitution therapy programme[26]. Of the methadone-related deaths identified in a study in New Mexico (1998-2002), 22% were due to methadone alone, 24% were due to a combination of methadone and other prescription drugs, 50% were due to the combination of methadone and other illicit drugs and 3% were due to the combination of methadone and alcohol[243].

One factor that significantly increases mortality risk for all opioids (whether heroin or prescription) is the use of multiple depressant drugs. Concurrent use of pharmaceutical opioids and benzodiazepines, with and without alcohol[247-248], are commonly associated with unintentional drug overdose deaths[221, 243, 247]. Deaths attributed to oxycodone are also usually associated with polydrug use in which oxycodone was combined with psychostimulants, other opioids, antidepressants, benzodiazepines or alcohol[27, 249-250]. The contribution of the CNS depressant drugs, benzodiazepines and alcohol, is particularly important.

# 6. Pharmaceutical opioid availability, use, injection and HIV

In this section, we summarise pharmaceutical opioids available for the treatment of pain and for OST, from peer reviewed and grey literature, in particular the INCB consumption estimates[18-19]. Data from extensive searches are presented on misuse, injection, and HIV among injectors of these drugs.

INCB data are the only data collected internationally on opioid pharmaceutical availability. The following issues make it difficult to comprehensively evaluate adequate coverage of required medical needs or estimate the scale of misuse/diversion across different countries:

- The INCB only collects data on total narcotic (opioid) "consumption", as per the terms of the 1961 UN *Single Convention on Narcotic Drugs*[vi] and psychotropic drugs (including buprenorphine) as per the 1972 UN *Convention on Psychotropic Substances*[vii].

- "Consumption" includes opioids that are used by the population, *as well as* those used in the manufacture of other opioid-containing preparations, which may include medications that combine morphine, codeine, dextropropoxyphene and opium with other drugs. Opioids contained in these other compound opioid preparations may be transported to other countries and/or consumed domestically; because governments have no obligation to report on the export and import of these Schedule III preparations, this export and consumption is not recorded in INCB reports[18].

- The INCB presents information on the average consumption of narcotic drugs in each country calculated as *defined daily doses for statistical purposes* (S-DDD) per million inhabitants per day. These exclude Schedule III preparations[18]; we list these in the tables.

In many countries, the primary response to concerns about diversion and injection seems to be a reluctance to provide opioids for the treatment of pain and, to a greater extent, for OST. To provide insufficient pharmaceutical opioid coverage (for pain *and* illicit opioid dependence) is against the recommendations of international health and regulatory bodies. Such an approach also clearly fails to preclude misuse, diversion and injection.

## 6.1. Eastern Europe and Central Asia

In many countries in this region, large populations of injecting heroin users have become firmly established, and HIV has become prevalent among these IDUs. In general, availability of pharmaceutical opioids for OST is also limited and treatment entry difficult, or completely lacking in some countries (Table 6). Pain management seems limited in some countries in this region, which will limit the availability of drugs such as morphine for medical and extra-medical use (Table 6). In some countries, there is evidence of injection of pharmaceutical opioids among these established populations of heroin-dependent IDUs, but injection was not necessarily occurring in the context of good provision of opioids for medical purposes (Table 7). We briefly summarise trends below.

[vi] See: http://www.incb.org/pdf/e/conv/convention_1961_en.pdf
[vii] See: http://www.incb.org/pdf/e/conv/convention_1972_en.pdf

In **Armenia**, a significant problem has emerged with the injection of heroin, related to a favourable climate for cultivating opium poppies and well-developed access routes into Iran ensuring a relatively good supply of heroin from Pakistan and Afghanistan[251]. No mentions of the extent of pharmaceutical opioid diversion or injection were located, but opioid pharmaceuticals appear to be available on the illicit market[252]. The extent of use of opioid medication for medical purposes in the country is low (Table 6); in general, access to WHO essential medicines was judged to be very poor in this country due to "an extremely low level of both public pharmaceutical expenditures and population incomes" (p.10)[253]. It was estimated in 2000 that HIV prevalence among heroin IDUs in **Armenia** was 14%, and IDU is a major route of HIV transmission in the country, accounting for 54% of infections[251-252]. Although injecting harm reduction such as NSPs has been introduced, no OST is available[251].

Low levels of opioid consumption per capita are reported for **Azerbaijan**; no information on the injection or misuse of pharmaceutical opioids was found.

**Belarus** has traditionally received significant supplies of heroin from Afghanistan through the Russian Federation which ensured the development of a population of heroin IDUs[254]. In recent years, cases of methadone misuse and diversion have been recorded, including injection in combination with heroin and opium[254]. In 2005, 166 registered patients (1.7%) were in treatment for methadone use problems (up from one in 2003), concentrated in Minsk City and Mogilev Oblast. According to the Ministry of Interior, illicit methadone seizures grew by 14 times from 1997-2005. Methadone "has been gradually replacing heroin as the drug of choice"[254], although homemade opium typically dominates. Few users request treatment because of fear of reprisals, so "treatment" is only provided if users are detected by police. No OST is available in the country and no treatment guidelines exist[254-255]. HIV is an issue among IDUs in the country. The first outbreak was in Svetlogorsk in the late 1990s[256], with over 90% of HIV-positive persons having injected narcotics and transmission thought to be due to injection of "a ready-made HIV-infected drug which had been supplied for sale"[256], presumably home-produced opium[254]. At the end of 2005, IDUs accounted for 62% of prevalent and 37% of incident HIV infections in **Belarus**[254].

No reports of opioid pharmaceutical injection or diversion were found in **Bosnia and Herzegovina**, although heroin injection is an issue. Methadone has been established for both withdrawal and maintenance treatment[255, 257]. No measures of prevalence among IDUs were identified but HCV among methadone clients was reported to be 68-81%[257].

In **Bulgaria**, heroin appears to be the major opioid problem and is mentioned in over 95% of drug treatment episodes[258-260]; however, reports exist of methadone diversion[259-261] and 28% of IDUs not in treatment report extra-medical methadone use[258]. Between 1996 and 2000, "other opioids" were mentioned in 2% of acute drug poisonings[262]. In the general population, 0.2% report using opioids other than heroin, 0.6% of males less than 30 years of age had used methadone at some point in their lifetime and 1.8% of men and 0.7% of women had used morphine, codeine or pethadine[260]. There were 670 methadone patients as of 2003[258] but no other OST is available[255, 259]. A trial of slow release oral morphine as substitiution treatment for heroin dependence has been conducted, with promising results[263].

In **Croatia**, heroin is a problem for many drug treatment entrants and methadone has been established as a widely used OST for some time[255, 264-265]. Although there have been reports of methadone on the black market, it is reportedly very expensive and is detected in less than 10% of overdose deaths in the country[265].

In the **Czech Republic**, an increase in the number of people using buprenorphine sourced from the black market was reported in 2004[266]. Buprenorphine is reported as the primary drug of choice for 1.8% of IDUs[267] and was used by 41% of drug users at a low-threshold centres and outreach programmes[267].

Among outpatients treated for opioid dependence, methadone and other opioids are the primary drugs of dependence for 3.5% and 13% respectively[259]. Approximately 2,000-3,000 persons were in OST in 2004. Methadone can only be prescribed in a specialist clinic[268-269], but buprenorphine can be prescribed by any GP regardless of training[259, 266]; a recent survey found that many current prescribers were willing to prescribe the drug[270]. It is estimated that approximately 7-9% of the 5,200 GPs in the Czech Republic prescribe buprenorphine[266]. Methadone is rarely a diverted drug in the Czech Republic, but buprenorphine has been identified as a diverted and injected drug[266, 271-272]. Buprenorphine injection may be more common than heroin injection in some cities[266]. Some have called for greater training of physicians who prescribe this drug, and for the introduction of buprenorphine-naloxone[272]. Rates of HCV and HBV among methadone clients are high, with 72% testing positively to one or both[273], but HIV is almost zero among IDUs in the country and there are some indications that HCV prevalence may be decreasing[266]. No overdoses have been identified involving any OST drug[266].

**Estonia** has an established population of heroin injectors. In a 2005 study, 59% of IDUs were reported to have injected fentanyl as their main drug in the past four weeks[274]. There is significant treatment demand for OST, with methadone treatment numbers rising consistently since its introduction in 2003[259, 275-276]; buprenorphine has also been introduced[276]. There are reportedly insufficient services to meet growing demand, probably related to the high cost of providing methadone through specialised services (of which there are very few)[259]. HIV prevalence has been very high (54%) among IDUs[277], as has HCV, but there are signs that incidence is decreasing[275].

In a 2000 study of IDUs in **Georgia**, the primary drugs of injection were heroin, homemade opiates (from poppy straw) and opium, but no mention was made of pharmaceutical opioids[278]. This has changed dramatically in recent times, with recent reports of an "epidemic" of buprenorphine misuse and injection in the country, with users apparently seeing the drug as a "cleaner" alternative to heroin and 70% of "drug addicts" injecting it[4]. The drug is reportedly being smuggled over the border from countries providing buprenorphine as an OST, including France[4]. Calls to introduce the drug as an OST have so far gone unheeded[4]. Among IDUs, prevalence of HIV and HCV are 2% and 68%, respectively.

Heroin has been a common drug used among IDUs for many years in **Hungary**[279-280] and the use of OST (methadone) has been in place for 20 years[259, 281], but not without disagreement between medical professionals and police, and unfavourable media depictions[282]; consensus clinical guidelines were not drafted for 10 years[281]. No reports of diversion of OST or injection of pharmaceutical opioids were found; however, 2.3% of outpatients treated for opioid dependence reported methadone and 23% opioids other than heroin as their primary drugs of choice[259]. Opioids were reported as the second most commonly detected drug in army conscripts[283] and 0.3% of the general population report having used opioids other than heroin[148].

No data could be located on misuse or diversion of pharmaceutical opioids in **Kyrgyzstan**. Outbreaks of HIV have been recorded among IDUs[284], presumably among those injecting heroin. No OST is available for the treatment of heroin dependence.

In **Latvia**, 0.4% of the general population reported having used opioids other than heroin[148]. The country had 54 methadone and 38 buprenorphine maintenance clients in 2004[285]; OST in the country has been described as "underdeveloped" with treatment provided through specialist hospitals[255, 259]. In 2004, it was noted that fewer clients were presenting for outpatient non-OST or OST treatment for heroin use problems. Few reports of pharmaceutical opioid use among clients were noted by methadone clinics; however, around 10% of outpatient non-OST treatment episodes and 31% of new treatment entrants in 2004 were for problems with opioids other than heroin[285]. Reduction in HIV transmission due to IDU has occurred since 2001[285].

**Lithuania** has had both methadone and buprenorphine available as OST for illicit opioid dependence for over a decade, through specialised and private treatment centres; methadone was provided to 332 patients[259]. Treatment clients' details are registered in a central registry and OST is typically administered in a supervised fashion, although takeaway doses are permitted for stable clients[286]. Use of pharmaceutical opioids was not reported among methadone maintenance treatment (MMT) entrants[287]. HIV prevalence is low among IDUs (but nonetheless comprises 75% of HIV infections in the country), but HCV is more prevalent[288].

In the **Republic of Moldova**, no data could be located about pharmaceutical opioid misuse. Attention has been drawn to the very low coverage of pain management with pharmaceutical opioids for cancer and HIV/AIDS palliative care[289] (Table 6). There is insufficient funding to support even a palliative care system in the country, although plans were drawn up for one in 1994[290]. Opioids are incredibly expensive to purchase in the country and only 770 patients received them in 2002 out of a total population of 4.4 million[290].

Opioid use in **Poland** evolved with the expanding economy from the use of poppy straw or "kompot" during the late 1960s and 1970s to heroin or "brown sugar" in the late 1990s; smoking was initially the dominant route of administration, but injecting became entrenched among some users. The first case of HIV among IDUs was detected in 1988[291] and it has spread since then; a recent study estimated HIV prevalence at 12% and HCV at 60%[292]. OST was introduced in 1992, largely methadone although buprenorphine is allowed[259, 293]. Treatment is free, but some clients wait for over two years to enter treatment[255]. No reports of diversion of pharmaceutical opioids could be found.

In **Romania**, pharmaceutical opioid availability has been traditionally limited for all indications. Recently, a national policy for palliative care was developed to address this issue[294-295]. Heroin injection is commonly reported among drug treatment entrants in the country[296], with 21% of such clients receiving methadone OST in 2004[259]; buprenorphine is available but reportedly too expensive for most clients, and is little used. No reports of diversion, misuse or injection of pharmaceutical opioids were located in this review.

In the **Russian Federation**, considerable harm related to injecting heroin use exists, with the country having the most explosive HIV epidemic in Eastern Europe among IDUs[297]. Methadone is prohibited and no OST or treatment guidelines are available[255, 298], despite the HIV epidemic and considerable lobbying on the part of clinicians and researchers[299-301]. Pharmaceutical opioid availability for pain treatment is extremely limited. No reports of diversion, misuse or injection of pharmaceutical opioids were located in this review.

**Slovakia** has had an established heroin use problem for some time[302-303]. In recognition of this, OST has been introduced for treatment of opioid dependence[259, 303]. Opioid pharmaceutical prescribing for pain, particularly morphine, is very low, although some increases have occurred in recent years[304]. Among clients of a low-threshold agency, pentazocine and buprenorphine were used by 7% and 1% respectively[305]. In Košice, 53% of low-threshold agency clients cited pentazocine as their primary drug[305]. Opioids other than heroin were the primary problem among 3% of all users in one treatment sample[305] and among 10% of outpatient clients being treated for opioid dependence[259]. Among opioid users in treatment, 29% were reported to be inject opioids other than heroin[305].

In **Tajikstan** and **Turkmenistan**, no reports were obtained of pharmaceutical opioid misuse, diversion or injection. This is not surprising, given the low level of availability of drugs in those countries for any indication, including OST, despite good evidence of established heroin/opium injecting populations in those countries[306-308], some with very high HIV prevalence[308].

In the **Ukraine**, 72% of HIV is attributable to IDU[309]. Recognition of the problem of injecting heroin use, with high risk of HIV transmission[310-311], has led to the introduction of OST and other injecting harm reduction projects in the country[255, 312-314]. No reports of pharmaceutical opioid diversion were located for this report.

No reports of diversion, misuse or injection of pharmaceutical opioids in **Uzbekistan** or **Kazakhstan** were located in this review.

**Table 6: Availability of pharmaceutical opioids in Eastern Europe and Central Asia, by country**

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Armenia** | Codeine, Fentanyl, Morphine, Piritramide, Trimeperidine | n/a | 22 |
| **Azerbaijan** | Codeine, Fentanyl, Morphine, Trimeperidine | Methadone | 22 |
| **Belarus** | Codeine, Dextropropoxyphene, Ethylmorphine, Fentanyl, Methadone, Morphine, Trimeperidine | n/a | 61 |
| **Bosnia & Herzegovina** | Codeine, Methadone, Morphine, Pethidine, Pholcodine, Thebaine, Tilidine | Methadone | 95 |
| **Bulgaria** | Codeine, Dextropropoxyphene, Dihydrocodeine, Ethylmorphine, Fentanyl, Methadone, Morphine, Pethidine, Tilidine | Methadone | 540 |
| **Croatia** | Alfentanil, Buprenorphine, Codeine, Ethylmorphine, Etorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone, Pethidine, Sufentanil, Tilidine | Methadone Buprenorphine | 1,633 |
| **Czech Republic** | Acetyldihydrocodeine, Alfentanil, Alphaphrodine, Bezitramide, Buprenorphine, Codeine, Dextropropoxyphene, Dihydromorphine, Ecgonine, Ethylmorphine, Etorphine, Fentanyl, Heroin, Hydrocodone, Ketobemidone, Levorphanol, Methadone, Morphine, Norcodeine, Normethadone, Oxycodone, Oxymorphone, Pethidine, Pirtramide, Remifentanil, Sufentanil, Thebaine, Tilidine | Methadone, Buprenorphine | 1,283 |
| **Estonia** | Alfentanil, Buprenorphine, Codeine, Dihydrocodeine, Ethylmorphine, Fentanyl, Hydromorphone, Ketobemidone, Methadone, Morphine, Oxycodone, Pethidine, Remifentanil, Sufentanil | Methadone, Buprenorphine | 746 |
| **Georgia** | Codeine, Fentanyl, Methadone, Morphine, Trimeperidine | Methadone | 74 |
| **Hungary** | Alfentanil, Codeine, Dextropropoxyphene, Dihydrocodeine, Diphenoxylate, Ethylmorphine, Etorphine, Fentanyl, Methadone, Morphine, Oxycodone, Pethidine, Sufentanil | Methadone | 1,826 |
| **Kazakhstan** | Codeine, Fentanyl, Morphine, Thebaine | n/a | 69 |
| **Kyrgyzstan** | Fentanyl, Methadone, Morphine, Trimeperidine | Methadone | 129 |
| **Latvia** | Buprenorphine, Codeine, Fentanyl, Ketobemidone, Methadone, Morphine, Oxycodone, Pethidine, Remifentanil, Trimeperidine | Methadone | 858 |
| **Lithuania** | Fentanyl, Methadone, Buprenorphine, Morphine, Pethidine, Rifentanil | Methadone, Buprenorphine | 505 |
| **Moldova** | Codeine, Ethylmorphine, Fentanyl, Methadone, Morphine, Pethidine, Piritramide, Thebaine, Trimeperidine | Methadone | 74 |
| **Poland** | Alfentanil, Buprenorphine, Codeine, Dextromoradomide, Dihydrocodeine, Ethylmorphine, Fentanyl, Heroin, Methadone, Morphine, Oxycodone, Oxymorphine, Pethidine, Remifentanil, Sufentanil | Methadone | 1,052 |
| **Romania** | Codeine, Dihydrocodeine, Fentanyl, Methadone, Morphine, Oxycodone, Pethidine, Remifentanil, Sufentanil | Methadone, Buprenorphine | 257 |
| **Russian Federation** | Codeine, Dihydrocodeine, Fentanyl, Morphine, Thebaine, Trimeperidine | n/a | 129 |
| **Slovakia** | Buprenorphine, Codeine, Diphenoxylate, Ethylmorphine, Hydromorphone, Methadone, Morphine, Oxycodone, Pethidine, Remifentanil, Sufentanil, Thebaine, Tilidine | Methadone | 901 |
| **Tajikistan** | Codeine, Ethylmorphine, Etorphine, Fentanyl, Morphine, Trimeperidine | n/a | -- |
| **Turkmenistan** | Codeine, Ethylmorphine, Fentanyl, Hydrocodone, Morphine, Trimeperidine | n/a | 5 |
| **Ukraine** | Buprenorphine, Codeine, Dextropropoxyphene, Fentanyl, Morphine, Thebaine, Trimeperidine | Methadone | 106 |
| **Uzbekistan** | Codeine, Fentanyl, Morphine, Remifentanil, Sufentanil, Thebaine,Trimeperidine | n/a | 6 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.2. South Asia

In some South Asian countries, there have been marked problems related to pharmaceutical opioid misuse and increasingly, injection, particularly in **India**, **Nepal**, **Pakistan** and **Bangladesh**. The pharmaceutical opioids being misused in this region are typically lower potency opioids such as codeine, nalbuphine and dextropropoxyphene, in contrast to the pharmaceutical opioids being used by IDUs in other regions around the globe that include oxycodone and morphine, and high-dose buprenorphine.

Some have suggested that a shift from heroin smoking to pharmaceutical opioid injection may have been related to reduced availability or increased costs of heroin at certain times, the low cost and easy availability of pharmaceuticals, and legal controls introduced in India to address heroin supply[316-317]. Some of the reasons for shifting from heroin smoking to pharmaceutical opioid injecting deriving from studies in the region[179, 318-319] include:

- non-availability of heroin for smoking;
- injecting less costly compared to heroin smoking;
- smoked/chased heroin failing to elicit the desired effect due to increased tolerance;
- the influence of peers;
- in order to give up heroin smoking (learnt by those who were admitted for drug treatment and treated with buprenorphine injection by the treating physicians); and
- consistent quality and better "high" of the pharmaceuticals compared to the heroin available on the streets.

These problems have occurred despite very low levels of licit opioid medication consumption for medical purposes in this region (Table 8) suggesting that misuse has not been avoided simply through having supplies of the drug for medical purposes. Consistent reports indicate that prescribing for all types of pain is inadequate in this region; OST is available in some countries but better coverage is needed, particularly since IDU is driving the HIV epidemic in some countries. HIV and HCV co-infection are common among IDUs in the region.

A recent United Nations Office on Drugs and Crime (UNODC) report concluded that the diversion of pharmaceutical opioids for misuse and trafficking is occurring on a large scale both within and outside the region primarily because "drug law enforcement agencies in the region such as police and customs have other primary responsibilities and hence drug law enforcement does not receive the attention it deserves. Often, the officers are also not adequately trained or equipped to undertake drug law enforcement" (p.4)[320]. Due to limited enforcement of pharmaceutical regulations, it is thought that **India** accounts for significant large-scale diversion both within the country and to other countries in the region[321], and to countries further afield through illegal online pharmacies based in India[320].

Over the past 15 years, a decline in use of natural opiates in India has been accompanied by an increase in pharmaceutical opioid injection. Injection as a route of administration in general has increased in multiple states, particularly in the North East[150, 153]. Buprenorphine was not originally recommended for international control[322] and in India its ease of availability over the counter at pharmacies, its purity, and lower cost probably led to misuse and diversion[153]. It was available in injection ampoules of 2ml (equivalent to 0.6mg of buprenorphine) and also 0.2 mg sublingual tablets[6]. The first case of buprenorphine misuse was documented in 1987 and the problem has been growing ever since[6, 323]. It was recently reported that considerable proportions of IDUs in India are using buprenorphine, dextropropoxyphene and pentazocine along with benzodiazepines and antihistamines[150]. It has been

reported that in some urban centres, up to 100% of IDUs inject pharmaceutical opioids[316]. One study in Darjeeling found that 42% of IDUs injected morphine, and 25% injected dextropropoxyphene[177]. HIV prevalence among these IDUs was 12%, and HCV 48%[177]. About 52% of IDUs had visited sex workers, and 15% had had a sexually transmitted infection (STI) during the same period[177]. Among active female sex workers, 13% reported injection of propoxyphene[324]. In a sample of 35 Indian women in treatment for drug dependence, 60% were dependent upon opioids, almost all using pentazocine and dextropropoxyphene[325]. Most injected the drug, and a significant proportion had originally been prescribed opioids because of pain conditions[325]. Another study investigation "at-risk young people" found that 10% had used pharmaceutical opioids. Drug treatment in India is largely abstinence based, although there is some availability of slow release oral morphine as an OST[326] and high-dose buprenorphine has been introduced as an OST. Nine percent of OST entrants reported pharmaceutical opioids as their primary drug problem in one study[327]; in another, 52% of IDUs receiving OST were injecting dextropropoxyphene (with or without heroin)[328]. With the exception of north-eastern states, NSPs are "the exception rather than the norm" (p.961)[153]. HIV is prevalent among IDUs in the country – 10% in 2005[150] – but areas of very high prevalence have been documented (prevalence can range from 2-63%)[153].

In **Nepal**, buprenorphine has reportedly emerged as the favoured drug of injection among IDUs[150, 153, 329] and is smuggled over the border from India[153]. There is no specialised drug treatment sector; non-government organisations (NGOs) provide abstinence-oriented treatment, and methadone is no longer available[153]. Among IDUs in Nepal, HIV prevalence may be 40%, with rates of 70% in Kathmandu[153]; HIV is thought to have spread into this population from India rather than South East Asia[330].

In **Bangladesh**, the most commonly injected drug among IDUs is buprenorphine[150, 331-332], which has been a shift from heroin smoking[150, 153]. The common causes cited in one study for switching to injecting were low cost and easy availability of injectable preparations[150]. There is also thought to be a problem with phensedyl®, a codeine-based cough syrup, which is thought to be smuggled over the border from India[331, 333] – many buprenorphine users reported typically combining it with other drugs including benzodiazepines in one study[331]. Six percent of treatment entrants report using pharmaceutical opioids[334]. Among female drug users who injected drugs (many of whom sold sex), injection of buprenorphine was reportedly "common"[335], and at the time of their last injection, most shared the ampoule of buprenorphine[335]. HIV prevalence has reached 7% among IDUs in Bangladesh[336], and in some cities is as high as 10.5%[336]. Among female IDUs, HCV prevalence was found to be 16.5%[335] but is reported to be much higher among males: 56% in Dhaka[336]. The introduction of NSPs is thought to have reduced needle sharing and other HIV risk behaviour among IDUs[332, 337], but coverage in the country is "suboptimal"[153]. Drug treatment is very limited, and OST is not available[153].

In **Pakistan**, prescription of pain medication is only premitted through hospitals[338], and as Table 8 shows, opioid medications are very seldom prescribed. In the general population, 18% of young people have ever used pharmaceutical opioids[339]. Not all heroin users inject[340], but most IDUs inject heroin[150, 341]. There have been some reports of very limited pharmaceutical opioid injection[153]. "Synthetic drugs" may be more likely to be injected by younger, more at-risk IDUs[150]. Sharing of injection equipment among heroin users is common[341] and many have poor HIV knowledge[342]. Many current injectors have limited contact with treatment centres[343], which appear to focus upon withdrawal and abstinence oriented approaches to treatment[153]. In Pakistan, overall HIV prevalence may still be low among IDUs[344], but HCV prevalence is high[150, 179, 341]. In one setting in Quetta, HIV prevalence among IDUs was 24% and HCV 50%, with co-infection at 20%[345]. One source reported 80% of IDUs as being HCV positive[344].

In the **Islamic Republic of Iran**, no opioids are available over the counter, and with the exception of codeine and tramadol, only medical specialists can prescribe them. Not surprisingly, given the proximity

to the world's largest opium producing areas, though, the population prevalence of illicit opioid dependence is thought to be very high: over one million people are thought to be currently dependent on the drug according to a population-based survey, the "Epidemiological Study of Drug Abuse in Iran, 2001"[346]. Most smoked opium, but 25% reportedly injected heroin[346]. According to the Iranian Drug Control headquarters, 1,000 tonnes of opioids are consumed annually in the country – it was not clear according to this source how much of this was opium, morphine and heroin[346]. Buprenorphine and methadone are being rapidly introduced around the country as OST for illicit opioid dependence[347-348], given the high prevalence of dependent use and the rapid spread of HIV among risk populations, particularly prisoners.

Levels of *pharmaceutical* opioid misuse and injection in the Islamic Republic of Iran were difficult to ascertain for this report, although reports of buprenorphine "availability" were noted in a rapid assessment, presumably referring to buprenorphine on the black market[349]. There are reports of buprenorphine and methadone injection occurring in some areas[349] but heroin remains the most commonly injected opioid[350]. In a school sample, 0.5% of male students but no female students reported pharmaceutical opioid use[351]. Among at-risk youth, 1-8% reported using pharmaceutical opioids[339]. In a study of opioid use (including heroin) among pain patients, 29% used opioids at admission[352]. There was no significant relation between opioid use and chronic pain, but there was a relationship with previous opioid use by friends, occupation, cigarette smoking, consultation for a psychological problem, and death of a spouse[352]. In other words, among an Iranian pain population, the risk factors for opioid use were fairly similar to those in other pain populations in high income countries: comorbid drug use, mental health problems and traumatic life events.

In **Afghanistan**, narcotic analgesics are reportedly widely available over the counter[353]. According to a 2005 UNODC survey, 3.2% of Afghanistan's population use illicit drugs (920,000 people), with 0.2% using heroin, 0.6% using opium and 0.8% using "pharmaceuticals". Some evidence exists of the use and injection of pharmaceutical opioids among drug users[354] and the transition to pharmaceutical opioid injection has been reported[355] but heroin remains the dominant drug injected[356]. Among IDUs, high rates of needle sharing have also been reported.

Though use is thought to be very low, in **Bhutan** there have been anecdotal reports of some opioid use (presumably heroin or opium), including injecting[150]. In the **Maldives**, heroin was mentioned as a drug of concern, but no reports of pharmaceutical opioid misuse were obtained in a recent rapid situation assessment[357]. In **Sri Lanka**, no reports of pharmaceutical opioid injection were located. It is estimated that there are currently about 45,000 regular heroin users in the country; very few (1-2%) are injecting the drug[150]. In all of these three countries, HIV rates among IDUs is reported to be low[316].

## Table 7: Availability of pharmaceutical opioids in South Asia, by country

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Afghanistan** | Codeine, Dextropropoxyphene, Diphenoxylate, Morphine, Pethidine, Pholcodine | n/a | Not reported |
| **Bangladesh** | Fentanyl, Morphine, Pethidine, Pholcodine | n/a | 4 |
| **Bhutan** | Codeine, Dextropropoxyphene, Fentanyl, Morphine, Pethidine | n/a | Not reported |
| **India** | Buprenorphine, Codeine, Dextropropoxyphene, Diphenoxylate, Ethylmorphine, Fentanyl, Hydrocodone, Methadone, Morphine, Pethidine, Pholcodine, Sufentanil, Thebaine, Trimeperidine | Buprenorphine, Morphine | 8 |
| **Islamic Republic of Iran** | Alfentanil, Buprenorphine, Codeine, Diphenoxylate, Fentanyl, Morphine, Oxycodone, Pethidine, Remifentanil, Sufentanil, Thebaine | Methadone, Buprenorphine | 597 |
| **Maldives** | Fentanyl, Morphine, Pethidine | n/a | 6 |
| **Nepal** | Codeine, Dextropropoxyphene, Ethylmorphine, Etorphine, Fentanyl, Methadone, Morphine, Pethidine, Pholcodine | Methadone | 7 |
| **Pakistan** | Buprenorphine, Codeine, Dextropropoxyphene, Diphenoxylate, Fentanyl, Morphine, Fentanyl, Pethidine, Pholcodine | n/a | 2 |
| **Sri Lanka** | Codeine, Etorphine, Fentanyl, Methadone, Morphine, Pethidine | n/a | 238 |

n/a: Opioid substitution treatment not available in this country according to official statistics

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.3. East and South East Asia

In East and South East Asia, pain relief has been noted as "poor" in this region[358-359] with very poor availability of opioid medications (see Table 10), but some efforts are being made to increase coverage[360]. Few reports of pharmaceutical opioid diversion or injection were noted[361], with the exception of **Singapore**.

This was in contrast to the prominence of heroin as a drug of dependence in this region[361]; all countries are close to the heroin producing region of the "Golden Triangle". Opioid dependent users are presenting for treatment in this region, with considerable demand for OST. OST availability has traditionally been extremely limited, but in recent years, concerted efforts have been made to establish and roll out OST in several countries, particularly **China, Malaysia, Thailand** and **Indonesia**.

In **Cambodia**, use of pharmaceutical opioids among a very small percentage of medical staff has been reported (0.7% of clinical nurses) but no indication of more widespread use or injection was identified. IDU does occur in the country; NSPs have been implemented and OST is currently planned[362-365].

In **China,** medical opioid coverage for pain is low (Table 10). In one hospital of Nanjing Military Region, there have been some increases in opioid purchases, but this was largely for pethidine; morphine and fentanyl were less commonly used[359]. Methadone is being quickly rolled out as an OST, given good evidence of large populations of heroin users[361, 366].

In the **Democratic People's Republic of Korea**, there are reportedly adequate controls over narcotic drugs to the detriment of adequate medical access to opioids. The INCB recently urged the government to ensure appropriate coverage for medical purposes[19].

In **Indonesia**, no reports of problems related to pharmaceutical opioid misuse or diversion were located in the research for this report[367]. Opioid prescribing levels are low, at six doses per million of population per day (Table 10). There is a substantial problem related to IDU, primarily heroin use, however, and recognition of increasing HIV among IDUs sparked the development of a comprehensive public health policy in the country, which includes methadone as an OST, from 2002[287, 368].

In **Japan**, in 1987**,** the Ministry of Health established a new policy on palliative care, edited manuals on palliative care for terminally ill cancer patients, which included guidelines on cancer pain management, and revised narcotics control measures in order to improve the accessibility of opioids to cancer patients[360]. The annual consumption of morphine for medical purposes was only 65 kg in 1986 in Japan, but it rose to 973 kg in 1999[360]. The current morphine consumption per capita in Japan is still less than one-sixth of the consumption in the United States[360]. Morphine is typically orally prescribed and two-thirds of morphine preparations consumed are MS Contin Tablets. Approximately 70% of medical and nursing schools in Japan initiated the educational curriculum for cancer pain relief and palliative care. There have been government-sponsored, medical, nursing and pharmaceutical societies-sponsored seminar courses on appropriate morphine use in cancer pain management, palliative care and opioid availability, all of which have increasingly strengthened postgraduate education[360].

In **Malaysia**, methadone is widely used as an OST[369-370]. Naltrexone was introduced for the treatment of opioid dependence in 1999, buprenorphine was introduced in 2001, and methadone in 2003[369]. Agonist maintenance programmes were embraced rapidly by the medical community in Malaysia. Currently, over 30,000 opioid-dependent patients are treated with OST by more than 500 medical practitioners in Malaysia[369].

Morphine injection in Malaysia has been reported as a problem for some IDUs[361, 371]; in 2005, 25% of "drug addicts" used morphine[371]. Some evidence of extensive diversion through over-prescription by a few doctors led to their investigation and prosecution, and increased controls on imports of buprenorphine, with apparently marked reductions in diversion resulting[7].

In **Mongolia**, opioid medications are very limited in use[372]. The National Trauma Hospital in Ulaanbaatar uses more opioids for the treatment of non-malignant pain than any other facility in Mongolia, but only used 1,300 ampoules of morphine and 1,470 ampoules of fentanyl in 2004, only for very severe pain and under very strict conditions[372]. In 2006, doctors at the hospital became able to prescribe oral tramadol for the management of pain following discharge[372]. Among morphine IDUs interviewed (n = 22) in a recent Mongolian rapid assessment, most had a history of chronic pain for which they were prescribed injectable morphine[372]. These patients had developed dependence on morphine, using increasing doses and frequency, continuing to obtain the medication on prescription from pharmacies and supplementing with other means. Numbers presenting with such histories are reportedly very rare[372].

In the **Philippines**, there were reports of injection of nalbuphine hydrochloride in Manila, including among methamphetamine IDUs[80]. It is unclear how widespread this practice is. There is a clear reticence to prescribe opioids for non-cancer pain, with very low levels of opioid consumption in the country[373] (Table 10). Among doctors who typically possessed a narcotics licence, all of whom saw pain patients in their practice, 75% reportedly prescribed opioids, most commonly morphine, meperidine and nalbuphine[373]. It is unclear how the disparity between survey and official consumption data can be rectified, since only 15kg of the INCB allocation of 87kg are consumed every year[373].

In **Singapore**, buprenorphine was initially not a controlled drug[374]; it was introduced in 2002 to address heroin dependence. It was widely available in the primary care setting[375], and could be prescribed as an OST by GPs who, in the opinion of clinicians in the country, were "inexperienced" in treating the client group because of "grossly inadequate" training in addiction medicine (p.448)[376]. Fairly soon after its introduction, IDUs began presenting for treatment for their buprenorphine use, with 82% injecting[377], small numbers presented to hospitals with sometimes serious injection-related problems[180, 191, 374, 377-378], and deaths related to the drug slowly increased[235, 379-380]. One study of drug treatment entrants found that although many buprenorphine misusers had first started in order to attempt to cease heroin use, a significant proportion had initiated use out of "curiosity"[377].

High rates of buprenorphine injection have been observed among IDUs presenting for drug dependence treatment in Singapore, with most combining it with other drugs[377]. Among a sample of dependent buprenorphine injectors entering treatment, HCV prevalence was 43%. Risks of HCV were 5.6 times higher among those sharing needles, and 6.3 times higher among those using with others (peers or partners)[381]. It is considered the primary drug problem there, but recent data suggests that most buprenorphine users swallow the drug[361].

As a result of these increasing problems, in 2005, the Singapore Ministry of Health introduced a range of initiatives: clinical guidelines for the treatment of opioid dependence[380], central logging of prescriptions[374], and buprenorphine was made a controlled substance in 2006[380]. Takeaway doses, previously freely given, were discontinued, and all dosing supervised[380]. No new patients can now begin treatment, and a "voluntary rehabilitation programme" started, which essentially involved detoxification from the drug[380]. It is unclear to what extent this has had an impact on misuse, diversion, injecting, HIV or HCV.

In the **Taiwan Provence of China**, use of opioid prescription medication for pain is very low[382]. Heroin use appears to be the primary problem among IDU[361, 383-384]; however, in one study methadone was

detected in 0.4% of urine samples of individuals from "at-risk-groups"[385]. HIV is of increasing concern in the country: IDUs accounted for 69% of new HIV-1 cases in 2006, and rates among IDUs may be 15%[386]. In recognition of the severity of the problem, both NSPs and methadone as OST were implemented in 2005, with positive impacts – a 10% reduction in new cases of HIV among IDUs in the following year[386].

In **Thailand**, there is poor provision of opioids for pain relief[358]. There is a substantial problem related to illicit heroin dependence in the country[361, 387], with a high incidence and prevalence of IDUs who inject heroin[388-392], and prisons representing a risk environment for HIV infection[393-394]. Methadone programmes have been implemented as OST in the country as a result[287]. No reports were found of significant misuse or diversion of pharmaceutical opioids; methamphetamine and heroin use is seen as a more significant issue in this country[387, 389, 391, 395].

In **Vietnam,** no reports of pharmaceutical diversion or IDU were obtained for this report – heroin and opium appear to be the major drugs of injection in the country[396-397]. Pharmaceutical opioids are highly restricted, and one report noted that codeine is "the only practical opiate widely available both in and out of hospitals…many doctors are intimidated by the restrictions or fear of diversion. Most hospital pharmacies demand a return of used ampoules from the ward, doctor or patient before issuing a further supply"[398]. Not surprisingly, given this restriction, prescribing is very low in the country (Table 10) and pain relief is probably inadequate.

No reports of diversion, misuse or injection of pharmaceutical opioids in **Brunei Darussalam** or the **Republic of Korea** were located in this review.

## Table 8: Availability of pharmaceutical opioids in East and South East Asia, by country

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Brunei Darussalam** | Alfentanil, codeine, ecgonine, fentanyl, heroin, morphine, pethidine, remifentanil | n/a | 47 |
| **Cambodia** | Codeine, dextropropoxyphene, fentanyl, morphine, pethidine | n/a | 2 |
| **China** | Codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, fentanyl, hydrocodone, methadone, morphine, oxycodone, pethidine, pholcodine, remifentanil, sufentanil, thebaine, tilidine | Methadone | 41 |
| **Democratic People's Republic of Korea** | Codeine, dihydrocodeine, fentanyl, morphine, trimeperidine | n/a | 40 |
| **Indonesia** | Buprenorphine, codeine, ethylmorphine, fentanyl, heroin, methadone, morphine, pethidine, sufentanil | Methadone | 6 |
| **Japan** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, dihydromorphine, drotebanol, ethylmorphine, fentanyl, hydrocodone, hydromorphine, levorphanol, methadone, morphine, norlevorphanol, oxycodone, pethidine, remifentanil, sufentanil, thebaine | n/a | 543 |
| **Lao People's Democratic Republic** | Codeine, fentanyl, morphine, pethidine | n/a | 2 |
| **Malaysia** | Alfentanil, buprenorphine, codeine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone, pethidine, pholcodine, sufentanil | Buprenorphine, Methadone | 99 |
| **Mongolia** | Codeine, dihydrocodeine, fentanyl, morphine | n/a | 22 |
| **Myanmar** | Codeine, diphenoxylate, etorphine, fentanyl, morphine, pethidine | n/a | 3 |
| **Philippines** | Codeine, fentanyl, morphine, oxycodone, pethidine, sufentanil | n/a | 11 |
| **Republic of Korea** | Alfentanil, buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 249 |
| **Singapore** | Alfentanil, alphaphrodine, aniferidine, buprenorphine, codeine, dextropropoxyphene, diphenoxylate, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphine, pethidine, pholcodine, remifentanil, sufentanil, thebaine, tilidine | Buprenorphine | 505 |
| **Thailand** | Codeine, dextropropoxyphene, diphenoxylate, fentanyl, heroin, hydrocodone, hydromorphone, methadone, oxycodone, pethidine, thebaine | Methadone | 102 |
| **The Taiwan Provence of China** | -- | Methadone[386] | -- |
| **Timor Leste** | Codeine, fentanyl, morphine, pethidine | n/a | Not reported[18] |
| **Viet Nam** | Codeine,, dextropropoxyphene, fentanyl, methadone, morphine, pethidine, pholcodine, remifentanil, sufentanil | n/a | 9 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.4. Caribbean

Coverage of opioids for medical purposes is clearly inadequate in many countries in this region (Table 12). Governments are preparing legislation to improve controls over pharmaceutical substances: this includes **the Bahamas** and **Dominica**[19]. Few data could be located on the extent of pharmaceutical opioid misuse, injection or diversion. Given the low levels of consumption, it seems likely that the extent of pharmaceutical opioid misuse and diversion is not great, but there is a need for much better coverage of opioid medications for the treatment of pain and for OST.

This is particularly the case in **Puerto Rico**, where IDU is a major cause of HIV transmission and heroin is the most commonly injected drug[399-400]. The general population prevalence of HCV in San Juan is 6.3%, with estimates of 39% for heroin injectors[401]. HIV incidence rates are much higher among IDUs in Puerto Rico than in New York[402], whereas methadone and HIV treatment coverage is much worse[399], although methadone has been piloted in prison settings[403].

In **Cuba**, a comprehensive policy was taken at a national level in 1996 to address the limited use of medicines for major diseases, acknowledging the low levels of medicine use. A National Pharmacoepidemiology Network conducts regulatory, administrative, educational and information initiatives, including prescribing monitoring, training of health professionals, and monitoring of adverse events[404]. The use of opioids was not mentioned in a discussion of this network[404] and pharmaceutical opioid consumption remains at low levels (Table 12).

## Table 9: Availability of pharmaceutical opioids in the Caribbean, by country

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Antigua and Barbuda** | Codeine, dihydrocodeine, diphenoxylate, fentanyl, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 105 |
| **Bahamas** | Codeine, dextropropoxyphene, ecgonine, fentanyl, heroin, hydrocodone, morphine, oxycodone, pethidine, sufentanil, thebaine | n/a | 321 |
| **Barbados** | Codeine, fentanyl, methadone, morphine, oxycodone, pethidine, sufentanil | n/a | 1990 |
| **Commonwealth of Puerto Rico[#]** | -- | Methadone | -- |
| **Cuba** | Codeine, dextropropoxyphene, dihydrocodeine, dihydromorphone, diphenoxylate, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, pethidine, thebaine | n/a | 61 |
| **Dominica** | Fentanyl, morphine, pethidine | n/a | 59 |
| **Dominican Republic** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, levorphanol, methadone, morphine, nicomorphine, norcodeine, oxycodone, oxymorphine, pethidine, pholcodine, remifentanil, sufentanil, thebacon, thebaine | n/a | 23 |
| **Grenada** | Alfentanil, codeine, dihydrocodeine, fentanyl, methadone, morphine, pethidine | n/a | 93 |
| **Haiti** | Codeine, fentanyl, morphine, pethidine | n/a | 6 |
| **Jamaica** | Codeine, fentanyl, morphine, pethidine | n/a | 65 |
| **Saint Kitts and Nevis** | Codeine, fentanyl, methadone, morphine, pethidine | n/a | 113 |
| **Saint Lucia** | Codeine, fentanyl, methadone, morphine, oxycodone, pethidine | n/a | 133 |
| **Saint Vincent & Grenadines** | Codeine, fentanyl, morphine, pethidine | n/a | 52 |
| **Trinidad and Tobago** | Alfentanil, codeine, fentanyl, heroin, methadone, morphine, pethidine, remifentanil | n/a | Not reported |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.5. Latin America

The availability of pharmaceutical drugs in general is poor in many countries of Latin America. This is in part because of the high cost of drugs, but many countries in the region have developed methods for encouraging generic brands of these medications and ensure swift registration[405].

Access to opioids for pain and drug dependence is inadequate; few mentions of pharmaceutical drugs in this region could be found, with most focus in this region being upon cocaine production, trafficking and use[19]. Access to opioid medication is very low[89, 406]. A meeting of cancer pain physicians, researchers and government representatives over a decade ago considered the use of opioid medication in Latin America[406] and concluded that opioids were severely under-utilised for the treatment of cancer pain in all countries in the region because of cost, bureaucratic requirements that dissuaded physicians from prescribing stronger opioids, a clinical orientation to short-term mild opioids for acute pain only, and limited training leading to fear of prescribing by doctors and failure to stock medications by pharmacists[406].

In **Brazil**, pain prescribing is considered inadequate[88, 407]. The INCB noted that the availability of opioids for medical purposes in **El Salvador** was very low[19]. In several countries, governments were recently preparing legislation to improve controls over controlled pharmaceutical substances[19]. In **Costa Rica**, this included the implementation of a national database to cross check sales of controlled substances, pharmacies and doctors[19]; the country has seen some improvement in morphine prescriptions for severe cancer pain over the past decade[88].

Efforts have been made to improve inadequate standards of care for dependent drug users. In **Nicaragua**, the government recently approved a bill for "minimum standards of care" for drug users[19].

Use and injection of opioids in general (including heroin) is thought to be low in this region[19]. The exception to this is **Mexico**, which has an established population of heroin users (and injectors), and is one of the heroin producing countries of the world[408]. Heroin is the most common drug used by Mexican IDUs and increased poppy cultivation, greater security at the US border, and reduced prices may be related to the establishment of significant heroin use in the country[408]. Risky practices among IDUs are reportedly high and risk perception is low; there are some indications that HIV prevalence may be increasing among this group[408], with estimates of 4% prevalence in 2003[409]. OST treatment has been available in Mexico since 2001[408], but it is not widely available, usually only through private programmes rather than government-funded programmes. No reports of pharmaceutical opioid diversion were located from studies of treatment or out-of-treatment drug users[408, 410].

## Table 10: Availability of pharmaceutical opioids in the Latin America, by country

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Argentina** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pethidine, pholcodine, remifentanil, sufentanil, thebaine | n/a | 148 |
| **Belize** | Codeine, fentanyl, hydrocodone, morphine, oxycodone, pethidine | n/a | |
| **Bolivia** | Alfentanil, codeine, dextropropoxyphene, ethylmorphine, fentanyl, methadone, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 17 |
| **Brazil** | Alfentanil, codeine, dextromoradomide, dextropropoxyphene, difenoxin, dihydrocodeine, diphenoxylate, dipipanone, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, levorphanol, methadone, morphine, nicomorphine, norcodeine, normethadone, normorphine, pethidine | n/a | 230 |
| **Chile** | Alfentanil, codeine, ethylmorphine, fentanyl, methadone, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 254 |
| **Colombia** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, ethylmorphine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pethidine, remifentanil, sufentanil, thebaine | n/a | 118 |
| **Costa Rica** | Codeine, fentanyl, heroin, methadone, morphine, pethidine | n/a | 174 |
| **Ecuador** | Codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, fentanyl, hydrocodone, methadone, oxycodone, remifentanil | n/a | 45 |
| **El Salvador** | Buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, methadone, morphine, oxycodone, pethidine, remifentanil | n/a | 148 |
| **Guatemala** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, fentanyl, hydrocodone, methadone, morphine, oxycodone, pethidine, pholcodine, remifentanil | n/a | 4 |
| **Guyana** | Codeine, fentanyl, morphine, pethidine | n/a | 32 |
| **Honduras** | Codeine, dextropropoxyphene, fentanyl, morphine, oxycodone, pethidine, pholcodine | n/a | 1 |
| **Mexico** | Buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pethidine, remifentanil, sufentanil, thebaine | Methadone | 83 |
| **Nicaragua** | Codeine, dextropropoxyphene, fentanyl, hydrocodone, morphine, pethidine | n/a | 132 |
| **Panama** | Codeine, fentanyl, methadone, morphine, oxycodone, pethidine, remifentanil | n/a | 107 |
| **Paraguay** | Alfentanil, codeine, ethylmorphine, fentanyl, morphine, oxycodone, pethidine | n/a | 107 |
| **Peru** | Codeine, dextropropoxyphene, fentanyl, methadone, morphine, oxycodone, pethidine, remifentanil | n/a | 62 |
| **Suriname** | Codeine, fentanyl, morphine, pethidine, piritramide, sufentanil | n/a | 65 |
| **Uruguay** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, ethylmorphine, fentanyl, hydrocodone, methadone, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 444 |
| **Venezuela** | Alfentanil, codeine, diphenoxylate, fentanyl, methadone, morphine, oxycodone, pethidine, remifentanil | n/a | 109 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption[18-19, 82, 315]

## 6.6. Oceania and the Pacific

Pharmaceutical opioid misuse was not noted as an issue in most countries in this region. This is almost certainly because of very minimal availability of these drugs for medical use. Most countries in this region will have significantly inadequate treatment of pain, given the levels of opioid consumption reported to the INCB[18] (see Table 16). Two exceptions are Australia and New Zealand. These countries have comparatively high opioid consumption, including comparatively good levels of coverage for pain care[18].

In **Australia**, the availability of OST for the treatment of illicit opioid dependence is very well established and coverage of the opioid dependent population is probably good. OST is highly regulated through systems that include: registration of patients receiving OST; requirements for an "authority to prescribe" OST for dependent opioid users; required accreditation for doctors to prescribe OST; and highly regulated availability of other opioid medications. Publicly funded treatment places are primarily provided, but private OST is also available[411]. OST is considered a "low threshold" treatment, in accordance with a policy designed to minimise harms associated with illicit opioid use. This means no restrictions on the length of time in treatment, less intensive or absent urine testing, and drug use while on the program does not necessarily result in expulsion from treatment[411]. Pregnant, indigenous, HIV-positive opioid users, or those recently released from prison all receive priority for entry into public methadone treatment programmes. Although low-threshold treatment programmes may offer less intensive services than more restricted treatment programmes, the aim is to make a greater public health impact by providing treatment to the greatest number of opioid users.

Markets for diverted opioids in Australia have been described as "small scale" and "disorganised", through a network of small-scale doctor shopping and diversion[57, 74-75]. In 2004, 3% of the general population reported having "misued" a pharmaceutical opioid[412]. However, most pharmaceutical opioid misuse and injection appears to occur primarily among established heroin injectors, tends to be sporadic, and is probably related to the availability of their preferred opioid (heroin). Important jurisdictional differences have been documented in the prevalence, frequency and types of pharmaceutical opioids misused and injected. In states where heroin has traditionally been less available, the injection of morphine and methadone tablets (prescribed for pain in this country) is more common among regular IDUs[74, 155, 413]. Morphine injection is also more common among IDUs in rural areas where heroin availability is poorer than in larger cities[79], although morphine injection has increased among regular IDUs across the country against a backdrop of sustained reductions in heroin availability in this country[54, 413].

In 2006, 35% of regular IDUs in Australia reported that pharmaceutical opioids were the last drug they had injected[413]. This was more commonly non-OST opioids (18% morphine) rather than OST opioids (8% methadone, 6% buprenorphine). Although 32% reported that these drugs were the most frequently injected drugs in the past month, few (5%) reported they were their preferred drug: heroin remains the most favoured opioid and the most commonly nominated favourite drug among this group (48%)[413]. In 2005-2006, 4% of all non-OST drug treatment episodes in Australia were for the treatment of a primary problem with pharmaceutical opioids[414]. In the 2006 annual NSP survey, 25% of IDUs reported that the last substance they had injected was a pharmaceutical opioid: 11% morphine, 8% methadone and 5% buprenorphine[415]. HIV prevalence in 2006 among this group was less than 1%, and HCV was 70%[415].

The misuse and injection of OST differs across the country and has been associated with different treatment policies. In New South Wales (NSW), methadone syrup injection has at times been prevalent (but infrequent) among IDU, including some who are in treatment[158]; buprenorphine injection is less

common[416]. In contrast, methadone injection is considerably less common in Victoria[222] where doses are less commonly available as takeaways and the syrup is highly diluted; buprenorphine injection is, however, much more common and frequent, and accompanies a much less supervised method of dosing through pharmacies in that state[417]. Pharmacists suspect that 33 instances of non-adherence or diversion may occur per 100 patients per month[418]. One NSW study of methadone injectors found that some began injecting methadone because they felt they were on inadequate doses[182]; other factors included the "rush" and quicker onset of effects[182].

In **New Zealand**, misuse and injection of prescription opioids has been a much more long-standing issue, related no doubt in large part to the poor availability of heroin for many years as a result of the disruption of a major heroin trafficking ring in the 1970s[419]. In 1990, 81% of opioid users presenting to a drug treatment clinic for treatment of their opioid dependence reported the injection of buprenorphine within the past month, and 68% had injected morphine[420]. In 2006, 0.13% of the general population reported having misused pharmaceutical opioids in their lifetime[421]. Following the introduction of buprenorphine-naloxone in 1991, among clients presenting for treatment, 25% were injecting buprenorphine-naloxone only, 32% buprenorphine and buprenorphine-naloxone, and 86% morphine[420]. Notably, the authors of this study observed that patients had learnt to inject buprenorphine-naloxone at doses and frequencies that would allow them to avoid the withdrawal precipitation that has been demonstrated in animal and experimental studies[420].

In 2006, morphine, "homebake" heroin (made from codeine tablets) and opium extracted from poppy straw were commented upon by regular illicit drug users[421]. Among regular IDUs, 77% had used morphine or homebake in the past six months, and 74% had used methadone[421]; use was very regular among this group and 96% injected[421]. HIV prevalence is zero and HCV is 52% among regular IDUs[421]. Buprenorphine-naloxone has not been linked to any overdose deaths in the country[420], but methadone and morphine have (overdose rates are not high)[422].

## Table 11: Availability of pharmaceutical opioids in Oceania and the Pacific

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **American Samoa** [#] | Codeine, fentanyl, morphine, pethidine | n/a | 27 |
| **Australia** | Alfentanil, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, dihydrocodeine, diphenoxylate, ecgonine, ethylmorphine, etorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, normorphine, oxycodone, oxymorphone, pethidine, pholcodine, remifentanil, sufentanil, thebaine, thiofentanyl | Methadone, buprenorphine | 7070 |
| **Federated States of Micronesia** | Codeine, fentanyl, morphine, pethidine | n/a | 68 |
| **Fiji** | Codeine, fentanyl, methadone, morphine, pethidine | n/a | -- |
| **French Polynesia**[#] | Alfentanil, fentanyl, hydromorphine, methadone, morphine, pethidine, remifentanil, sufentanil | n/a | 1205 |
| **Guam**[#] | -- | n/a | -- |
| **Kiribati** | Codeine, fentanyl, morphine, pethidine | n/a | -- |
| **Marshall Islands** | Codeine, diphenoxylate, fentanyl, hydrocodone, morphine, pethidine | n/a | 76 |
| **Nauru** | Codeine, fentanyl, morphine, pethidine | n/a | 13 |
| **New Caledonia**[#] | Alfentanil, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, remifentanil, sufentanil | n/a | 1148 |
| **New Zealand** | Alfentanil, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, diphenoxylate, ethylmorphine, etorphine, fentanyl, heroin, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pethidine, pholcodine, piritramide, remifentanil, sufentanil, thebaine | Methadone, Buprenorphine | 5538 |
| **Palau** | Codeine, dextropropoxyphene, fentanyl hydrocodone, methadone, morphine, oxycodone, pethidine | n/a | 445 |
| **Papua New Guinea** | Codeine, dextropropoxyphene, diphenoxylate, fentanyl, methadone, morphine, pethidine, pholcodine | n/a | 28 |
| **Samoa** [#] | Codeine, fentanyl, morphine, pethidine | n/a | 27 |
| **Solomon Islands** | Dihydrocodeine, morphine, pethidine | n/a | 21 |
| **Tonga** | Alfentanil, codeine, fentanyl, morphine, pethidine, pholcodine | n/a | 1265 |
| **Tuvalu** | Codeine, fentanyl, morphine, pethidine | n/a | 5946 |
| **Vanuatu** | Codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, fentanyl, methadone, morphine, oxycodone, pethidine, pholcodine | n/a | 13 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.7. Canada, United States and Western Europe

In terms of extra-medical use, injection and diversion, the **United States** appears to have the largest per capita problem in the world. Even the INCB voiced significant concern about the extent of problems in the country[19]. It accounted for half (49%) of the world's estimated morphine consumption in 2005, despite only comprising 4.7% of the world's population[18]. Controlled-release oxycodone is widely misused[27, 113], and the country accounts for 99% of the world's consumption of this opioid[423]. It has been estimated that 2.3% of the general population may misuse pharmaceutical opioids and 0.5% may be dependent[424]; 11% of students have reportedly misused pharmaceutical opioids[425]. It was estimated in 2001 that prescription opioid misuse cost US$8.5 billion[426]; given that problems seem to be increasing, the figure is likely to be much larger today.

A total of 66,963 narcotic analgesic items were identified by federal, state, and local forensic laboratories in 2006. Hydrocodone (39%) and oxycodone (30%) accounted for the majority of all narcotic analgesics reported, followed by methadone (10%), morphine (6%), codeine (4%), propoxyphene (2%), hydromorphone (2%), dihydrocodeine (2%), fentanyl (2%), and buprenorphine (2%)[427].

For 2005, the Drug Abuse Warning network (DAWN) estimated that 598,542 emergency department (ED) visits involved non-medical use of prescription or over-the-counter pharmaceuticals or dietary supplements. Of these visits, CNS agents composed 51% of non-medical-use visits. Among these, hydrocodone/combinations were seen in 51,225 ED visits, followed by oxycodone/combinations in 42,810 ED visits, and methadone in 41,216 ED visits. It is not possible to know, based on the documentation available in ED medical records, the extent to which these drugs came from legitimate prescriptions versus other sources, and it is not possible to distinguish methadone used for treatment of opioid dependence from the pill form that is prescribed for pain[427].

Dependence, non-fatal and fatal overdoses related to pharmaceutical opioid misuse continue to increase across the country, particularly those due to misuse of fentanyl and oxycodone[44, 47, 60, 113-114, 113, 115-118, 428]. Methadone is increasingly being used for pain management, and the number of dosage units of the tablets used for pain increased by 277% between 2000 and 2005, as compared to a 163% increase in diskettes used both for pain and opioid treatment, and a 99% increase in liquid used in opioid treatment[429]. Between 1999 and 2004, the number of poisoning deaths mentioning methadone increased by 390%, while the number of deaths mentioning other opiates such as oxycodone and hydrocodone increased by 90%[430].

Multiple formulations of varied opioids are available, and many appear easily obtained from GPs for diffuse, non-specified pain conditions. It seems to be this feature of the US policy context that is in part related to the extent of the problem with oxycodone, but other important aspects play a part[431]. The pharmaceutical company, Purdue Pharma, that manufactures the most popular of these products, OxyContin®, aggressively marketed the drug as a treatment for both cancer and chronic non-cancer pain to oncologists, palliative care physicians and pain specialists, claiming it had a low dependence liability[109]. The drug was also heavily promoted to primary care and family practitioners, who were encouraged to prescribe it liberally[110]. There was a major marketing campaign targeted at patients, where dependence risks were minimised, and those liable to misuse the drug were alerted to its misuse potential by the product information, which said patients should *not* crush or dissolve the tablets because this released a large dose[110]. In May 2007, the company agreed to pay $600 million in fines and other payments to resolve the criminal charge of "misbranding" its product[112].

OST availability in the United States has been traditionally poor despite the problems related to heroin and other opioid dependence. A recent study of attendees at OST found that among those with a history of prescription opioid misuse, the most commonly used forms were oxycodone (79%), hydrocodone (67%), methadone (40%) and morphine (29%)[105]. One-third (33%) had injected them, and they were more likely to have injected morphine and hydrocodone than oxycodone. The most common sources of pharmaceutical opioids were their doctors, friends, families, or regular "dealers". Prescription fraud and theft were rarely mentioned[105].

One study found that those patients who were identified during routine monitoring as misusing opioids were highly likely to have extensive histories of problematic drug use, suggesting that problematic use was a greater problem for those with established drug use histories[47]. Notwithstanding this, there is clear evidence of initiation to opioid use among formerly opioid naïve users as well as the addition of prescription opioid drugs to an extensive drug repertoire including heroin among a group of treatment entrants[432].

In a recent study of rural pharmaceutical opioid users in the United States, 35% reported injection. Risky injecting practices were reported by current injectors, including receptive needle sharing (11%), distributive needle sharing (26%), and sharing of other injection paraphernalia (42%)[433]. Self-reported HCV prevalence was 14.8% (compared to 1.7% among non-injectors), prompting the authors to highlight the need to educate pharmaceutical opioid injectors on safe needle practices in order to curb the transmission of HIV, HCV and other infectious diseases[433].

Some have claimed that the increase in problems is related to illegal internet sales of prescription medication[19]. Although a concern, it is not clear why the United States would experience a problem, with other countries apparently so much less likely to do so, *unless* this is occurring to sustain use and levels of demand for the drugs that have already developed. The liberal prescribing of opioids for chronic moderate to severe non-cancer pain, combined with aggressive marketing by pharmaceutical companies, appears to have driven this epidemic of use and problems. Efforts to control "diversion" have now been implemented in 25 states across the country[19] using prescription monitoring systems, which enable prescribing physicians to find out if a patient is being prescribed opioids by another prescriber.

In **Canada**, there has been sustained research and community attention upon the misuse and injection of pharmaceutical opioids among regular illicit opioid users[56, 434-436], with evidence of increasing use and injection of pharmaceutical opioids among regular opioid users[107, 437], probably related to the inconsistent heroin supply in most areas of the country. Despite this, population level data on illicit opioid use (including heroin) are very limited. Data suggest that OST coverage in the country is around 23%[436], representing a very substantial increase relative to the poor availability of OST until a decade ago[438]. There is no national monitoring system in place to identify and track the diversion and extra-medical use of prescription drugs[439] although district-level systems are in place.

One cohort study of out-of-treatment opioid users found that the most commonly used opioid was hydromorphone (Dilaudid), used by 38% and more common than heroin (30%)[116]. Other evidence clearly shows that oxycodone misuse is increasing across the country[440]. A latent class anlaysis of opioid users has suggested three classes of extra-medical opioid users in Canada: prescription opioid users, distinguished by use of prescription opioids and benzodiazepines and high rates of pain disorders; non-injecting crack and heroin users; and injecting heroin and other drug users[209]. Levels of risk behaviours and HCV infection differed among the groups, with the prescription opioid group having the lowest levels of risk and HCV infection[209].

Among Canadian patients entering OST, 83% were using prescription opioids, which were most commonly oxycodone and codeine[432], followed by morphine and hydrocodone. Significant proportions

had pain disorders; injection of these drugs was uncommon[432]. A further study found that compared to non-injecting regular opioid users, those injecting opioids (largely pharmaceuticals) were more likely to be more socially disadvantaged and have poorer mental health and more severe current drug use problems[441]. Most current non-injectors had, however, injected at some point, with the authors suggesting that this provided further impetus for examination of effective interventions for encouraging IDUs to adopt non-injecting routes of administration[441].

Data suggest that diversion occurs from numerous sources. In one study of persons misusing pharmaceutical opioids, the drugs were largely obtained from doctors' prescriptions, friends and family, and on the street from regular dealers; theft or forgery of prescriptions was uncommon among users[81]. It is likely that those dealing diverted pharmaceutical opioids are involved in larger scale diversion that includes theft from pharmacies[440]. Population data on prescription forgeries suggests that oxycodone is most prominent[440], which is consistent with the high levels of use among those misusing opioids described above. Among detections of diversion, codeine and oxycodone rank most highly[440].

Of concern were the findings from one study, in which hydromorphone use in particular remained a significant predictor of non-fatal overdose among IDUs in Canada[442], probably related to the high potency of this opioid. Deaths attributed to injection of fentanyl derived from patch formulations have been observed in some cities[199]; this is not surprising, given the very high attractiveness of this opioid for IDUs in the country[62]. Heroin use has found to predict HIV seroconversion among IDUs, whereas methadone was protective[443-444], probably related to reductions in injecting risk behaviours among methadone treatment clients[445].

In Western Europe, there is certainly less population-level consumption of these drugs compared to Canada and the United States (Table 18), and it is not related to OST coverage; in many countries (e.g. France) OST coverage is decidedly superior. Some countries had notably low levels of pharmaceutical opioid consumption, such as **Albania**, **Andorra**, **Serbia**, and **Montenegro**, and no data could be located on the existence or extent of misuse or diversion in these countries (Table 19). There is a need for better coverage of OST in some of these areas, however, given evidence of heroin dependence and HIV prevalence among these popualtions[446].

Misuse and diversion is occurring in this region. Although very good monitoring occurs through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), routine reporting does not appear to differentiate between heroin and pharmaceutical opioids. As a result, it is not clear in some countries to what extent problems related to these pharmaceuticals are a concern. Future monitoring might separate heroin from other opioids.

In **Finland**, there have been very high levels of well-documented diversion of buprenorphine from OST for some years[447]. In 2004, 26% of drug treatment entrants[448] and 96% of outpatient clients treated for opioid dependence[148, 259] used pharmaceutical opioids as their primary drug. In 2005, 29% of drug trement clients reported having misused buprenorphine[147]. Buprenorphine has been identified as the most frequently injected drug among IDUs attending a NSP[447] (73%) and also among the majority of clients entering OST (90%)[449]. It is reported that buprenorphine is commonly used among injectors to avoid withdrawal and because of the poor availability of heroin[447]. Some evidence has suggested that it might be a more common problem among younger drug users[447].

There has been some evidence that Finnish drug users have been obtaining prescriptions in France and taking them back for diversion in Finland[63, 450]. Since the introduction of buprenorphine-naloxone, many IDUs said that they had injected the drug (68%) but 80% of these users reported a negative experience[63]; the street price of this formulation was also reportedly half that of buprenorphine[63]. Overdose deaths are likely to involve buprenorphine, but overdose rates in the country are low.

In **France**, a problem has been reported with buprenorphine injection[162, 184, 450-454], but much of the misuse appears to be among users enrolled in treatment, which is widely available and dispensed through pharmacies[162]. In 2000, 30% of those in buprenorphine maintenance treatment had injected buprenorphine in the last month[452]. A 1997 study found 59% of NSP attendees had injected the drug as well as evidence of a younger cohort of IDUs who *only* injected buprenorphine (not heroin or cocaine) compared to an older group who also injected these other drugs, they injected drugs more frequently and were more likely to be enrolled in buprenorphine treatment[162]. Another study found that buprenorphine injectors were more likely to be polydrug users[455]. As noted earlier, there is evidence of doctor shopping and prescription fraud among OST clients: one study found two profiles for forged prescriptions: males under 45 years, presenting with stolen prescription forms and requesting opioids; and women aged over 45 years presenting with altered prescriptions for benzodiazepines or opioids[456].

It should be noted that other pharmaceutical opioids such as morphin have also been reported as being misused[457].

These harms need to be placed in the context of documented benefits of OST, and buprenorphine in particular, in the form of population-level reductions in opioid overdose, and lower population rates (by a factor of 14 times) of overdose due to buprenorphine compared to methadone when adjusted for the number in treatment for each of these OST forms[458]. Additonally, the prevalence of HIV infection *and* HIV risk behaviours were significantly lower among buprenorphine injectors[162].

In **Germany**, 17% of medications misused by outpatient clients in 2004 were OST medications; 8% using buprenorphine, 7% methadone, and 2% levomethadone[459]. After concerns about increases during the late 1990s in methadone-related deaths following a rapid expansion of easy access to takeaway one-week methadone doses[460], the proportion of drug-related deaths where OST also played a role is now decreasing, from 40% in 2002 to 25% in 2005[459]. The injection of pharmaceutical opioids has also been reported among outpatients in drug treatment[459]. Among the general population, 0.3% had misused pharmaceutical opioids[148].

In **Austria**, most OST clients are continuing clients; demand exceeds the number of places and calls have been made for expansion of the programme[461]. Slow release oral morphine has been trialled as an additional OST to methadone and buprenorphine, with conflicting findings in comparison to these other OST[462-463]. Some evidence of low levels of pharmaceutical opioid misuse has been reported in a study of OST clients, with around 3-5% of patients screening positively for morphine at some point during a four-year trial, with some evidence it was more likely among younger clients[207]. No prevalence data specific to IDUs injecting pharmaceutical opioids could be found, but among IDUs generally HIV is almost zero and HCV 40%[464].

In **Belgium**, morphine consumption for medical purposes is reportedly lower than less potent opioids such as Tramadol, and also lower than much more potent opioids such as fentanyl[465]. In a sample of drug users, 35% report having used methadone, 12% buprenorphine and 17% codeine[466]; around one-fifth had injected methadone or buprenorphine[466]. Prescribing of methadone has increased in recent years, with reports that the availability of methadone on the black market has also increased[467]. Small numbers of methadone-related fatalities have been recorded (32 cases over a six-year period), often involving other drugs such as benzodiazepines and most with blood levels within "therapeutic ranges"[467].

In **Denmark**, there has been an expansion of the methadone programme as a form of OST in recent years, with evidence of population level decreases in overall overdose rates[468-469]. Significant problems have been reported, however, with respect to methadone-related deaths[468-469]. Increasing proportions of the Danish population are also using pharmaceutical opioids via prescription, typically weaker opioids,

but including oxycodone, fentanyl and buprenorphine patches[470]. Repeat users of these strong forms of opioid were often new opioid users[470].

In **Ireland**, rapid increases in heroin-related mortality[471] prompted the introduction of OST, particularly methadone, into the country. Further, among one sample of heroin-dependent persons, HIV prevalence was 17% and HCV 79%[472]. There has been evidence that methadone, widely provided for OST, has been diverted by opioid dependent persons, but data on its extent were not located. Methadone was detected in half of the opioid-related fatalities in Dublin in 1999[473]. In the general population, 0.5% reported using opoids other than heroin[148].

In **Italy**, opioids are available, yet traditionally under-utilised for pain management and OST (both methadone and buprenorphine are available as OST[218, 474-477]). In one study of terminally ill cancer patients (1993-2000), it was found that only one-third (38%) of prescriptions were adequate, and on average 56 defined daily doses *per patient* were warranted, yet not prescribed[478]. A further survey of their doctors found knowledge of opioid medications inadequate, and it was thought that this contributed to under-prescription[478]. Notably, the country has taken steps to address this with the development of a national pain and palliative care plan in collaboration with the international Pain & Policy Studies Group (PPSG)[295].

A study of OST clients in Italy also concluded that treatment was being delivered at inadequate doses in over 80% of cases[479]. Nevertheless, there is some evidence to suggest that overdose rates declined following the expansion of OST in the early 1990s[480], and data suggest that riskier and more dependent clients as well as those who are HIV positive are given priority for OST[481]. Given this context, it is probably no surprise that no discussions or papers examining diversion were located for this review. Only very low levels of pharmaceutical opioid use by outpatient opioid clients was reported: 0.3% had used misused methadone and 0.5% other pharmaceutical opioids[259].

In the **United Kingdom**, multiple forms of OST have been available for over a century, including prescription of diamorphine for heroin dependence[144, 482] and relatively liberal prescribing policies, with GPs being allowed to prescribe strong opioids for varied conditions. At times, this has led to doctors apparently over-prescribing some patients, with several high profile cases involving doctors who were unwittingly supplying very large black markets for sizeable populations of opioid dependent populations[431]. Buprenorphine is increasingly used for OST[237, 483]; and there is some evidence that doctors are unwilling to prescribe heroin for OST[143]. There has been clear evidence of injection of buprenorphine among IDUs[484].

In one of few cross-national investigations of heroin and methadone overdose in comparison to treatment policy, Hall et al compared overdose mortality related to heroin and methadone in the United Kingdom with that of Australia, and also considered the relative treatment coverage of methadone in each country[485]. Despite methadone being more widely used in Australia (population adjusted), mortality related to methadone was relatively greater in the United Kingdom than in Australia (although methadone still accounted for fewer deaths in the country than heroin[486]). The treatment policies differed widely: in Australia, takeaway dosing of methadone was comparatively limited, whereas provision often occurred without supervision in the United Kingdom and large takeaway doses were often available[485]. Interestingly, following changes in prescribing and treatment practices and guidelines in the United Kingdom, with greater limitations upon takeaway dosing provisions, methadone-related mortality dropped significantly[487].

Among the general population in **England** and **Wales**, 0.1% reportedly had used opioids other than heroin[148]. In the United Kingdom, in 2004, 5% of outpatient opioid treatment patients had misused methadone and 4% had misused other opioids[259].

In **Switzerland**, heroin is available in a highly controlled manner for opioid dependent patients considered "treatment resistant"[145, 488-490]; protective effects for mortality have been demonstrated for this group relative to illicit heroin injectors[491]. One study located reports of misuse and injection: in a sample of clients maintained on methadone, 43% of patients indicated ever having injected methadone, 21% had injected in the preceding month with a mean frequency of 10.3 injections[492].

**Table 12: Availability of pharmaceutical opioids in Canada, United States and Western Europe, by country**

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Albania** | Codeine, fentanyl, methadone, morphine, pethidine, pholcodine, sufentanil | Methadone | 45 |
| **Andorra** | Fentanyl, heroin, methadone, morphine, pethidine, remifentanil | n/a | 1034 |
| **Austria** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, nicocodine, oxycodone, pethidine, piritramide, remifentanil, sufentanil, tlilidine | Methadone, Buprenorphine, slow release Morphine | 7730 |
| **Belgium** | Acetyldihydrocodeine, alfentanil, alphacetylmethadol, bezitramide, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, difenoxin, dihydrocodeine, diphenoxylate, dipipanone, ecgonine, ethylmorphine, etorphine, etoxeridine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, ketobemidone, levomoramide, levorphanol, methadone, morphine, nicomorphine, normethadone, normorphine, oxycodone, pethidine, phenazocine, phenoperidine, pholcodine, piritramide, racemethorphan, remifentanil, sunfentanil, thebacon, thebaine, tilidine | Methadone | 17018 |
| **Canada** | Alfentanil, alphaphrodine, anileridine, codeine, dextropropoxyphene, difenoxin, dihydrocodeine, dihydromorphine, diphenoxylate, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levorphanol, methadone, morphine, normethadone, oxycodone, oxymorphone, pethidine, remifentanil, sufentanil, thebaine | Methadone | 12840 |
| **Denmark** | Alfentanil, alphacetylmethadol, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, dihydrocodeine, diphenoxylate, ecgonine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, levorphanol, methadone, morphine, nicomorphine, oxycodone, oxymorphone, pethidine, pholcodine, remifentanil, sufentanil, thebacon, thebaine | Methadone | 12545 |
| **Finland** | Acetylmethadol, alfentanil, buprenorphine, codeine, dextropropoxyphene, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydromorphone, methadone, morphine, norcodeine, oxycodone, pethidine, pholcodine, remifentanil, sufentanil, thebaine | Buprenorphine, Methadone | 3856 |
| **France** | Acetyldihydrocodeine, Alfentanil, alphacetylmethadol, alphamethadol, alphaphrodine, anileridine, bezitramide, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, dihydrocodeine, dihydromorphine, diphenoxylate, dipipanone, ecgonine, ethylmorphine, etonitazene, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, methadone, morphine, oxycodone, pethidine, phenoperidine, pholcodine, piritramide, remifentanil, sufentanil, thebaine, tilidine | Buprenorphine, Methadone | 4218 |
| **Germany** | Alfentanil, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, dihydrocodeine, dihydromorphine, ecgonine, ethylmorphine, etonitazene, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, hydromorphinol, hydromorphone, ketobemidone, levorphanol, methadone, methyldihydromorphine, morphine, noracymethadol, norcodeine, normorphine, oxycodone, oxymorphone, pethidine, pholcodine, piritramide, remifentanil, sufentanil, thebacon, thebaine, tilidine | Methadone | 10802 |
| **Greece** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, fentanyl, methadone, morphine, pethidine, remifentanil | Methadone, Buprenorphine | 1571 |

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Iceland** | Alfentanil, codeine, dextropropoxyphene, difenoxin, dihydrocodeine, diphenoxylate, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone, pethidine, sufentanil | n/a | 6138 |
| **Ireland** | Alfentanil, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, dihydrocodeine, dipipanone, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, levorphanol, methadone, morphine, normorphine, oxycodone, pethidine, pholcodine, remifentanil, sufentanil, thebaine, tilidine | Methadone | 6605 |
| **Italy** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, ecgonine, ethylmorphine, fentanyl, heroin, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pethidine, pholcodine, remifentanil, sufentanil, thebaine | Methadone | 3067 |
| **Liechtenstein** | -- | -- | -- |
| **Luxembourg** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, pethidine, piritramide, remifentanil, sufentanil, thebacon, tilidine | Methadone, Buprenorphine | 6840 |
| **Malta** | Alfentanil, codeine, fentanyl, heroin, methadone, morphine, pethidine, remifentanil, sufentanil | Methadone | 2857 |
| **Monaco** | -- | -- | -- |
| **Montenegro** | Alfentanil, codeine, methadone, morphine, pethidine, pholcodine, remifentanil, sufentanil, tilidine | Methadone | 309* |
| **Netherlands** | Alfentanil, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, methadone, morphine, nicomorphine, oxycodone, oxymorphone, pethidine, pholcodine, piritramide, remifentanil, sufentanil, thebaine | Methadone | 5159 |
| **Norway** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, ethylmorphine, ketobemidone, morphine, opium, oxycodone, pethidine, pholcodine, thebaine | Methadone | 6273 |
| **Portugal** | Buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, methadone, morphine, norcodeine, normorphine, oxycodone, oxymorphone, pethidine, pholcodine, piritramide, remifentanil, sufentanil, thebaine | Methadone | 4590 |
| **San Marino** | -- | -- | -- |
| **Serbia** | Alfentanil, codeine, methadone, morphine, pethidine, pholcodine, remifentanil, sufentanil, tilidine | Methadone | 309* |
| **Slovenia** | Alfentanil, codeine, dihydrocodeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, piritramide, remifentanil, sufentanil | Methadone | 3951 |
| **Spain** | Acetylmorphine, alfentanil, buprenorphine, codeine, desomorphine, dextropropoxyphene, dihydrocodeine, diphenoxylate, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, levorphanol, methadone, morphine, oxycodone, pethidine, pholcodine, piritramide, remifentanil, thebaine, tilidine | Methadone | 7551 |
| **Sweden** | Alfentanil, buprenorphine, codeine, dextropropoxyphene, diphenoxylate, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphine, ketobemidone, methadone, morphine, oxycodone, pethidine, piritramide, remifentanil, sufentanil | Methadone | 4280 |
| **Switzerland** | Alfentanil, buprenorphine, codeine, dextromoradomide, | Heroin, | 11345 |

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| | dextropropoxyphene, difenoxin, dihydrocodeine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, nicomorphine, oxycodone, oxymorphone, pethidine, pholcodine, remifentanil, sufentanil, thebaine, tilidine | Methadone Buprenorphine | |
| **The Former Yugoslav Republic of Macedonia** | Alfentanil, codeine, fentanyl, methadone, morphine, pholcodine, piritramide, remifentanil, sufentanil, thebaine, tilidine | Methadone | 989 |
| **United Kingdom** | Alfentanil, buprenorphine, codeine, dextromoradomide, dextropropoxyphene, dihydrocodeine, dihydromorphine, diphenoxylate, dipipanone, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, levorphanol, methadone, morphine, oxycodone, pethidine, pholcodine, remifentanil, sufentanil, thebaine, tilidine | Heroin, Methadone, Buprenorphine | 3664 |
| **United States** | Acetylmethadol, alfentanil, allylprodine, alphacetylmethadol, alphaprodine, betacetylmethadol betameprodne, betamethadol, betaprodine, buprenorphine, codeine, dextropropoxyphene, difenoxin, dihydrocodeine, dihydromorphine, diphenoxylate, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypehtidine, isomethadone, levomethorphan, methadone, morphine, noracymethadol, norlevorphanol, normethadone, oxycodone, oxymorphone, pethidine, propiram, remifentanil, sufentanil, thebaine, trimeperidine | Methadone, Buprenorphine | 29500 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.8. Middle East and Northern Africa

According to the INCB, pharmaceutical preparations containing controlled substances are easily obtained on unregulated markets in this region, with considerable unregulated sale of pharmaceuticals over the counter without prescriptions occurring[19]. Misuse of these preparations is reported to be taking place among persons "in all social strata" but no data were available to quantify this[19]. Drug control legislation prohibiting such practices is in place in most countries, but it is often not adequately implemented and enforced. Due to insufficient funds, there is a shortage of trained pharmacists and pharmacy inspectors in many African countries, which is often exacerbated by a lack of funds to fill vacancies. The INCB also recently voiced concern about controlled drugs being sold via illegally operating internet pharmacies in larger cities[19]. Data on the extent of this possible problem are seriously lacking (Table 21).

In **Cyprus**, among outpatient clients in treatment for opioid use, 0.7% had misused methadone 0.7% and had misused buprenorphine. No other information on the misuse of pharmaceutical opioids was identified[259].

In an **Israeli** study of patients in methadone substitution therapy, after one year of treatment, benzodiazepine users more frequently reported social problems (single, prison history, unemployment, family history of drug dependence/mental illness), problematic drug use (initiated illicit drug use at a younger age, more frequent illicit drug use) and psychopathology and negative mood. They had significantly higher rates of HCV seroprevalence and reported higher rates of injection-related HIV/HCV risk behaviours[214].

Little information was on the use of pharmaceutical opioids in **Kuwait**; however, it was reported that opioids are rarely detected in patients undergoing toxicology screening[493]. In **Lebanon**, few data exist on the scale of the problem. At a recent conference it was reported that prescription opioid use was a problem[494] and it is reported that 11% of admitted psychiatric patients are opiod dependent. No additional data could be found to verify magnitude of pharmaceutical opioid misuse. It was reported that HIV is an issue among IDUs and 2,700 persons were living with HIV in 2003[494]. At a recent forum in Lebanon¸ it was suggested that buprenorphine might be available for opioid substitution treatment but there were no further details on this[494].

There is no mention of opioids in the drug overdose data for **Oman**[495]. No specific information on pharmaceutical opioid misuse was identified in this review.

Medication for severe pain is inadequate in supply in many countries in the region (Table 20). In **Tunisia**, there are limited pain medications available. Efforts are underway to increase the availability of opioids for cancer pain, with some promising signs[496]. Pharmacists in Tunisia thought opioids important, although only 86% had them (this included hospitals) and only 30% thought that the seven-day limit upon prescribing should be relaxed because of fears about fraud and dependence[497].

**Turkey** is located on the main overland connection between Asia and Europe through which heroin is trafficked from Afghanistan to European markets; problems related to heroin use have been clearly identified as a serious concern in the country. There have been reports of pharmaceutical opioid use in the country but the extent is unknown[498]. Between 1997 and 2001, opioids were mentioned in 92% of drug overdoses in the country. Small numbers mentioned codeine, fentanyl and methadone; large numbers involving morphine were probably heroin-related deaths[498].

## Table 13: Availability of pharmaceutical opioids in the Middle East and Northern Africa, by country

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Algeria** | Algeria, buprenorphine, codeine, dextropropoxyphene, etorphine, fentanyl, morphine, pholcodine, sufentanil | n/a | 437 |
| **Bahrain** | Alfentanil, etorphine, fentanyl, methadone, morphine, oxycodone, pethidine, remifentanil | n/a | 132 |
| **Cyprus** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, etorphine, fentanyl, heroin, hydrocodone, methadone, morphine, oxycodone, oxymorphone, pethidine, remifentanil, sufentanil, thebaine | n/a | Not reported |
| **Egypt** | Codeine, dihydrocodeine, diphenoxylate, fentanyl, morphine, oxycodone, pethidine, pholcodine, remifentanil, sufentanil | n/a | 60 |
| **Iraq** | Codeine, dextropropoxyphene, diphenoxylate | n/a | 2 |
| **Israel** | Buprenorphine, codeine, dextropropoxyphene, morphine, oxycodone, pethidine | Methadone | 3452 |
| **Jordan** | Codeine, dextropropoxyphene, diphenoxylate, morphine, pethidine | n/a | 100 |
| **Kuwait** | Alfentanil, codeine, dextropropoxyphene, fentanyl, hydrocodone, methadone, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 76 |
| **Lebanon** | Alfentanil, codeine, dextropropoxyphene, fentanyl, methadone, morphine, pethidine, pholcodine, remifentanil, sufentanil | n/a | 216 |
| **Libyan Arab Jamahiriya** | Alfentanil, fentanyl, morphine, pethidine | n/a | 41 |
| **Morocco** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, morphine, pethidine, pholcodine, sufentanil | n/a | 346 |
| **Oman** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, ecgonine, etorphine, fentanyl, heroin, hydrocodone, methadone, morphine, pethidine, pholcodine, remifentanil, sufentanil | n/a | 53 |
| **Qatar** | Alfentanil, dihydrocodeine, etorphine, fentanyl, morphine, pethidine, remifentanil | n/a | 164 |
| **Saudi Arabia** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, etorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, remifentanil, sufentanil | n/a | 141 |
| **Sudan** | Fentanyl, morphine, pethidine | n/a | 1 |
| **Syrian Arab Republic** | Alfentanil, codeine, dextropropoxyphene, diphenoxylate, fentanyl, morphine, pethidine, remifentanil, sufentanil | n/a | 24 |
| **Tunisia** | Alfentanil, alphaphrodine, anileridine, bezitramide, codeine, dextromoradomide, dextropropoxyphene, difenoxin, dihydrocodeine, diphenoxylate, dipipanone, ecgonine, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, levorphanol, methadone, morphine, nicomorphine, normethadone, normorphine, oxycodone, oxymorphone, pethidine, phenoperidine, pholcodine, piritramide, remifentanil, sufentanil, thebacon, thebaine, tilidine | n/a | 105 |
| **Turkey** | Alfentanil, codeine, diphenoxylate, ethylmorphine, fentanyl, morphine, pethidine, remifentanil, sufentanil | n/a | 214 |
| **United Arab Emirates** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, methadone, oxycodone, pethidine, remifentanil | n/a | 245 |
| **Yemen** | Codeine, fentanyl, morphine, pethidine, pholcodine, remifentanil, sufentanil | n/a | 2 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

## 6.9. Sub-Saharan Africa

Provision of pharmaceutical opioids for the management of severe pain is severely limited in this region and repeated calls are being made for dramatic changes to availability and use. There are significant structural barriers to the provision of medication in some countries, and doubtless fears of limited capacity to control diversion add to difficulties in achieving change.

An added issue is the fact that many African countries now serve as routes for the trafficking of illegal drugs, including heroin, through to the richer markets of Europe. This has led to the development of noticeable drug problems in multiple transit countries[499], with many countries unequipped with national policy frameworks to address these issues[499-500]. Policies are being introduced across the continent to address illegal drug use and related harm[499]. The development of populations of dependent heroin users is an issue of significant concern, given the very high population prevalence of HIV already existing in the region. OST should be introduced as a matter of priority in countries where heroin injection has become an issue.

In **Djibouti**, there is currently limited capacity for the government to monitor and control internationally controlled substances[19], although there are no data on the extent of drug misuse in the country and the INCB recently called for a rapid assessment into drug use in the country[19].

In **Malawi**, there is inadequate availability of opioids for pain management[19]. The INCB recently urged the government to assess the medical and scientific needs of the country, and ensure that sufficient supplies of opioids were available[19].

In **Mauritius**, the HIV epidemic shifted dramatically in the past decade from sexual to IDU transmission. Heroin injection is a considerable issue in the country and buprenorphine has been introduced as an OST as a result. Recently, a shortage of heroin to supply the existing population of IDUs, is thought to have led to a move by traffickers to import buprenorphine, which has been reflected in increasing seizures of the drug and increases in injection among IDUs[19].

In **Sierra Leone**, opioid treatment of severe pain is almost non-existent[501]. Under Sierra Leonean law, morphine may only be handled by a pharmacist or doctor, but there are only 100 doctors – one for every 54,000 people, compared with one for every 350 in the United States[501]. Given the low coverage of the population with antiretroviral treatment (ART), there is an urgent need not only for management of cancer pain but also for pain related to the end stages of AIDS[501].

Limited prescription of opioid analgesics occurs in primary care settings in **South Africa**[502]. It has been claimed that delays and bureaucracy mean that the country takes four times longer than the international average to approve new medicines; and although recommended and considered extremely important for the country, regulations allowing nurses to prescribe medications, including antiretrovirals (ARVs), remain lacking[503]. Lack of knowledge about cancer pain management by both patients and providers were commonly cited problems that limited access in a study of opioid availability in South Africa[504].

Some diversion and/or misuse of pharmaceutical opioids is occurring, however, usually involving lower potency opioids. In South Africa, analgesic misuse occurred in a significant minority of drug treatment attendees. It was usually codeine-containing medicines, many of which are available over the counter – they were used by 3-7% of drug treatment attendees in 2005[505]. Older people and women were more likely to have this drug class as their primary drug problem; men were more likely to be using a range of drugs[506].

Injecting is reportedly increasing in **Tanzania** and HIV infection has been detected in up to 95% of syringes in some neighbourhoods[507]. Heroin seems to be the major drug of injection, and injecting is increasing in this country[507-508]. No reports were obtained of the provision of OST for heroin dependence. No reports of pharmaceutical opioid diversion in this country were found for this report.

Limited provision of morphine in **Uganda** deriving from confusion and complexity in storage and authorisation rules led to discontinuation of opioid pain management at the patient level, and public fear of opioids led to under-prescribing. This is being addressed through a national public health approach, including free oral morphine, increasing education of physicians, dedicated palliative care professionals and allowing nurses to prescribe to patients[509-512].

Different reports documenting drug use in **Cameroon**[513], **Ethiopia**[514], **Kenya**[515-516] and **Nigeria**[496, 517-518] did not report the injection or misuse of pharmaceutical opioids.

## Table 14: Availability of pharmaceutical opioids in Sub-Saharan Africa, by country

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| **Angola** | Alfentanil, codeine, dextromoradomide, fentanyl, morphine, pethidine, sufentanil | n/a | |
| **Benin** | Codeine, fentanyl, morphine, pethidine, sufentanil | n/a | |
| **Botswana** | Alfentanil, codeine, dihydrocodeine, dipipanone, fentanyl, morphine, pethidine, sufentanil, tilidine | n/a | |
| **Burkina Faso** | Dextromoradomide, etorphine, fentanyl, morphine, pethidine, phenoperidine | n/a | |
| **Burundi** | Codeine, diphenoxylate, fentanyl, morphine, pethidine | n/a | |
| **Cameroon** | Codeine, dextromoradomide, etorphine, fentanyl, morphine, pethidine | n/a | |
| **Cape Verde** | Alfentanil, fentanyl, morphine, pethidine | n/a | 7 |
| **Central African Republic** | Codeine, fentanyl, morphine, pethidine | n/a | 798 |
| **Chad** | Fentanyl, morphine, pethidine | n/a | 1 |
| **Comoros** | Dextromoradomide, fentanyl, morphine, pethidine, phenoperidine | n/a | 2 |
| **Côte d'Ivoire** | Codeine, dextropropoxyphene | n/a | 1 |
| **Democratic Republic of the Congo** | Alfentanil, codeine, diphenoxylate, fentanyl, methadone, morphine, pethidine | n/a | 16 |
| **Djibouti** | Alfentanil, fentanyl, morphine, pethidine, sufentanil | n/a | 2 |
| **Equatorial Guinea** | Codeine, diphenoxylate, fentanyl, methadone, tilidine | n/a | Not reported |
| **Eritrea** | Codeine, fentanyl, morphine, pethidine | n/a | 2 |
| **Ethiopia** | Codeine, morphine, pethidine | n/a | Not reported |
| **Gabon** | Alfentanil, codeine, dextromoradomide, dextropropoxyphene, fentanyl, morphine, pethidine, phenoperidine, pholcodine | n/a | 1 |
| **Gambia** | codeine, dihydrocodeine, heroin, morphine, pethidine, thebaine | n/a | Not reported |
| **Ghana** | Codeine, dextropropoxyphene, dihydrocodeine, fentanyl, heroin, methadone, morphine, pethidine, thebaine | n/a | 50 |
| **Guinea** | Codeine, fentanyl, morphine, pethidine | n/a | 3 |
| **Guinea-Bissau** | Morphine, pethidine | n/a | 53 |
| **Kenya** | Codeine, dextropropoxyphene, dihydrocodeine, etorphine, fentanyl, heroin, morphine, pethidine, remifentanil | n/a | 1 |
| **Lesotho** | Dihydrocodeine, fentanyl, morphine, pethidine | n/a | 9 |
| **Liberia** | Codeine, dihydrocodeine, morphine, pethidine | n/a | 11 |
| **Madagascar** | Codeine, dextropropoxyphene, ethylmorphine, morphine | n/a | 1 |
| **Malawi** | Alfentanil, codeine, etorphine, fentanyl, methadone, morphine, pethidine, sufentanil, tilidine | n/a | Not reported |
| **Mali** | Alfentanil, anileridine, codeine, dextromoradomide, dextropropoxyphene, ethylmorphine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, levorphanol, methadone, morphine, nicomorphine, normethadone, oxycodone, oxymorphone, pethidine, phenoperidine, pholcodine, piritramide, remifentanil, sufentanil, thebacon, thebaine | n/a | 19 |
| **Mauritania** | Codeine, dextromoradomide, dextropropoxyphene, fentanyl, morphine, pethidine | n/a | |
| **Mauritius** | Alfentanil, buprenorphine, codeine, fentanyl, heroin, methadone, morphine, pethidine | Methadone, buprenorphine | 83 |
| **Mozambique** | Codeine, diphenoxylate, fentanyl, morphine, pethidine, pholcodine | n/a | 6 |
| **Namibia** | Alfentanil, codeine, dipipanone, etorphine, fentanyl, methadone, morphine, pethidine, remifentanil, sufentanil, tilidine | n/a | 94 |
| **Niger** | Codeine, fentanyl, morphine, pethidine | n/a | Not reported |
| **Nigeria** | Codeine, dihydrocodeine, fentanyl, morphine, pethidine, pholcodine | Methadone | Not reported |
| **Republic of the Congo** | Congo, fentanyl, morphine, pethidine | n/a | Not reported |
| **Rwanda** | Alfentanil, codeine, dextromoradomide, dihydrocodeine, etorphine, fentanyl, morphine, pethidine, remifentanil | n/a | Not reported |
| **Sao Tome and Principe** | Alfentanil, fentanyl, morphine, pethidine | n/a | 68 |
| **Senegal** | Alfentanil, codeine, dextromoradomide, fentanyl, morphine, | n/a | 3 |

| | Opioid medications listed as available for medical and scientific use | Opioid substitution therapy | Average consumption of opioids defined in daily doses per million inhabitants per day |
|---|---|---|---|
| | pethidine, sufentanil | | |
| **Seychelles** | codeine, fentanyl, morphine, pethidine | n/a | 266 |
| **Sierra Leone** | Codeine, dihydrocodeine, diphenoxylate, methadone, morphine, pethidine | n/a | 17 |
| **Somalia** | Codeine, morphine, pethidine | n/a | Not reported |
| **South Africa** | Alfentanil, codeine, dextropropoxyphene, dihydrocodeine, dihydromorphine, diphenoxylate, dipipanone, ecgonine, etorphine, fentanyl, heroin, hydromorphone, methadone, morphine, norcodeine, normorphine, pethidine, pholcodine, remifentanil, sufentanil, tilidine | Methadone | 546 |
| **Swaziland** | Alfentanil, codeine, dihydrocodeine, dipipanone, fentanyl, methadone, morphine, pethidine, tilidine | n/a | 16 |
| **Togo** | Alfentanil, fentanyl, morphine, pethidine | n/a | 1 |
| **Uganda** | Codeine, etorphine, fentanyl, morphine, pethidine | n/a | 26 |
| **United Republic of Tanzania** | Codeine, etorphine, heroin, methadone, morphine, pethidine, thebaine | n/a | 9 |
| **Zambia** | Codeine, dextropropoxyphene, dihydrocodeine, diphenoxylate, etorphine, fentanyl, heroin, methadone, morphine, pethidine, pholcodine, thebaine, tilidine | n/a | 31 |
| **Zimbabwe** | Alfentanil, codeine, dextropropoxyphene, diphenoxylate, dipipanone, etorphine, fentanyl, methadone, morphine, pethidine, pholcodine, sufentanil, tilidine | n/a | 30 |

n/a: Opioid substitution treatment not available in this country according to official statistics

--: Indicates no data were available for this country

Note: Average consumption of the nine most consumed narcotic drugs, expressed in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day, taken from the INCB annual estimated consumption reports[18-19, 82, 315]

# 7. Discussion

Pharmaceutical opioids have an important role in the treatment of a range of medical and psychological conditions, but, globally, they are inadequately prescribed for the conditions for which we know they are highly effective. Patients (particularly those who are terminally ill) should be given relief from severe pain, and OST should be introduced to help dependent users and avoid the significant risks of HIV transmission and other harm.

Diversion and injection of pharmaceutical opioids is occurring in many countries, but it is important to consider this within the context and the manner of licit availability. Considering the level of concern about its occurrence, there is comparatively little data with which to understand the extent and nature of extra-medical use in each country, but it seems reasonable to expect some level of diversion will occur.

Responses to misuse, diversion and injection should *not* further discourage what we know are inadequate levels of medical use of opioids for the treatment of pain. Unfortunately, there has been little research examining the relative benefits of different policy interventions, a gap that would benefit from systematic research examining different contexts and policy responses across countries[431], and there seems to be few cases where national policies spanning palliative care, HIV and AIDS, OST and other pain management have been produced. There is much that is not known about how, why, where, and how much diversion is occurring.

For users who have developed dependent use, treatment should be provided: it has positive impacts upon illicit drug use, physical and mental health, and public amenity. OST is an effective HIV prevention strategy that should be considered for implementation as a treatment for IDUs with opioid dependence in communities at risk of HIV epidemics[29]. We summarise some ways to limit the extent of diversion, injection and related harms in this section; future research requirements are highlighted throughout.

## 7.1. Epidemiology

Surprisingly little is known about the misuse, diversion and injection of pharmaceutical opioids, despite the tight scheduling of these drugs, and the likelihood that in some low income countries, this is the most commonly injected drug type. Monitoring of trends in South Asia and South East Asia is important – these countries are likely to account for the majority of users injecting pharmaceutical opioids. The evidence of associated harms of pharmaceutical injection is dominated by research in high income countries where use and diversion of pharmaceutical opioids probably differs from low and middle income countries.

### 7.1.1. Evidence on extra-medical use and injection

Different opioids have different dependence potential, and the forms available may also affect the likelihood of misuse and diversion for injection. There needs to be much more routine monitoring work conducted on this issue, to provide data on the extent of the problem (or otherwise).

There appears to be a general tendency for those opioids that are more available to be those which are more likely to be misused. If a range of pharmaceuticals is available, those which are more potent appear to be more sought after and misused. In countries where strong opioids are not available (e.g. India) other less potent opioids are still used and injected. Where pharmaceutical opioids (even those which are less potent ones) are introduced without sufficient regulation, it seems that there is a risk of misuse and diversion (e.g. United States and Singapore). The challenge, discussed below, is ensuring that such problems do not lead to overly restrictive policy implementation[96].

On the basis of the current evidence, misuse, diversion and injection of pharmaceutical opioids appears to be a significant problem for the United States, South Asia, South East Asia and some Eastern European countries. The nature of the populations injecting these pharmaceuticals seems very different across

countries. For example, in India, populations of IDUs appear to be developing dependent, injecting use of these drugs; in Australia, injection may be more common among IDUs whose preference is heroin and for whom injection of pharmaceutical opioids is less frequent; in the United States, a generalised epidemic of pharmaceutical opioid use appears to have been driven by overly liberal prescribing for non-specific pain states, leading to a new cohort of dependent opioid users who may switch to injecting their medication, or to injection of heroin if pharmaceutical opioid availability becomes overly restricted.

In terms of injecting risk, the evidence on this topic is limited. Some studies have suggested increased injecting risk among pharmaceutical opioid injectors compared to other IDUs; others have not. The context of opioid use – whether it is among IDUs in contexts where OST is currently available, or whether pharmaceuticals are largely used by otherwise naïve IDUs – may be related to this. The prevalence of HIV and HCV among this group of IDUs is poorly documented in almost every country, except where these drugs are the major drugs of injection. The evidence on the magnitude of HIV risk associated with pharmaceutical opioid injecting – relative to other opioids such as heroin – is limited, although it may be lower if injection occurs less frequently.

### 7.1.2. Evidence on diversion

Several different mechanisms through which diversion occurs were apparent across different countries. One important factor includes whether injection of these drugs has emerged among existing populations of illicit opioid injectors. A second factor concerns diversion because of inadequate or absent regulation of these drugs. A third involves more limited diversion or injection of OST by those in treatment.

Notwithstanding arguments about their share of the "market", patients represent a major possible source of diverted medication in every country where opioids can be obtained on prescription. Not all patients are at the same risk of diverting medication. Unfortunately, discussions of "diversion" rarely examine this issue with clarity. All too often, very diverse patient groups are somehow treated as one group, the group being discussed is not explicitly stated, and/or conclusions are made about diversion that might be inappropriately extended to other groups at different diversion risk.

Better monitoring of use, risks and harm among known at-risk populations is required. Problematic use seems concentrated within high-risk groups in many countries; population prevalence estimates of past year use are of limited usefulness for providing information about the extent to which use is causing harm. Treatment data should not be taken to accurately reflect levels of problematic use, since misuse or diversion may reflect a reluctance to enter formal drug treatment for many opioid IDUs in some countries. Such routine data collections are also absent in many countries. Data on patterns of use among at-risk groups should be collected wherever possible, and reported regularly.

More detail is required if effective demand and harm-reduction responses are to be appropriately formulated. Issues such as the patterns of misuse, methods of preparation and extent of other risk behaviours associated with pharmaceutical injection must be investigated.

## 7.2. Clinical uses of pharmaceutical opioids

Despite clear evidence that pharmaceuticals are highly effective in the treatment of pain and in the treatment of illicit opioid dependence, they typically remain under-utilised for the conditions for which they are most effective: severe malignant pain, severe chronic non-malignant pain, and as a treatment for illicit opioid dependence.

Conversely, in some countries where opioid prescription occurs more liberally and can be provided by GPs with limited training in chronic pain, there may be some over-prescribing to patients presenting with conditions causing chronic non-malignant pain. We consider some guidelines for these three indications, and some general principles are summarised below:

- More education for physicians on how to manage pain and avoid over-prescribing
- Careful and considered diagnoses

- Clear therapeutic goals
- Use of non-drug therapies where appropriate
- Prescription of appropriate type, quantity and formulation of pharmaceuticals
- Education for patients on risks of dependence and effects of medications (and interactions)
- Regular medication reviews
- Monitoring of patients with intractable pain who require ongoing opioid medication

One expert wrote of the US situation that "the more immediate question for doctors in the US and elsewhere is how they should control their own prescribing so that interference by regulators does not discourage appropriate medical use of opiates" (p.812)[96]. This summarises one of the core issues that threaten appropriate treatment of pain conditions that health professionals face if prescribing of pharmaceuticals is to continue without being threatened by over-regulation.

### 7.2.1. Treatment of cancer and AIDS-related pain

Education of physicians in pain management must be improved, because it is a prerequisite for better assessment and treatment of patients suffering from pain[109] and there is inadequate coverage of pain with opioid pharmaceuticals.

The WHO has developed guidelines for the management of cancer pain. These consist of a staged approach, beginning with non-opioid analgesics before progressing to moderate then high-potency opioids. The use of combination therapy with opioids and non-opioids or other adjuvant modalities is encouraged. This model has been validated, and is reportedly effective in achieving relief in up to 88% of patients[109].

Patients suffering from cancer pain are generally considered to be unlikely to divert their medication. Regulatory controls will serve to minimise risks of others diverting medications intended for this source in many countries.

### 7.2.2. Treatment of chronic non-malignant pain

As noted in the beginning of this report, the term "chronic pain" refers to many conditions with different aetiologies. The experience of chronic pain is affected by premorbid conditions of the individual and the cultural context of the expression and experience of pain. There is a clear need to better understand both these conditions and the uncertainty about the best ways in which opioids can be used for chronic pain. It seems clear that research is needed to investigate which patients benefit from this form of therapy, and in which circumstances[96].

This gap is important. There were clear indications that when opioids are available and generally prescribed for this condition, a significant risk for misuse and diversion exists. The striking US example of poorly managed and relatively unregulated use of opioid medications for diffuse pain conditions, which included liberal prescribing by GPs without sufficient experience in pain management, lay testament to the problems inherent in prescribing a drug of dependence for a chronic condition without careful assessment, differential diagnosis, and ongoing supervision. It is highly unlikely that the doctors prescribing oxycodone for pain patients in the United States are sufficiently trained, or are monitoring patient progress carefully, yet experts warn that this is a critical task[519].

### 7.2.3. Opioid substitution treatment for dependent opioid users

OST should be available for the treatment of IDUs who have developed dependent use of pharmaceutical opioids[135, 520]. OST is associated with reductions in the frequency of illicit opioid use, fewer injections and injection-related HIV risk behaviours, lower HIV prevalence and incidence, and lower HCV incidence[135, 521-523]. OST is generally superior to non-drug and antagonist treatments.

OST must be delivered in accordance with evidenced-based guidelines[29]. In countries where such guidelines have not been developed, this must be addressed. Guidelines need to address[29]: criteria to define eligibility for substitution treatment; contra-indications; best practice guidelines and relevant

government regulations. Adequate training must be provided for those who will be prescribing OST to ensure appropriate clinical care and patient assessment and monitoring.

Higher methadone doses are associated with longer treatment retention[524] and improved outcomes, especially reduced heroin use. The concurrent provision of additional medical services may further improve patient functioning[411]. Ancillary services such as counselling and primary health care also provide a positive contribution to the outcomes of OST[411].

Flexible dosing policies instead of dose restrictions are associated with better retention, and the length of time in treatment is associated with enhanced outcomes. The difference in uptake of buprenorphine and methadone in France can be seen as an illustration of the impact of treatment accessibility[525]. Methadone is dispensed daily from registered clinics with compulsory urine testing, whereas buprenorphine is prescribed by GPs with no urine testing and takeaway doses permitted. Buprenorphine recipients outnumber methadone recipients by nearly eight to one[525].

Supervised administration of dosing is a common feature of OST[29]. The obvious rationale is to reduce the likelihood of diversion of this medication. Takeaway dosing is nonetheless available in numerous countries. The extent to which takeaway doses may be associated with extensive misuse or diversion probably varies across pharmaceutical opioid preparations. One Australian study found that takeaway methadone dosing was associated with greater diversion and injection among IDUs (diversion and injection was also related to heroin availability, drug preferences and treatment availability in general)[526]. Similarly, where buprenorphine is dispensed through community pharmacies (as opposed to specialist drug treatment clinics), pharmacists suspect a high level of diversion[418]. Further policies such as diluting takeaway doses, closer monitoring of supervised doses, and increased dosages, have been suggested as ways to reduce the levels of OST injecting[159].

The unattractiveness of OST for some dependent opioid users may arise from overly restrictive requirements[527]. Methadone often requires daily attendance at a dispensing clinic or pharmacy, which limits a client's movements and his/her ability to work, especially if extended travel is involved. Some treatment services may also require regular supervised urine samples and high levels of security at the clinic, contributing to the treatment's unattractiveness. Patients often have clear ideas about which treatment they want and dissatisfaction in being allocated an unwanted treatment is one common reason for early drop-out of randomised controlled trials. It is important that a range of treatment options is available and patients are informed about these options.

## 7.3. Regulatory responses to ensure medical availability and minimise diversion

"Optimally-designed" drug diversion control programmes have three goals: a) to limit access to only those with a legitimate need for the drug; b) to track and identify cases where control over this access is compromised; and c) to minimise the effect of these controls upon legitimate medical practice[528]. These general principles must be used to produce a mix of strategies to apply to the context of a given country. The question is: how does a country balance the needs and risks? The "solution" most countries have chosen is very clear: limit supply, at the expense of sufficient availability of opioids for medical and scientific purposes[295].

In some countries – particularly in Africa – there is little apparent misuse; there is also inadequate treatment of severe pain for patients that could be relieved. At the other end of the spectrum, there are case examples of countries where access to pharmaceuticals is relatively good for those experiencing even diffuse pain – the United States is a particularly notable one. This access appears to have been aided by relatively liberal regulations allowing GPs to prescribe opioids for those patients who appear to be suffering from pain – both cancer and chronic non-cancer, combined with highly aggressive marketing by pharmaceutical companies selling the products. This has come at the expense of considerable misuse, diversion, and, ultimately, injection among populations of established IDUs, but

certainly in the case of the United States, has also meant all too ready access for a group of otherwise relatively drug naïve persons who are now suffering from established dependent patterns of use.

Diversion of opioid medication should not be considered an issue to be addressed primarily by those involved in the drug and alcohol field (either treatment or research). The work of experts in the area of pain is an important avenue through which responses to this issue are more appropriately focused. Policies and programmes aimed at providing effective treatment for the multiple patient groups considered here should be led by pain specialists.

## 7.3.1. International regulations

International bodies can and do play an important role in determining pharmaceutical opioid availability. The INCB in particular can place pressure upon countries to increase or further regulate pharmaceutical opioid availability. They have urged many countries to make opioids better available for the effective management of pain, and this is an important change that must be made.

The INCB can also play an important part in ensuring the availability of opioids for OST where illicit opioid dependence is an issue. Given the documented benefits of widespread OST implementation – reduced HIV transmission, reduced opioid overdose, improved wellbeing for patients and improved public amenity – there is a clear public health imperative that should encourage international agencies to assist countries to make OST available where it is required.

The retention of opioid drugs such as buprenorphine under the 1971 UN Convention is important, particularly in countries where more potent opioids are difficult to introduce as OST. It is also appropriate: buprenorphine has effects that are significantly different from morphine (which determines a drug's inclusion under the 1961 Convention); it is a competitive partial agonist, with clear ceiling effects and comparatively lower dependence potential.

## 7.3.2. National policies on palliative care and pain management

Palliative care, whether for people with HIV or for others with chronic illness, is an essential part of any health care system. The WHO has identified three foundation measures to scaling up the provision of such care[529]. The following is taken directly from the WHO report on this topic:

"1. *Development of a national policy:* Palliative care is not recognized in many government plans. For example, Uganda is the only country in sub-Saharan Africa that has adopted WHO's foundation measures for establishing a palliative care service. While a handful of other countries in the region have some provision for palliative care, this is provided outside the government health service. Advocacy for provision of palliative care as part of the essential health service system by the government will be a move towards ensuring some budget allocation for provision of care for those with chromic illnesses.

2. *Training for health workers and public education:* Understanding of what palliative is, and training to carry it out, is necessary for policy makers, health professionals and families. For HIV, such training needs to be linked to training on areas specific to HIV such as transmission and control of transmission, issues of stigma and discrimination, and respect for confidentiality.

*3. Pain control:* Pain is as important in HIV infection as it is in cancer. Some studies have shown that pain is reported as a primary symptom by more than half of people with HIV. In many countries, this will require training and awareness raising among health professionals, and advocacy to change laws to make effective pain relief available."[529]

Innovative work is being conducted by pain experts to aid countries to develop more effective policies and regulations regarding pharmaceutical opioids[295]. The US PPSG has developed methods and resources to assist governments and pain and palliative care groups to examine national policies and make regulatory changes, and has already worked with Romania, India, and Italy (who had overly restrictive policies towards opioid availability). It is developing a training program for fellows from low and middle income countries, enhanced support of collaborators working on opioid availability, an internet course in international pain policy, an improved website with policy resources and country

profiles, and new approaches to the study of opioid consumption indicators[295]. The comparative over-emphasis of most research and policy work on illicit opioid use and IDU has been at the expense of the much larger group of patients who require pain relief.

## 7.3.3. Opioid availability and regulation

More opioid medications should be developed and registered in many countries. As the tables in this report show, many countries not only have highly inadequate opioid supply, they also do not stock the medicines listed by WHO as essential in the treatment of acute and chronic pain of cancer and non-cancer types. Fewer still stock the model medicines for treatment of illicit opioid dependence.

Pharmaceutical regulation is a highly challenging task. Simplistic attempts to restrict availability are liable to have negative therapeutic implications for legitimate patients[49], both those suffering from chronic pain *and* those who wish to address their dependent opioid use. Over-regulation will inappropriately reduce supply for pain patients and for persons who have developed opioid dependence. If unaccompanied by other interventions, efforts directed at reducing the supply of one type of pharmaceutical might lead to the increased use of another[50].

The case of India, where additional regulations were introduced in 1985, is an excellent example of what can go wrong: in the 12 years following the introduction of laws aimed at reducing the extent of diversion of morphine, the country's morphine consumption had fallen by 97%[5]. **The careful development of policies for provision of opioids for severe pain, and trial of outpatient treatment, has seen successful treatment of thousands of patients with limited or no diversion by either patients or medical professionals**[5].

When changes are made to such systems, changes will occur in the level of prescriptions. In Spain, treatment of cancer pain was considered inadequate due to excessive paperwork required of physicians; when the restrictions were relaxed, with less paperwork required for patient prescriptions to be made, prescriptions increased in Spain, particularly for slow release oral morphine[530].

**In countries where OST is not currently available but where illicit opioid dependence is an issue, OST should be introduced.** The following regulatory issues need to be considered: legislative and regulatory controls over access; registration or accreditation of treatment providers; registration of individuals receiving OST; and mechanisms for monitoring treatment quality and outcomes[29].

## 7.3.4. Monitoring of drug marketing

Pharmaceutical companies can and will play an important role in opioid pharmaceutical use and misuse. The US example of oxycodone highlights the fact that unbalanced depictions of dependence risk and overly generalised marketing to health professionals may pose a very significant risk for populations that are predisposed to taking up medications for a variety of health conditions[27, 112-113].

Pharmaceutical companies have considerable resources, often much greater than a country does for regulation. In the case of Italy, government responses to inadequate prescription of pharmaceutical opioids led to changes in government regulations for doctors' prescribing, which had no impact[19, 531]. In contrast, changes in the costs of fentanyl patches, and a massive marketing drive by the company selling them in Italy, resulted in a large increase in the prescription and use of this form of medication as a first line treatment (despite recommendations advising otherwise)[531].

**One way in which availability needs to be regulated therefore includes monitoring of drug company promotion of pharmaceutical opioids to the medical profession and the broader commnunity** to ensure that appropriate use occurs.

## 7.3.5. Prescription monitoring and professional standards for prescribers

Prescribers play an obvious role in ensuring appropriate provision of opioids for patients who need them, while minimising the risks for misuse and diversion among their patients. There is a need for appropriate training to be provided to medical professionals about the characteristics of different opioid

medications, strategies that might be used to reduce diversion, and methods to suggest to patients to reduce the likelihood of over-dosing and misuse. Prescribers must be given adequate training.

Prescription monitoring systems – whereby medical professionals are required to fill in multiple forms to prescribe, with forms being sent to health authoroties for recording – will attenuate "inappropriate" (or ill-considered) prescribing. There is a high risk, however, that under-prescribing of pain medications may be exacerbated by programs that monitor prescriptions. They typically involve greater paperwork, and sometimes multiple bureaucratic steps. These sorts of systems may lead to the substitution of less potent drugs and under-treatment of pain[528, 532-533]. There is evidence from multiple countries to suggest that the introduction of overly onerous reporting mechanisms deters doctors from prescribing these drugs where such drugs might have proven useful[192, 532-533]. Such systems need to be carefully developed.

In the United States, some states have implemented methods of monitoring prescriptions in which the prescriber writes a prescription for controlled drugs on a pre-printed, serially numbered prescription form in either duplicate or triplicate, with one copy being sent by the dispenser to the state regulatory agency who enters it into a database. The database can then be used to monitor aberrant prescribing and dispensing, as well as doctor-shopping by patients. The limitation of electronic data transfer systems is that the majority of pharmacies must have computer capabilities[528] – these systems are well outside the capacity of many low income countries, but they should be implemented in countries with sufficient resources.

## 7.4. Drug preparations and formulations

### 7.4.1. Less injectable formulations and preparations

**The pharmacological formulation of different pharmaceuticals may impact on their potential for misuse and/or injection[534]. Research in this area should be continued for obvious public health reasons.**

There is increasing debate among experts in this field about the ways in which formulations less prone to being misused or injected can be developed[534-539]. One example is a formulation of both buprenorphine and naloxone, developed to deter injection of buprenorphine[194, 540]. When taken sublingually, the effects of the buprenorphine-naloxone combination are the same as for buprenorphine alone (no appreciable amounts of naloxone are absorbed[23]), but when injected by heroin or methadone-dependent persons, naloxone may precipitate unpleasant withdrawal symptoms[viii], [23, 540-542]. Other agonist-antagonist preparations are being investigated including a mixed methadone-naloxone preparation[66].

Even formulations developed to be less prone to injection (and diversion) will not be completely successful. There is evidence that some users continue to inject buprenorphine-naloxone[420], at least in situations where heroin or methadone supply is inconsistent on the illicit market. In some contexts, those who inject buprenorphine-naloxone may have adapted to continue injecting the formulation while also avoiding withdrawal symptoms. In other cases, this formulation may be injected by heroin injectors when in withdrawal, thereby *reducing* the intensity of heroin withdrawal symptoms.

The preparation may also deter injection among some IDUs. Dilution of methadone syrup may decrease the likelihood that it is injected[543]. In the case of temazepam (a benzodiazepine), the removal of a gel capsule preparation in Australia following persistently high levels of injection among regular IDUs[11, 544] was associated with reductions in the injection of this drug, and in some states, a reduction in benzodiazepine injection overall[545]. There may have been some unintended shifting of harms for some users in areas where illicit drug availability is traditionally low, with some evidence that injection of benzodiazepine tablets or antihistamine gel capsule formulations began after temazepam gel capsules were removed[74].

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[viii] Louisa Degenhardt, Briony Larance and Richard P. Mattick have received an untied educational grant from Reckitt Benckiser to examine the extent of misuse, diversion and injection of buprenorphine-naloxone in Australia, 2006-2008.

Notably, these responses to diversion for injection, even if totally effective in stopping *injection*, will not necessarily impact upon *misuse* generally.

### 7.4.2. Injectable formulations for opioid substitution treatment

Not all people who inject drugs will cease injecting, and some will inject a formulation or preparation that is designed not to be injected. Some countries have considered injectable formulations to be provided under treatment to some IDUs who have not responded to standard OST[141, 546-548]. This includes injectable morphine and heroin, which have been trialled and implemented in some countries, with an emphasis upon improving patient acceptability of the OST formulation so that treatment-resistant users are more motivated to enter and continue in treatment[549], because they have pharmacokinetic profiles mimicking diacetylmorphine, with rapid peak concentrations of diacetylmorphine and 6-acetylmorphine[546]. Some have concluded that there is a "mounting onus on the realm of politics to translate the largely positive data from completed HAT [heroin assisted treatment] science into corresponding policy and programming in order to expand effective treatment options for the high-risk population of illicit opioid users" that this form of treatment aims to help (p.552)[549].

The use of injectable formulations involves a number of logistical and clinical issues[142, 550-556]. No studies have compared the effectiveness of injectable methadone/heroin with the provision of oral methadone delivered in optimal treatment conditions (e.g. high dose >80mg, <100mg; daily supervised administration; psychosocial support, etc.), although there is a large randomised trial underway in the United Kingdom[142]. The cost of injectable opioids is likely to be high if given under medically supervised conditions, as in Switzerland.

Notwithstanding this, **for those dependent opioid injectors who have tried other OST forms and repeatedly struggled to remain in treatment, injectable heroin or morphine may represent one alternative to allow them to become more stabilised**[557]. Further research is needed to examine the feasibility and cost effectiveness of such OST forms. This form of treatment is obviously applicable only in countries where OST is currently available and there is a demonstrated population of treatment-resistant opioid dependent persons.

## 7.5. Harm reduction

### 7.5.1. Opioid substitution treatment

As described early in this report, OST reduces the level of HIV risks and HIV transmission[29, 135] and allows for stabilisation of persons who have already contracted HIV[136-140]. The expansion of OST provision in some countries is thought to underlie the reductions in HIV incidence where IDU was in an important vector[140]. It is also thought to underlie the reduction in opioid overdose and AIDS mortality rates in countries which significantly expanded their OST coverage[558-559].

**OST can therefore be seen as an HIV harm-reduction measure in addition to an intervention to reduce demand for diverted pharmaceutical opioids.**

### 7.5.2. Needle and syringe programmes

**NSPs have been shown to reduce HIV transmission and injecting risk behaviour. Injecting equipment must be made available as a matter of priority in regions where access is currently limited, yet pharmaceutical opioid injection is occurring, and HIV risk behaviours are common, such as South Asia.**

Although sharing of injecting equipment is generally perceived as dangerous by IDUs, a considerable proportion of them reportedly share them in South Asian settings – the driving force being individual economics, as most of them are poor. There are also some misperceptions that stand in the way of safer injecting practices in some instances[183], underscoring the importance of education for people who inject drugs. A rapid assessment in 2006 of AusAID/United Nations Development Program (UNDP) supported Harm Reduction Projects in Nepal by nine non-governmental organisation (NGO) partners across the

country clearly revealed that the project management unit of UNDP played a very crucial role in managing and monitoring these projects, with some sites recording near zero sharing of injection equipment by IDUs[560].

Another issue is whether injecting equipment that facilitates injection of pharmaceutical preparations (e.g. pill filters, large barrels/needles and vein infusion kits) should be made available. Some have recommended *reducing* the availability of equipment for injection of non-injectable formulations such as methadone syrup[543]. Not all IDUs will cease injecting, however. Among those IDUs who continued to inject methadone syrup after equipment was banned, there was greater re-use of equipment, with the recommendation that additional policy initiatives were required to further address this issue[159]. There is a tension, then, between providing equipment that facilitates injection of these non-injectable drugs, and reducing overall injection at the expense of those who choose to continue doing so. It has been suggested that more comprehensive responses (e.g. including dilution of methadone syrup) are required[182], since removing access to equipment for injecting methadone syrup clearly has not led to a complete cessation of injecting for some IDUs.

### 7.5.3. Education for injecting drug users

**Particularly in countries where pharmaceutical opioid injection is occurring, attempts should be made to provide factual information to IDUs about the risks of injecting these medications, and ways in which harm can be reduced.** This includes:

- Education among IDUs regarding overdose risk, HIV/HCV risk behaviour and risks associated with non-sterile injecting practices.

- Education regarding risks associated with injecting pharmaceuticals intended for oral administration – vascular damage and infectious/non-infectious complications.

## 7.6. HIV treatment

**Interventions to address HIV among those who inject pharmaceutical opioids should be consistent with the UNAIDS essential package for prevention and care of injecting drug users**[ix]**.** Some of these have already been discussed above. The package includes:

- information, education and communication (IEC);
- full range of OST options;
- implementation of harm-reduction measures;
- voluntary confidential HIV counselling and testing;
- prevention of sexual transmission of HIV;
- access to primary heath care;
- access to antiretroviral therapy; and
- promotion, protection and respect for human rights – and particularly anti-stigma and discrimination measures.

OST should be integrated with other HIV preventive interventions and services, and with treatment and care of people living with HIV[29]. HAART should be available to those who need it[561]. In low and middle income countries, access to such treatment is often especially difficult. Discussions of treatment

[ix] See for example http://data.unaids.org/UNA-docs/cco_idupolicy_en.pdf

coverage are beyond the scope of this review, but access to effective treatment for HIV will vary importantly across the globe for persons with HIV, including those who are opioid dependent.

Poor adherence to HIV medication may be more common among those who have untreated drug use problems[562-564]. Persons presenting with opioid dependence who are also HIV positive should be encouraged to address their drug use[562]; OST has been shown to increase HIV treatment adherence among this population[565].

**Those actively using drugs should be offered treatment for HIV, but clinicians should provide good support to assist clients with adhering to medication[562]. Part of good clinical practice involves assessment for potential non-adherence and this should be conducted carefully.** This should be ongoing but evidence suggests that a particular focus should be placed upon maintaining adherence in the first four to six months of treatment, which has been found to be an important factor in improving the treatment outcome[562].

## 7.7. Future research

There is an imperative for good research on this topic[566]. Concerns about inappropriate responses to evidence of diversion and injection can no longer preclude research into this issue. Lack of data on the topic will only serve to maintain the status quo, which appears to be a tendency to limit availability for pharmaceutical opioids for medical and scientific purposes. Some areas of research need include but are not limited to:

- systematic collection of detailed data on pharmaceutical opioid availability for medical purposes;
- regular collection of data on the extent and nature of extra-medical use of pharmaceutical opioids, including injection;
- studies examining the relationship between pharmaceutical opioid injection among IDUs and the availability of other illicit drugs;
- studies examining the reasons for pharmaceutical opioid extra-medical use and injection among users from different country contexts and different subpopulations of users within countries;
- studies examining the factors that maximise attractiveness of OST while minimising diversion risk;
- research documenting the prevalence of HIV and HCV among those who inject pharmaceutical opioids;
- research into formulations of pharmaceutical opioids that reduce the risk of injection;
- research into formulations of pharmaceutical opioids that pose less risk of harmful use;
- evaluation of national policies for regulation of pharmaceutical opioids in low and middle income countries;
- research to examine the feasibility and cost effectiveness of injectable forms of OST for those clients who have not succeeded in standard forms of OST;
- further research into the ways in which opioids can be used for chronic pain: which patients benefit from this form of therapy, and in which circumstances;
- research examining the influence of policy in both facilitating and restricting health promotion and harm reduction among those who inject pharmaceutical opioids; and
- review of current national and international legislation through which pharmaceutical companies can be held accountable for policies and procedures that facilitate large scale diversion of their products.

# 8. Conclusions

Pharmaceuticals have a legitimate and important role in the treatment of a range of medical and psychological conditions. They are under-utilised globally for the indications for which they have been demonstrated and regarded as essential. These medications must be provided to patients who would benefit from them. Diversion should be anticipated to occur and steps should be taken to limit its extent and mitigate the negative consequences of this practice.

On the basis of the current evidence, misuse, diversion and injection of pharmaceutical opioids appears to be a significant problem for the United States, South Asia, some Eastern European countries, and, to a lesser extent, Canada, New Zealand and Australia. The nature of the populations injecting these pharmaceuticals seems very different across countries. The prevalence of HIV among those injecting these drugs also probably varies widely across countries but was not specifically reported for the vast majority of countries.

The current review of the evidence on the epidemiology, and consideration of responses, leads to the following recommendations:

- International regulations that do not place pharmaceuctical opioids under overly restrictive schedules under International Treaties.
- Development of comprehensive national policies on palliative care, pain management and OST.
- Adequate provision of pharmaceutical opioids for the treatment of pain.
- Expansion of OST in countries where illicit opioid dependence has developed.
- Regulation of pharmaceutical opioids including consideration of prescription monitoring.
- Training and continuing education for those prescribing opioids on safe levels of prescribing, precautions required to ensure patients have optimum doses while minimising overdose risk, and other mechanisms to ensure appropriate care of patients.
- Systematic collection of data on pharmaceutical availability for medical purposes, compiled with data on patterns of injecting drug use, including pharmaceutical opioid injection, and considering the availability of other illicit drugs.

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# Appendix A: Method

This study comprised a desk-based literature review of peer-reviewed and grey literature.

Searches of the electronic databases of Medline and EMBASE (via the OVID platform) and PubMed were conducted. Further details of these searches are given below.

The following drug and alcohol databases and related online libraries were searched for grey literature: The Australian National Drug and Alcohol Research Centre (NDARC) library; The Alcohol and other Drugs Council of Australia (ADCA); The CORK network catalogue; Asian Harm Reduction Network (AHRN). Searches of the internet using the Google search engine were also conducted on a country-by-country basis.

Material retrieved from these searches was deemed appropriate for inclusion in this review if it was an original research study, a commentary, a policy analysis, a review or report that described any of the following: availability of pharmaceutical opioids for medical use; controls on availability and use of pharmaceutical opioids; the diversion of pharmaceutical opioids; the prevalence or incidence of extra-medical use of pharmaceutical opioids by injected and non-injected routes of administration; harms associated with extra-medical use of pharmaceutical opioids; HIV prevalence and risk behaviours extra-medical pharmaceutical opioid users; treatment and policy addressing extra-medical use of opioid pharmaceuticals.

In addition, UNODC and WHO country and regional offices were requested to provide any relevant material available to them.

Additional literature cited within the retrieved material was also consulted.

As a general principle, more recent literature was preferred over older data. In all estimates of prevalence, the most recent data only were included in tables.

For some of the grey literature, material retrieved data on sample sizes, methodology, and/or the organisation conducting the research could not be identified. If a country has no estimate, it means that either no data was available.

## Medline Search Strategy

The following keywords and "MeSH" terms (in **bold**) were used in the searches of the literature for each region:

**Injecting Drug Use**

IDU OR IDUs OR "injecting drug" OR "intravenous drug" OR "intravenous substance" OR "injecting substance" OR **exp substance abuse, intravenous/**

**Drugs and drug use**

heroin OR cocaine OR amphetamine$ OR methamphetamine$ OR opioid$ OR opium OR opiate OR drug abuse OR drug use$ OR drug misuse OR drug dependenc$ OR substance abuse OR substance use$ OR substance misuse OR substance dependenc$ OR addict$ OR **exp designer drugs/** OR **exp street drugs/** OR **exp Cocaine/** OR **exp crack cocaine/** OR **exp amphetamines/** OR **exp amphetamine/** OR **exp methamphetamine/** OR **exp Opium/ or exp Heroin/** OR **exp substance-related disorders/** OR **exp amphetamine-related disorders/** OR **exp cocaine-related disorders/** OR **exp opioid-related disorders/** OR **exp heroin dependence/** OR **exp morphine dependence/** OR **exp psychoses, substance-induced/**

**HIV/AIDS**

OR HIV or AIDS OR HIV/AIDS OR "Human Immunodeficiency Virus" OR "Human Immune Deficiency Virus" OR "Acquired Immunodeficiency Syndrome" OR "Acquired Immune Deficiency Syndrome" OR **exp HIV/** OR **exp HIV-1/** OR **exp HIV-2/** OR **exp HIV infections/** OR **exp acquired immunodeficiency syndrome/** OR **HIV seropositivity/** OR **exp HIV seroprevalence/** OR **exp AIDS serodiagnosis/**

**Pharmaceuticals**

"prescription drug$" OR pharmaceutical$ OR **exp prescriptions, drug/** OR **exp pharmaceutical preparations/**

**Pharmaceuticals 'misuse'**

"self medication" OR "non medical use"
**exp self medication/**

**Pharmaceutical opioids**

"pharmaceutical opioid$" or biodone OR suboxone OR alfentanil OR alphaprodine OR "opioid analgesics" OR benzomorphans OR buprenorphine OR butorphanol OR codeine OR cyclazocine OR dextromoramide OR dextrorphan OR dihydromorphine OR diphenoxylate OR diprenorphine OR ethylketocyclazocine OR ethylmorphine OR etorphine OR fentanyl OR hydrocodone OR hydromorphone OR levallorphan OR levorphanol OR meperidine OR meptazinol OR methadone OR methadyl acetate OR morphinans OR morphine derivatives OR morphine OR nalbuphine OR nalorphine OR narcotic$ OR noscapine OR opiate alkaloids OR oxycodone OR xymorphone OR pentazocine OR phenazocine OR henoperidine OR pirinitramide OR promedol OR ropoxyphene OR sufentanil OR thebaine OR tilidine OR tramadol OR **exp alfentanil/** OR **exp alphaprodine/** OR **exp analgesics, opioid/** OR **exp benzomorphans/** OR **exp buprenorphine/** OR **exp butorphanol/** OR **exp codeine/** OR **exp cyclazocine/** OR **exp dextromoramide/** OR **exp dextrorphan/** OR **exp dihydromorphine/** OR **exp diphenoxylate/** OR **exp diprenorphine/** OR **exp ethylketocyclazocine/** OR **exp ethylmorphine/** OR **exp etorphine/** OR **expfentanyl/** OR **exp hydrocodone/** OR **exp hydromorphone/** OR **exp levallorphan/** OR **exp levorphanol/** OR **exp meperidine/** OR **exp meptazinol/** OR **exp methadone/** OR **exp methadyl acetate/** OR **exp morphinans/** OR **exp morphine derivatives/** OR **exp morphine/** OR **exp nalbuphine/** OR **exp nalorphine/** OR **exp narcotics/** OR **exp noscapine/** OR **exp opiate alkaloids/** OR **exp oxycodone/** OR **exp oxymorphone/** OR **exp pentazocine/** OR **exp phenazocine/** OR **exp phenoperidine/** OR **exp pirinitramide/** OR **exp promedol/** OR **exp propoxyphene/** OR **exp sufentanil/** OR **exp thebaine/** OR **exp tilidine/** OR **exp tramadol/ exp** OR**exp narcotic antagonists/** OR **exp buprenorphine/** OR **exp butorphanol/** OR **exp cyclazocine/** OR **exp diprenorphine/** OR **exp levallorphan/** OR **exp meptazinol/** OR **exp nalbuphine/** OR **exp nalorphine/** OR **exp naloxone/** OR **exp naltrexone/** OR **exp pentazocine/**

## PubMed Search Strategy

The following keywords and "MeSH" terms (in **bold**) were used in the searches of the literature for each region:

**Injecting drug use**

IDU OR IDUs OR "injecting drug" OR "intravenous drug" OR "intravenous substance" OR "substance abuse, intravenous" OR "**substance abuse, intravenous**" [MH]

**Drug use**

"Drug abuse" OR "drug use" OR "drug user" OR "drug users" OR "drug misuse" OR "drug dependence" OR "drug dependency" OR "drug dependent" OR "substance abuse" OR "substance use" OR "substance user" OR "substance users" OR "substance misuse" OR "substance dependence" OR "substance dependency" OR "substance dependent" OR addict OR addicts OR addiction OR "substance-related disorders" OR "amphetamine-related disorders" OR "cocaine-related disorders" OR "opioid-related disorders" OR "heroin dependence" OR "morphine dependence" OR "**substance-related disorders**" [MH] OR "**amphetamine-related disorders**" [MH] OR "**cocaine-related disorders**" [MH] OR "**opioid-related disorders**" [MH] OR "**heroin dependence**" [MH] OR "**morphine dependence**" [MH]

**HIV/AIDS**

HIV OR AIDS OR AIDS [sb] OR "HIV/AIDS" OR "**Human Immunodeficiency Virus**" OR "**Acquired Immunodeficiency Syndrome**" OR "**HIV-1**" OR "**HIV-2**" OR "**HIV seropositivity**" OR "**HIV seroprevalence**" OR "**AIDS serodiagnosis**" OR "**HIV-1**" [MH] OR "**HIV-2**" [MH] OR "**HIV seropositivity**" [MH] OR "**HIV seroprevalence**" [MH] OR "**AIDS serodiagnosis**" [MH]

**Pharmaceuticals**

"prescription drug*" OR pharmaceutical* OR **prescriptions, drug** [MH] OR **pharmaceutical preparations/**

**Pharmaceuticals 'misuse'**

"self medication" OR "non medical use" OR **self medication** [MH]

**Pharmaceutical opioids**

"pharmaceutical opioid*" or biodone OR suboxone OR alfentanil OR alphaprodine OR "opioid analgesics" OR benzomorphans OR buprenorphine OR butorphanol OR codeine OR cyclazocine OR dextromoramide OR dextrorphan OR dihydromorphine OR diphenoxylate OR diprenorphine OR ethylketocyclazocine OR ethylmorphine OR etorphine OR fentanyl OR hydrocodone OR hydromorphone OR levallorphan OR levorphanol OR meperidine OR meptazinol OR methadone OR methadyl acetate OR morphinans OR morphine derivatives OR morphine OR nalbuphine OR nalorphine OR narcotic$ OR noscapine OR opiate alkaloids OR oxycodone OR xymorphone OR pentazocine OR phenazocine OR henoperidine OR pirinitramide OR promedol OR ropoxyphene OR sufentanil OR thebaine OR tilidine OR tramadol OR **exp alfentanil** [MH] OR **alphaprodine** [MH] OR **analgesics, opioid** [MH] OR **benzomorphans** [MH] OR **buprenorphine** [MH] OR **butorphanol** [MH] OR **codeine** [MH] OR **cyclazocine** [MH] OR **dextromoramide** [MH] OR **dextrorphan** [MH] OR **dihydromorphine** [MH] OR **diphenoxylate** [MH] OR **diprenorphine** [MH] OR **ethylketocyclazocine** [MH] OR **ethylmorphine** [MH] OR **etorphine** [MH] OR **expfentanyl** [MH] OR **hydrocodone** [MH] OR **hydromorphone** [MH] OR **levallorphan** [MH] OR **levorphanol** [MH] OR **meperidine** [MH] OR **meptazinol** [MH] OR **methadone** [MH] OR **methadyl acetate** [MH] OR **morphinans** [MH] OR **morphine derivatives** [MH] OR **morphine** [MH] OR **nalbuphine** [MH] OR **nalorphine** [MH] OR **narcotics** [MH] OR **noscapine** [MH] OR **opiate alkaloids** [MH] OR **oxycodone** [MH] OR **oxymorphone** [MH] OR **pentazocine** [MH] OR **phenazocine** [MH] OR **phenoperidine** [MH] OR **pirinitramide** [MH] OR **promedol** [MH] OR **propoxyphene** [MH] OR **sufentanil** [MH] OR **thebaine** [MH] OR **tilidine** [MH] OR **tramadol** [MH] OR **narcotic antagonists** [MH] OR **buprenorphine** [MH] OR **butorphanol** [MH] OR **cyclazocine** [MH] OR **diprenorphine** [MH] OR **levallorphan** [MH] OR **meptazinol** [MH] OR **nalbuphine** [MH] OR **nalorphine** [MH] OR **naloxone** [MH] OR **naltrexone** [MH] OR **pentazocine** [MH]

## EMBASE Search Strategy

The following keywords and "EMTREE" terms (in **bold**) were used in the searches of the literature for each region:

**Injecting Drug Use**

IDU OR IDUs OR "injecting drug" OR "intravenous drug" OR "intravenous substance" OR "injecting substance" OR **exp intravenous drug abuse/**

**Drug use**

Drug abuse OR drug use$ OR drug misuse OR drug dependenc$ OR substance abuse OR substance use$ OR substance misuse OR substance dependenc$ OR addict$ OR **exp substance abuse/** OR **exp drug abuse/** OR **exp analgesic agent abuse/** OR **exp drug abuse pattern/** OR **exp drug misuse/** OR **exp drug traffic/** OR **exp multiple drug abuse/** OR **exp addiction/** OR **exp drug dependence/** OR **exp cocaine dependence/** OR **narcotic dependence/** OR **exp heroin dependence/** OR **exp morphine addiction/** OR **exp opiate addiction/**

**HIV/AIDS**

HIV OR AIDS OR HIV/AIDS OR Human Immunodeficiency Virus OR Acquired Immunodeficiency Syndrome OR HIV status OR HIV diagnosis OR HIV screening OR HIV test$ OR HIV pre-test counselling OR HIV post-test counselling OR HIV notification OR AIDS sero$ OR HIV sero$ OR **exp human immunodeficiency virus/** OR **exp human immunodeficiency virus 1/** OR **exp human immunodeficiency virus 2/** OR **exp acquired immune deficiency syndrome/** OR **exp aids related complex/** OR **exp acquired immune deficiency syndrome/** OR **exp aids related complex/** OR **exp Human Immunodeficiency Virus Infection/** OR **exp human immunodeficiency virus prevalence/**

**Pharmaceuticals**

"prescription drug$" OR pharmaceutical$ OR **exp prescription/**

**Pharmaceuticals 'misuse'**

"self medication" OR "non-medical use" OR **exp self medication/**

**Pharmaceutical opioids**

"pharmaceutical opioid$" or biodone OR suboxone OR alfentanil OR alphaprodine OR "opioid analgesics" OR benzomorphans OR buprenorphine OR butorphanol OR codeine OR cyclazocine OR dextromoramide OR dextrorphan OR dihydromorphine OR diphenoxylate OR diprenorphine OR ethylketocyclazocine OR ethylmorphine OR etorphine OR fentanyl OR hydrocodone OR hydromorphone OR levallorphan OR levorphanol OR meperidine OR meptazinol OR methadone OR methadyl acetate OR morphinans OR morphine derivatives OR morphine OR nalbuphine OR nalorphine OR narcotic$ OR noscapine OR opiate alkaloids OR oxycodone OR xymorphone OR pentazocine OR phenazocine OR henoperidine OR pirinitramide OR promedol OR ropoxyphene OR sufentanil OR thebaine OR tilidine OR tramadol OR **exp narcotic agent/** OR **exp narcotic analgesic agent/** OR **exp acetorphine/** OR **exp acetylcodeine/** OR **exp acetylmethadol/** OR **exp alphaprodine/** OR **exp anileridine/** OR **exp azidomorphine/** OR **exp bezitramide/** OR **exp bremazocine/** OR **exp brompton mixture/** OR **exp buprenorphine/** OR **exp buprenorphine plus naloxone/** OR **exp butorphanol/** OR **exp butorphanol tartrate/** OR **exp ciramadol/** OR **exp cocodamol/** OR **exp cocodaprin/** OR **exp codeine/** OR **exp codeine iodide/** OR **exp codeine phosphate/** OR **exp codeine plus diclofenac/** OR **exp codeine sulfate/** OR **exp codydramol/** OR **exp cyclazocine/** OR **exp dextromethorphan plus morphine/** OR **exp dextromoramide/** OR **exp dextropropoxyphene/** OR **exp dextropropoxyphene napsilate/** OR **exp dextropropoxyphene plus paracetamol/** OR **exp dextrorphan/** OR **exp dezocine/** OR **exp diamorphine/** OR **exp diconal/** OR **exp digesic/** OR **exp dihydrocodeine/** OR **exp dihydroetorphine/** OR **exp dihydromorphine/** OR **exp dipipanone/** OR **exp "dynorphin a [1-8][1 (n methyltyrosine) 7 (n methylarginine) 8 dextro leucine n ethylamide]"/** OR **exp enadoline/** OR **exp eptazocine/** OR **exp ethylketazocine/** OR **exp ethylmorphine/** OR **exp etonitazene/** OR **exp etorphine/** OR **exp etoxeridine/** OR **exp furethidine/** OR **exp gelonida/** OR **exp hydrocodone/** OR **exp hydrocodone bitartrate/** OR **exp hydrocodone bitartrate plus ibuprofen/** OR **exp hydrocodone bitartrate plus paracetamol/** OR **exp hydromorphone/** OR **exp ibuprofen plus oxycodone/** OR **exp isomethadone/** OR **exp ketazocine/** OR **exp ketobemidone/** OR **exp ketogan/** OR **exp kyotorphin/** OR **exp lefetamine/** OR **exp levacetylmethadol/** OR **exp levomethadone/** OR **exp levorphanol/** OR **exp meptazinol/** OR **exp metazocine/** OR **exp methadone/** OR **exp**

**morphine/** OR **exp morphine 6 acetate/** OR **exp morphine 6 glucuronide/** OR **exp morphine sulfate/** OR **exp morphinomimetic agent/** OR **exp morphinone/** OR **exp nalbuphine/** OR **exp nicocodine/** OR **exp nicomorphine/** OR **exp noracymethadol/** OR **exp nordextropropoxyphene/** OR **exp normorphine/** OR **exp norpethidine/** OR **exp norpropoxyphene/** OR **exp opiate/** OR **exp oripavine/** OR **exp oxycodone/** OR **exp oxymorphone/** OR **exp pentamorphone/** OR **exp pentazocine/** OR **exp percocet/** OR **exp percodan/** OR **exp pethidine/** OR **exp phenadoxone/** OR **exp phenaridine/** OR **exp phenazocine/** OR **exp phencyclidine/** OR **exp phencyclidine derivative/** OR **exp phenoperidine/** OR **exp picenadol/** OR **exp piritramide/** OR **exp profadol/** OR **exp propiram/** OR **exp propiram fumarate/** OR **exp thebaine/** OR **exp tifluadom/** OR **exp tilidine/** OR **exp tonazocine/** OR **exp tonazocine mesilate/** OR **exp tramadol/** OR **exp trimeperidine/** OR **exp valoron n/** OR **exp valtran/** OR **exp fentanyl derivative/** OR **exp alfentanil/** OR **exp brifentanil/** OR **exp carfentanil/** OR **exp carfentanil citrate/** OR **exp droperidol plus fentanyl/** OR **exp fentanyl/** OR **exp fentanyl citrate/ or exp fentanyl isothiocyanate/ or exp beta hydroxymefentanyl/** OR **exp hypnorm/** OR **exp lofentanil/** OR **exp lofentanil oxalate/** OR **exp mefentanyl/** OR **exp mefentanyl isothiocyanate/** OR **exp "3 [4 methoxycarbonyl 4 (n phenylpropionamido)piperidino]propionic acid"/** OR **exp mirfentanil/** OR **exp remifentanil/** OR **exp sufentanil/** OR **exp sufentanil citrate/** OR **exp trefentanil/** OR **exp narcotic agent/** OR **exp n allylnormetazocine/** OR **exp alphacetylmethadol/** OR **exp paregoric/** OR **exp narcotic antagonist/** OR **exp buprenorphine plus naloxone/** OR **exp butorphanol/** OR **exp butorphanol tartrate/** OR **exp chlornaltrexamine/** OR **exp ciramadol/** OR **exp dextrallorphan/** OR **exp dezocine/** OR **exp diprenorphine/** OR **exp beta funaltrexamine/** OR **exp levallorphan/** OR **exp n methyllevallorphan mesylate/** OR **exp n methyllevallorphan/** OR **exp nalbuphine/** OR **exp nalmefene/** OR **exp nalorphine/** OR **exp naloxazone/** OR **exp naloxonazine/** OR **exp naloxone/** OR **exp naloxone 6 spirohydantoin/** OR **exp naltrexamine/** OR **exp 6alpha naltrexamine/** OR **exp 6beta naltrexamine/** OR **exp naltrexol/** OR **exp naltrexonazine/** OR **exp naltrexone/** OR **exp picenadol/** OR **exp profadol/**

Reference Group to the United Nations on

HIV and injecting drug use

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