

# THE WORLD MEDICINES SITUATION 2011

## ACCESS TO CONTROLLED MEDICINES

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## **The World Medicines Situation 2011**

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## SUMMARY

- Controlled medicines are medicines that are listed under the international conventions on narcotic and psychotropic drugs and their precursors. These were established to prevent harm from substance abuse and dependence. However, the international drug treaties state the imperative to make psychotropic and narcotic substances available for medical and scientific use.
- Some controlled medicines used to treat important health conditions are listed in the WHO Model List of Essential Medicines. Opioid analgesics, such as morphine for the treatment of moderate to severe pain; opioid agonists used for treatment of opioid dependence, such as methadone; ergometrine and ephedrine used in emergency obstetric care; and phenobarbital and benzodiazepine for treatment of epilepsy are essential medicines but they are also classified as controlled medicines.
- Global morphine consumption – an indicator of access to pain treatment – has increased over the past two decades, but mainly in a small number of developed countries. In 2003, six developed countries accounted for 79% of global morphine consumption. Developing countries, which represent about 80% of the world's population, accounted for only about 6% of global morphine consumption.
- Concern about abuse and dependence is a major factor in limiting access to opioids and other controlled medicines that are used in treating important health conditions. In practice, most patients, who are appropriately prescribed controlled medicines, do not become dependent from rational use of these medicines.
- The cost of opioid medicines at supplier level does not represent a substantial barrier to access. Methadone and morphine unit prices are only a few US cents, although buprenorphine is much more expensive than methadone. However, the retail prices of opioid medicines at country level can be prohibitive.
- Barriers to access to controlled medicines include lack of medical knowledge, national policies and regulations that are more stringent than is required by the international conventions, and obstacles in the supply of this category of medicines. The provision of reliable annual estimates on opioid medicines' requirements to the International Narcotics Control Board is also a barrier for several countries. The procurement of narcotic and psychotropic substances can often be a challenge given the complex system of export and import authorizations.

**1.1****INTRODUCTION**

Millennium Development Goal 8E aims for affordable access to essential medicines. Essential medicines, as defined by WHO, are those that “satisfy the health-care needs of the majority of the population” and that should therefore “be available at all times in adequate amounts”. However, there is a category of medicines that faces a unique challenge in terms of availability. These are the medicines governed by the international conventions on narcotic and psychotropic substances. “Controlled medicines” is the common definition for pharmaceuticals whose active principles are listed under the 1961 United Nations Single Convention on Narcotic Drugs as amended by the 1972 Protocol, such as morphine and methadone (1); the 1971 United Nations Convention on Psychotropic Substances, such as diazepam and buprenorphine (2); and the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, such as ergometrine and ephedrine (3). The conventions list substances in “Schedules” according to their different levels of potential for abuse and harm, and the commensurate severity of control measures to be applied by countries.

The conventions were established with the primary purpose of preventing substance abuse and dependence, and the social and health harm related to such abuse, but recognize that controlled medicines should remain available for medical and scientific purposes. Indeed, abuse of controlled medicines prescribed for medical purposes and therapeutic use, such as opioid analgesics, is rare. A recent systematic review reports only 0.43% abuse in patients using long-term opioid analgesics to relieve chronic non-malignant pain (4). Furthermore, diversion of narcotic substances from the licit to the illicit market is reported only from very few countries and is generally assumed to be “virtually non-existent” globally (5).

The international drug treaties clearly state that narcotic and psychotropic substances need to be made available for medical use and scientific research. More specifically, the 1961 convention recognizes that “medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering”, and that “adequate provision must be made to ensure the availability of narcotic drugs for such purposes.” Similarly, the 1971 convention affirms that “the use of psychotropic substances for medical and scientific purposes is indispensable and that their availability for such purposes should not be unduly restricted.” Essential medicines in the WHO Model List of Essential Medicines that are scheduled under the conventions are shown in Table 1.1. A number of unique barriers affect access to essential controlled medicines, including national control measures that are enforced beyond the requirements of the international drug control treaties.

This chapter specifically presents and analyses the situation related to the availability and access of two different classes of controlled medicines: opioid analgesics for pain relief and opioid agonists<sup>1</sup> for treatment of opioid dependence. Opioid analgesics, such as morphine, are the most effective medicines in treating moderate to severe pain while opioid agonists, such as methadone and buprenorphine, are essential medicines used for the treatment of opioid dependence in injecting drug users. For these two categories of essential medicines sufficient data and reports are available to allow an analysis of the current global situation and the challenges faced by countries. For other controlled medicines considered essential to

<sup>1</sup> In pharmacology, an agonist is a substance that binds to a receptor and triggers a response in the cell. Methadone is a full agonist for the  $\mu$ -opioid receptor, while buprenorphine is a partial agonist for the  $\mu$ -opioid receptor. These two medicines are used in the treatment of opioid dependence on heroin, morphine or other opioids for opioid maintenance and withdrawal. In this chapter, we will refer to methadone and buprenorphine as “opioid agonists for treatment of opioid dependence” or simplify this to “opioid agonists”.

**TABLE 1.1 Essential medicines that are listed under the international drug conventions**

International drug convention	Controlled medicines listed in the 2009 WHO Model List of Essential Medicines		Therapeutic category
1961 United Nations Single Convention on Narcotic Drugs <i>Schedule II and III</i>	Codeine	15, 30 mg tablet	Opioid analgesic, antidiarrhoeal
1961 United Nations Single Convention on Narcotic Drugs <i>Schedule I</i>	Morphine	10 mg/1 ml ampoule, 10 mg/5ml oral liquid, 10 mg tablet, 10, 30, 60 mg prolonged-release tablets, 20, 30, 60, 100, 200 mg modified-release granules	Opioid analgesic
	Methadone	5 mg/5 ml, 10 mg/5 ml oral liquid, 5 mg/ml, 10 mg/ml concentrate for oral liquid	Opioid agonist for treatment of opioid dependence
1971 United Nations Convention on Psychotropic Substances <i>Schedule III</i>	Buprenorphine	2 mg, 8 mg sublingual tablets <sup>a</sup>	
1971 United Nations Convention on Psychotropic Substances <i>Schedule IV</i>	Diazepam <sup>b</sup>	5 mg/ml/2 ml ampoule, 2 mg, 5 mg tablets, 5 mg/ml/0.5 ml gel or rectal solution, 2 ml, 4 ml tubes	Anxiolytic, antiepileptic, anticonvulsant, preoperative sedative
	Phenobarbital	200 mg/ml–15 mg/5 ml elixir, 15 to 100 mg tablets	Anticonvulsant, antiepileptic
1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances <i>Table I</i>	Ergometrine	200 microgr/1ml ampoule	Obstetric emergency (oxytocics)
	Ephedrine	30 mg/1 ml ampoule	Obstetric emergency (used in spinal anaesthesia to prevent hypotension)

<sup>a</sup> Dosages indicated in the "Proposal for inclusion of buprenorphine in the WHO Model List of Essential Medicines", 2005 [http://www.who.int/substance\\_abuse/activities/buprenorphine\\_essential\\_medicines.pdf](http://www.who.int/substance_abuse/activities/buprenorphine_essential_medicines.pdf). Refer to the WHO Report of the Expert Committee on the Selection and Use of Essential Medicines, p.33–34. 2005 <http://www.who.int/medicines/services/expertcommittees/essentialmedicines/TRS933SelectionUseEM.pdf>

<sup>b</sup> Other benzodiazepines listed in the 2009 WHO Model List of Essential Medicines.

treat different medical conditions, such as epilepsy and obstetric emergencies, no exhaustive reports have been published or global surveys undertaken to determine the extent to which regulatory barriers are affecting availability in countries.

## 1.2

### PRESENT SITUATION: CONSUMPTION AND AVAILABILITY OF CONTROLLED ESSENTIAL MEDICINES

Data and reports focusing on access to opioid analgesics and opioid agonists for treatment of opioid dependence allow analysis of the current global situation on availability, pricing and market size of these two categories of controlled medicines. The requirements set by the international drug conventions and national drug control regulations are also presented

in this section, as are barriers to access for these essential medicines and the impact of these barriers at country level.

### 1.2.1

#### Opioid medicines: essential and controlled

Table 1.1 outlines the medicines included in the WHO Model List of Essential Medicines and the corresponding international drug convention and schedule. Strong opioid analgesics and methadone, an opioid agonist, are strictly controlled under the 1961 United Nations Single Convention on Narcotic Drugs as amended by the 1972 Protocol, under Schedule I. Buprenorphine, the other essential opioid agonist, is listed under Schedule III of the 1971 United Nations Convention on Psychotropic Substances, which contains less stringent requirements than the Single Convention on Narcotic Drugs. These conventions recognize both the importance of prevention of abuse and dependence and the imperative of making opioids available for medical use (6).

### 1.2.2

#### Consumption of opioid analgesics for moderate to severe pain

The International Narcotics Control Board (INCB), is the United Nations body responsible for monitoring the implementation of the conventions on narcotic and psychotropic drugs. As strong opioid analgesics are listed as “narcotics” under Schedule I, they are subject to a system of annual reporting on production, importation/exportation and inventory by the signatory countries. This allows the INCB to gather and publish data on the annual consumption for medical use for each substance.<sup>1</sup>

*Developing countries, representing 80% of the world population accounted for about 6% of global morphine consumption.*

Global morphine consumption can be used as a proxy indicator on access to management of moderate to severe pain associated with various medical conditions. Although this has increased substantially over the past two decades, the increase has occurred only in some countries. The INCB acknowledged in its annual report that in 2003, six developed countries accounted for 79% of global morphine consumption. Conversely, developing countries which represent 80% of the world population accounted for only about 6% of global morphine consumption (6). The most recent data show that this gap persists. In 2007, six developed countries reported the highest level of morphine consumption and 132 of 160 signatory countries that reported consumption were below the global mean (see Figure 1.1). This implies that millions of patients with moderate to severe pain caused by different diseases and conditions are not getting treatment to alleviate their suffering.

### 1.2.3

#### Coverage of opioid agonists for treatment of opioid dependence

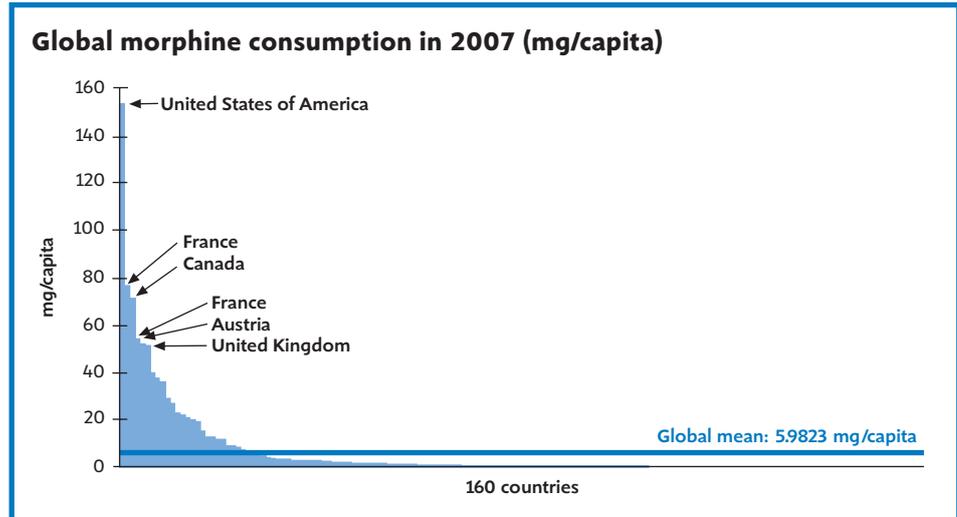
Methadone and buprenorphine are opioid agonists used for the treatment of opioid dependence. There are an estimated 16 million injecting drug users in the world, of whom 11 million inject heroin, mainly in Asia and Europe (7,8). In Western Europe, treatment with opioid agonists is a standard option for the treatment of heroin dependence and this reaches, on average, about 67% of the target population. Yet, globally, treatment of dependence with methadone and buprenorphine reaches only 8% of injecting drug users (9). In 2007, only 2% of injecting drug users in developing countries with injection-driven HIV epidemics were accessing treatment for opioid dependence. Several countries have introduced national programmes on drug dependence to tackle injecting drug use and HIV transmission

*Globally, only 8% of injecting drug users are treated with methadone and buprenorphine.*

<sup>1</sup> Consumption in this context relates to the amounts of narcotic substances that have been distributed to the peripheral level of the supply chain.

FIGURE 1.1

*Six developed countries accounted for 79% of global morphine consumption.*



Source: International Narcotics Control Board, United Nations data. Graphic created by the Pain and Policy Study Group, University of Wisconsin/WHO Collaborating Center, 2009.

through needle and syringe programmes and/or the provision of treatment with oral opioid agonists' formulations. Although the treatment of opioid dependence with methadone and buprenorphine is supported by medical, public health, human rights, social and economic arguments (10,11,12), access to this effective intervention is constrained by several factors, including the knowledge, regulatory and supply barriers related to these two medicines.

### 1.3

### BARRIERS TO ACCESS TO CONTROLLED ESSENTIAL MEDICINES

#### 1.3.1

#### Perceptions and attitudes towards the use of opioid analgesics and opioid agonists

*The main attitudinal barriers to use of opioid analgesics are fear of dependence and tolerance.*

One reason for the low rate of use of opioid analgesics is the fear of both health providers and patients that the latter will become dependent on or will abuse these medicines. Because of the lack of correct information, health professionals, patients and their families are often reluctant to use opioid analgesics for the relief of moderate and severe pain. Currently, the training curricula of medical doctors, nurses and other health professionals in many parts of the world fail to include the rational use of opioids. The main attitudinal barriers include fear of dependence, tolerance, hyperalgesia and dose escalation. There is an unfounded assumption that opioid pain treatment impairs quality of life. For example, patients incorrectly assume that opioid analgesics can only be administered parenterally; and medical practitioners believe that opioid analgesia may delay accurate diagnosis and that opioid doses should be related to the severity of the disease rather than the intensity of pain. There is widespread anxiety about the side-effects of opioid analgesics with a perception that their use is limited to end of life conditions, such as terminal cancer. The overall result is lack of access to adequate pain treatment and the denial of the human right to access the highest attainable standard of health, and the right not to be subject to torture or to cruel, inhuman or degrading treatment or punishment (13,14,15,16,17).

In several countries, drug dependence is not recognized as a disease and treatment with opioid agonists is not acknowledged as effective. There are reported cases of strong resistance and attacks by government officials against the provision of treatment for opioid dependence by governmental HIV programmes and by civil society organizations (11,18). Too many policy-makers disregard evidence on the effectiveness of the intervention in reducing

*Major efforts are needed to address the huge gaps in the provision of effective treatment of opioid dependence worldwide.*

the social and public health harm of opioid dependence, such as its impact on reducing the transmission of HIV and other blood-borne diseases (9). Moreover, injecting drug users are not considered patients in need of assistance and with a right to access treatment. In many countries, injecting drug use is approached as a criminal justice problem rather than a health problem. An extreme consequence is that the provision of buprenorphine and methadone treatment has been faced with enormous problems from law enforcement agencies in certain countries, and this has affected and is still impacting government and authorized NGO pilot projects. As an example, there have been well-documented cases of police harassment and patient arrests outside treatment centres (10,11,18,19,20). The situation regarding the provision of opioid agonists is changing in several countries. However, major efforts are needed to address the huge gaps in the provision of effective treatment of opioid dependence worldwide.

### 1.3.2

#### **International drug control and stringent national drug control regulations**

As has been stated, the availability of opioid analgesics and opioid agonists is influenced by the specific procedures and requirements for controlled substances. The requirements are set in the conventions and vary according to the scheduling of each controlled medicine in the conventions (Table 1.1). Accessing opioid medicines requires countries to comply with international and national drug control regulations. Countries that have ratified the international drug control conventions in their national laws and regulations have established bodies to deal with narcotic and psychotropic substances, and thus with controlled medicines. However, often national laws and regulations are more stringent than the conventions require, and this can hamper the availability of and access to controlled medicines for medical purposes.

#### 1.3.2.1

##### **Provision of estimates to the International Narcotics Control Board**

Every year, the signatory countries to the Single Convention on Narcotic Drugs are required to report on the imported and exported amounts of substances in Schedule I, such as morphine and methadone, to the INCB. In addition, countries are required to submit annual estimates of their requirements for narcotic substances and these are the basis for setting the limits on the quantities of medicines that the countries can procure for medical use for the next year. The treaty requires the INCB to confirm the national estimate before importation of narcotic substances under Schedule I occurs in the country. If an annual estimate proves to be inadequate, the competent national authority can submit supplementary estimates to the INCB during the course of the year. For psychotropic substances no estimates are required but for certain substances, such as buprenorphine, the INCB requires the annual submission of statistical reports on the quantities manufactured, exported and imported during the previous year.

Currently, several countries face difficulties in providing the INCB with adequate estimates of their requirements for narcotic substances under Schedule I to the INCB. As a result of this inaccuracy, they frequently submit supplementary estimates, although this procedure should only be used in the case of unforeseen circumstances and for the introduction of new treatments (5).

### 1.3.2.2

#### Importation and exportation licensing system for controlled medicines

Additionally, for all narcotics and many psychotropics, a complex system of import and export licences is in force. Hence, procurement of controlled medicines requires procurement officials to acquaint themselves with and to abide by the obligatory licences and procedures in both the exporting and importing countries. The international conventions require that all enterprises and individuals involved in the procurement, storage and distribution of controlled medicines are properly authorized or licensed by the national competent authority. Only authorized or licensed individuals can apply for an import certificate to be issued by the competent authority in the importing country. Similarly, only authorized agencies can apply for an export certificate from the competent authority in the exporting country. The sequence of steps to request and obtain the necessary certificates to import, export and receive shipments of narcotic and psychotropic substances requires specific knowledge and implies longer procurement timelines than for other essential medicines (21).

### 1.3.2.3

#### Supply chain challenges for controlled medicines

The storage, distribution and dispensing of controlled medicines require the adoption of measures to prevent diversion to the illicit market throughout the supply chain. Implementation of control measures, which are defined by national regulations, can be challenging and expensive. The conventions state, in general terms, the need to prevent diversion, but sometimes countries enforce very strict controls. For example, as anti-diversion measures some countries require the installation of alarm systems, safes and ironclad rooms to store medications and special vehicles to transport controlled medicines. Supply challenges also include overly stringent requirements for prescribing and dispensing opioid medicines, such as limitations on the daily dosage of opioid analgesics that physicians can prescribe and limitations on the number of days of treatment allowed in one prescription. In several countries, stringent and overly complicated regulations have also resulted in the disruption of the supply of opioid agonist treatment. An uninterrupted supply of medicines is essential if this treatment is to be effective (22).

### 1.3.2.4

#### National regulations going beyond the convention requirements

As mentioned above, several countries regulate controlled medicines even more strictly than required by the international conventions and may have undue provisions in their regulations that hinder medical use of opioids and other controlled medicines. For example, several countries handle buprenorphine – an opioid agonist – in their national laws and regulations as a narcotic drug although it is listed in the international convention of psychotropic substances under Schedule III. This makes buprenorphine's procurement and supply more onerous. There are also extreme situations in which regulatory constraints make controlled medicines unavailable in emergency situations (Box 1.1) and whereby essential medicines, not listed in the conventions, are handled in the national regulations as narcotic or psychotropic substances (Box 1.2). Governments often concentrate efforts on drug control without balancing the obligation to ensure availability for medical and scientific use and without considering the impact of control measures on the accessibility of essential medicines to those who need them. Law-makers often fail to ensure the availability of narcotic and psychotropic substances for medical use when defining national drug control laws and regulations (23,24).

*Law-makers often fail to ensure the availability of narcotic and psychotropic substances for medical use when defining national drug control laws and regulations.*

## BOX 1.1

**Accessing controlled medicines in emergency situations**

The Interagency Emergency Health Kit was conceived to provide all the necessary essential medicines, health products and medical equipment for 10 000 people for three months in humanitarian emergency situations. This includes opioid analgesics for trauma and surgery. The constraints in procuring and supplying controlled medicines in emergencies impacted the formulation of this kit. It has become common practice for organizations involved in the provision of medical supplies in emergency situations to disassemble it into two kits, a basic unit and a supplementary unit containing controlled medicines. The supplementary units are often blocked at the procurement agent's warehouse or while in transit awaiting the procurement authorizations required between importing and exporting countries. Despite the provision of guidance for facilitating the procurement of controlled medicines in emergency situations, regulatory constraints often result in populations affected by wars and natural disasters not receiving morphine for pain relief, antiepileptics, such as diazepam and phenobarbital, anaesthetics, such as ketamine (Box 2) and other controlled medicines in the kits. The lack of these medicines results in additional, unnecessary suffering.

Source: The interagency emergency health kit 2006. Geneva, World Health Organization, 2006. <http://apps.who.int/medicinedocs/en/d/Js13486e/#Js13486e>

## BOX 1.2

**Impact of drug control measures on medical availability of essential medicines: ketamine**

Ketamine provides an extreme example of an essential medicine whose access is limited by regulatory constraints. This affordable general anaesthetic is listed in the WHO Model List of Essential Medicines and The Interagency Emergency Health Kit. In developing countries, ketamine is widely used in adults and children for elective and emergency procedures, for general surgical, orthopaedic, obstetric and gynaecological interventions. In many rural district hospitals in low-income countries, anaesthesia is largely dependent on the availability of ketamine.

Ketamine is not listed in any of the international drug conventions. This medicine was reviewed in 2006 by the WHO Expert Committee on Drug Dependence, (the body that makes recommendations to the United Nations Commission on Narcotic Drugs on what, if any, control measures it considers appropriate). The Committee concluded that the information contained in the critical review was not sufficient to warrant scheduling of ketamine and that an updated critical review must be submitted to its next meeting.

While to date no recommendation has been made to schedule ketamine in the drug conventions, many countries started to classify it as a controlled substance and to enforce control measures on its procurement, supply and use for medical purposes. The extent to which ketamine is becoming less available is not known. In middle- and low-income countries where other general anaesthetics with good safety profiles are not available or are too expensive to access, the unavailability of ketamine may pose a serious threat to the provision of surgery care.

Sources: Hodges SC, Walker IA, Bösenberg AT. Paediatric anaesthesia in developing countries. *Anaesthesia*, 2007 Dec; 62(Suppl 1):26-31.

Hodges SC et al. Anaesthesia services in developing countries: defining the problems. *Anaesthesia*, 2007 Jan; 62(1):4-11.

WHO Expert Committee on Drug Dependence. Thirty-fourth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series No. 942). [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_942\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_942_eng.pdf)  
Report of the International Narcotics Control Board for 2008. New York, United Nations, 2009.

### 1.3.5

#### Cost of opioid medicines and their market size

The cost of essential opioid analgesics does not appear to be a barrier taking into consideration the prices in developed countries for morphine formulations at manufacturer and supplier levels. The price of morphine tablets is only a few US cents per unit (Table 1.2). However, studies and surveys have reported that opioid analgesic retail prices are a barrier in developing countries and that they are priced higher than in developed countries. Their high retail prices make them unaffordable to patients outside health system treatment schemes. Where palliative care programmes and pain relief are not subsidized by national health systems, the cost of opioid analgesics limits their accessibility, particularly in developing countries. In this case, the market size is based on the out-of-the-pocket purchasing power of patients, which may not make the market attractive to pharmaceutical companies. On the other hand, in places where purchasing power does exist it can lead to the situation in which opioid analgesics are marketed but at very high prices and only in the expensive dosage forms (25,26).

Similarly, prices for buprenorphine and methadone vary widely from country to country, from the order of cents to several US dollars per unit, as reported in public global price databases (Table 1.2) and by international harm reduction initiatives (10,11). Because buprenorphine is much more expensive than methadone, many countries are scaling up national programmes for opioid dependence treatment with methadone. However, both of these two medicines are necessary as they are alternatives to each other in case of adverse effects or when patients fail to respond to one of them (10,11,18,19). Opioid agonists are normally procured and provided through harm reduction programmes, but not all national programmes provide free treatment to patients. Surveys and data collection of prices paid in countries is extremely limited. No studies have been published to document the cost of these medicines in countries delivering opioid dependence treatment programmes, including those funded by major donors, such as the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria (27). Data on suppliers of quality-assured methadone and buprenorphine formulations suitable for use in opioid dependence treatment programmes, and their Ex-Works prices, are not readily available to countries initiating and scaling up national programmes to tackle opioid dependence.

The size of the current global medical opioid market is very small compared to the global need for pain relief and for opioid dependence treatment. The estimates on opioid analgesics and methadone, which countries are obliged to submit to the INCB in order to manufacture and procure, constitute the annual upper limit of the global opioid market for medical use. The annual estimates, published by the INCB, provide information on global production volumes.<sup>1</sup> Except for buprenorphine, the small market size seems due more to attitudinal, knowledge, policy and legal barriers that impact on the supply of opioid medicines than to the manufacturing cost of these essential medicines.

<sup>1</sup> Ex-Works is an International Commercial Term or INCOTERM which means that the seller, in this case the manufacturer, makes the goods available at his/her premises and the buyer is responsible for all charges. <http://www.iccwbo.org/incoterms/preambles/pdf/EXW.pdf>

**TABLE 1.2 Prices of opioid essential medicines as reported by three sources**

Opioids listed in the 2009 WHO Model List of Essential Medicines		eMIT prices (no VAT) <sup>b</sup> Rolling mean of 4 months prior procurement			MSH International Drug Price Indicator (Supplier) <sup>c</sup> Median			WHO GPRM (Buyer EX WORKS) <sup>d</sup> Mean (Range)
Medicine	Strength	Formulation	Pack size (unit or ml)	Pack price UK Pound	Unit price UK Pound	Pack size (unit or ml)	Pack price US\$	Unit price US\$
Morphine <sup>a</sup>	10 mg/1 ml (hydrochloride, sulfate)	ampoule	10	£2.36	£0.24	10	\$4.40	\$0.44
	10 mg (sulfate)	tablet	56	£3.63	£0.06	100	\$12.28	\$0.12
	10 mg (sulfate)	prolonged-release tablet	60	£1.81	£0.03	-	-	-
	30 mg (sulfate)		60	£4.34	£0.07	30	\$13.37	\$0.44
	60 mg (sulfate)		60	£8.59	£0.14	-	-	-
Methadone	5 mg/5 ml	oral liquid	30	£0.56	£0.02	-	-	-
			50	£0.93	£0.02	-	-	-
			500	£3.55	£0.01	-	-	-
Buprenorphine	5 mg/ml	concentrate for oral liquid	-	-	-	-	-	\$0.01 (0.01-35)
	10 mg/ml		150	£8.57	£0.06	1000	\$76.93	\$0.07
	2 mg	sublingual tablet	-	-	-	-	-	\$1.18 (0.92-1.18)
	8 mg	sublingual tablet	-	-	-	-	-	\$3.61

<sup>a</sup> For the oral liquid formulation of morphine (10 mg/5ml as hydrochloride or sulfate), no price data were retrieved from these three sources.

<sup>b</sup> Source: The Generic Pharmaceuticals Electronic Market Information Tool (eMIT) provides information pertaining to the generic pharmaceutical products that are covered within the framework agreements of the National Health Service in the United Kingdom of Great Britain and Northern Ireland. December 2008. <http://www.pasa.nhs.uk/PASAWeb/Productsandservices/Pharmaceuticals/Medicines/Generics/eMIT.htm>

<sup>c</sup> Source: Management Sciences for Health (MSH) International Drug Price Indicator contains a spectrum of prices from pharmaceutical suppliers, international development organizations, and government agencies. Supplier prices recorded in 2009 were considered for this table. [http://erc.msh.org/dmpguide/index.cfm?search\\_cat=yes&display=yes&module=dmp&language=english&year=2009](http://erc.msh.org/dmpguide/index.cfm?search_cat=yes&display=yes&module=dmp&language=english&year=2009)

<sup>d</sup> Source: The Global Price Reporting Mechanism (GPRM) is a web-based transaction database which contains information on transaction prices and quantities of medicines procured for HIV programmes since 2005. Information accessed in May 2009. <http://apps.who.int/hiv/amds/price/hdd/>

**1.3.6****Additional factors affecting the provision of opioid medicines in developing countries**

As described above there are overarching limiting factors for accessing controlled medicines because national controls, regulations and implementation measures have been introduced that are stricter than those set by the international drug control conventions for the procurement, distribution and dispensing of opioid medicines. Other factors affect primarily developing countries and contribute to the huge disparity in global provision and consumption between developed and developing countries. In developing countries, problems are exacerbated by the loss of the health work force through migration and by the limited financial resources for running health systems. The supply of controlled medicines is more challenging and difficult to operate in these countries. Opioid medicines supply requires: obtaining the necessary authorizations or certificates in both the importing and exporting country; formulating and submitting estimates; and reporting on production, importation, exportation and consumption to the INCB. These actions require the time, understanding and experience of country procurement officers, who are often working in difficult conditions. Even when opioid medicines are available at country level, the entire population may not have geographical access to them. Their use is often limited to specialized centres or to main regional and district hospitals without reaching patients in rural areas and in the community. The access problem in developing countries is intrinsically linked to the state of the countries' health system and work force.

**1.4****IMPROVING ACCESS TO CONTROLLED ESSENTIAL MEDICINES IN THE PAST DECADE**

Over the past five to 10 years, there has been evidence of improvements in access to opioid analgesics and opioid agonists for treatment of opioid dependence worldwide. However, countries are moving at different speeds. The benefits of opioid dependence treatment in reducing the HIV infection rate has been a crucial factor in fostering rapid progress in introducing and scaling up treatment in a number of countries. The promotion of access to opioid analgesics to relieve moderate to severe pain appears more complex.

**1.4.1****Inclusion of new controlled medicines and formulations in the WHO Model List of Essential Medicines**

Opioid analgesics, such as morphine, have always been included in the WHO Model List of Essential Medicines although this has not automatically resulted in their ensured availability in countries. More recently, in 2007, the list was extended to include oral slow-release formulations of morphine. In the same year, WHO issued the first Model List of Essential Medicines for Children. This list also includes opioid analgesic formulations as injectable, oral liquid, prolonged-released tablets and immediate-release tablets. Long-acting opioid agonists for the treatment of opioid dependence – methadone and buprenorphine – were only added to the WHO Model List of Essential Medicines in 2005. The two were added to the Complementary List,<sup>1</sup> as medicines that should only be used within established support programmes for the treatment of opioid dependence.

<sup>1</sup> The Complementary List presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed.

**1.4.2****Tackling attitudinal and educational barriers to access**

Because of the lack of correct information, health professionals, patients and their families are often reluctant to use opioid analgesics for the relief of moderate to severe pain. The main attitudinal barrier is fear of dependence. Steps to overcome attitudinal barriers to the rational use of opioid analgesics still have a long way to go although global advocacy campaigns have been launched by civil society organizations and UN reports have pledged increased access to these essential medicines. In 2007, WHO and the INCB jointly developed an assistance mechanism to facilitate adequate treatment of medical conditions using opioids, to be implemented by WHO's Access to Controlled Medications Programme (ACMP) (28,29). This initiative was a response to the worldwide shortfall of medicines for pain relief, and was launched at the request of other bodies, in particular the UN's Economic, Cultural and Social Council (ECOSOC) and WHO's World Health Assembly. One of ACMP's priorities is to develop WHO treatment guidelines for the management of chronic and acute pain in adults, children and infants. The provision and dissemination of these guidelines, which are currently in development, are intended to help overcome the attitudinal and educational barriers to opioid analgesics.

Attitudinal barriers to opioid agonists are being addressed forcefully. As a first step, the UN agencies, among them WHO, UNAIDS and UNODC, clearly stated in 2004, that their position is to support treatment with opioid agonists, such as methadone and buprenorphine (30). This joint statement on the efficacy of treatment with opioid agonists has enhanced a necessary change in the attitudes of politicians in several countries. Civil society organizations working on harm reduction at national and international levels are also playing a huge role in promoting access to opioid agonist therapy as part of the right to health and other human rights. The UN Special Rapporteur on the Right to Health has also devoted reports and interventions on the undeniable right to access harm reduction and opioid agonist treatment for injecting drug users (17,31,32). Technical documents have been developed to support implementation of projects and their scale up to attain the largest possible coverage for injecting drug users. In 2009, WHO published the *Guidelines for psychologically assisted pharmacological treatment of opioid dependence* (33). In the same year, WHO, UNAIDS and UNODC also jointly published a technical guide for countries to set targets for HIV prevention and treatment in injecting drug users, to assess countries' progress in providing a comprehensive package of core interventions (34).

**1.4.3****Tackling some of the supply chain problems**

UN agencies have also provided joint guidance for opioid agonist procurement to enable countries to initiate and scale up national programmes on drug dependence treatment. The algorithm on step-by-step procurement of opioid agonists can be used as guidance for opioid analgesics because the importation requirements for methadone are the same as for morphine and other strong opioid analgesics (25). WHO and the INCB acknowledge that one of the challenges countries face is to provide reliable estimates of opioid medicines' requirements, based on epidemiological needs and on the absorptive capacities of countries to procure, supply and use these medicines. The two organizations have therefore started to develop a manual to enable countries to provide the INCB with reliable annual estimates of opioid medicines, as required by the treaty on narcotic drugs. This manual is expected to be finalized and published by 2011.

**1.4.4****Improving access to pain management in middle- and low-income countries: recent success stories**

Although the intrinsic challenges of health systems in developing countries may suggest that the provision of pain management can be extremely difficult to operate, successes show that improvements are feasible regardless of a country's gross domestic product. Changes in policies, laws and regulations, training programmes and coordinated approaches to address country-specific barriers to pain relief can bring about a complete transformation. A number of examples can be quoted in this respect, such as those of Uganda, Romania and the State of Kerala in India (see Boxes 1.3, 1.4 and 1.5).

**BOX 1.3****CASE STUDY: Improving access to pain relief in Uganda**

**Uganda**, classified a least developed country, has been able to implement a comprehensive plan for integrating pain relief in its health system. This included training plans on pain management and rational use of opioids for nurses and other health-care workers, such as pharmacists, and also a change in the National Drug Policy and Authority Statute of 1993 to allow specialized palliative care nurses and clinical officers, (a specialized Ugandan health worker category), to prescribe morphine. By early 2009, 79 nurses and clinical officers had received training on pain management and been authorized to prescribe oral morphine; several thousand health-care workers had attended a short course on pain and symptom management; and 34 out of 56 districts in Uganda had oral morphine available and in use. Accessing palliative care is now a reality for many patients and their families in Uganda. Numerous challenges remain, however, including ensuring availability and affordability of oral morphine throughout the country and training all relevant health workers. No reports of abuse or of diversion have been documented following implementation of these initiatives to increase opioid availability for pain relief (16,23).

*Source:* Jagwe J, Merriman A. Uganda: Delivering analgesia in rural Africa: Opioid availability and nurse prescribing. *Journal of Pain and Symptom Management*, 2007, 33(5):547–551..

**BOX 1.4****CASE STUDY: Romania**

**Romania**, an upper-middle-income country, is addressing the lack of access to opioid analgesics in a holistic manner. The Romanian Ministry of Health has appointed a special commission to explore the changes required to improve access for patients affected by severe pain. It has sourced technical expertise to evaluate the national legislation and subsequently, drafted and approved a new narcotic control law in 2005. In 2007, additional regulations to implement the new law were issued, and these lifted a number of administrative constraints on the prescription of opioid medicines. For example, the length of time for which oral morphine can be prescribed at one time has been extended from 3 to 30 days. Recognizing that changes in legislation were insufficient to increase availability of medicines, the country developed and implemented a comprehensive plan for the dissemination of new policies and regulations, together with a nationwide programme to educate doctors and pharmacists (14,16,23).

*Source:* Mosoiu D, Ryan KM, Joranson DE, Garthwaite JP. *Lancet*, 2006, 367(9528):2110–2111.

## BOX 1.5

**CASE STUDY: The State of Kerala, India**

In Kerala, India, the state controlled substances regulations have been progressively simplified since the 1990s, and a new licensing system has increased the number of community-based palliative care centres with oral morphine, with little or any diversion or misuse. The positive example of the Indian State of Kerala contrasts with other Indian states. Indeed, not all states and territories in India have amended their state legislation and rules according to the revised central government legislation on opioids, and if they have done so, they omitted operationalizing policy changes and education for professionals, administrators and the public to ensure palliative care for their population. About 80 % of India's palliative care is reported to be delivered in Kerala State. In July 2009, the State Directorate of Health Services issued an order to integrate palliative care into the primary health-care system. The circular included a series of guidelines for service delivery, administration and reporting. Kerala, world leader in community participation in the provision of care to the terminally ill, is likely to become the first Government in the world to formally incorporate palliative care into primary health care (14,23).

Sources: Rajagopal MR, Joranson DE, Gilson AM. Medical use, misuse, and diversion of opioids in India. *Lancet*, 2001, 358(9276):139–143.  
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## BOX 1.6

**CASE STUDY: Ukraine**

Ukraine is in the process of rapidly scaling up treatment with opioid agonists – treatment that was initiated as a pilot project in 2004. Widespread and coordinated advocacy efforts contributed to reducing the persistent resistance to such treatment and to speeding up the regulatory changes needed to provide opioid agonists to injecting drug users. The Ukrainian President's involvement in issuing a decree eliminating barriers to the scale up of the programme at the end of 2007 was key for the introduction of methadone, in addition to the more expensive buprenorphine, which had been in use since 2004. Very substantial scale up started in 2008, taking the number of people in treatment from 500 to more than 4200 in less than a year and a half. The new drug control law, which became effective in early 2008, also cancelled the monopoly of Government-based structures for providing treatment, allowing scale up through NGOs. Despite the impressive achievements, Ukraine continues to face a number of challenges in reaching the national target of providing treatment to 20 000 injecting drug users. Challenges include: lack of domestic funding for opioid dependence treatment; the non-availability of more suitable formulations of methadone; the ban on dispensing take-home doses to patients; the absence of a functional referral system to ensure continuation of substitution therapy; legal liability for minor non-compliance, which results in medical personnel refusing to provide opioid agonist treatment; unavailability of treatment in prisons; and excessive costs and regulations for pharmaceutical distribution (10,11).

Sources: Substitution maintenance therapy in Ukraine: Can the community respond effectively to the challenges of HIV/AIDS? Kiev, The International HIV/AIDS Alliance in Ukraine, 2008. [http://www.aidsalliance.org.ua/ru/library/our/pbzt/pdf/pb\\_en.pdf](http://www.aidsalliance.org.ua/ru/library/our/pbzt/pdf/pb_en.pdf)  
Aggregate data on the patients of substitution maintenance treatment in Ukraine (as at 1 August 2009), Ukrainian Institute on Public Health Policy web site: <http://www.uiphp.org.ua/ua/resource/zvedeni-danni>

## 1.4.5

**From criminalization of injecting drug users to the provision of opioid agonists: country successes and challenges**

Besides health system constraints, access to opioid agonist treatment is very often affected by the criminalization of injecting drug use and misconceptions about the efficacy of methadone and buprenorphine for this category of patients. Criminalization has delayed and obstructed the onset of opioid agonist therapy and harm reduction programmes. However, as a result of civil society movements and funding availability, pilot projects have been introduced in a number of developing countries, in conjunction with efforts to reduce HIV transmission through syringe and needle programmes. In this context, there are a number of countries scaling up from pilot phases and facing up to the challenges in procuring and supplying opioid agonists (10,11). (See Boxes 1.6, 1.7 and 1.8.)

## BOX 1.7

**CASE STUDY: The Islamic Republic of Iran**

Iran is one of the countries most affected by opioid dependence, with over 200 000 injecting drug users, due to the replacement of the traditional recreational use of opium with readily-available heroin. Iran is also affected by a parallel HIV epidemic among injecting drug users. The Ministry of Health introduced opioid agonist treatment in 2002 as part of a comprehensive package of HIV-prevention measures and also made it available in prisons, with the support of the judiciary system. From 2004 to 2007, Iran increased the number of drug users receiving methadone maintenance treatment from 4300 to 57 000. Among these were over 19 500 people receiving methadone within the prison system in over 55 prison clinics, and 34 after-care centres outside prison. Progress has been facilitated by an evidence-based multisectoral approach, resulting in a large number of practical policy measures, such as a legal provision ensuring that injecting drug users in treatment programmes cannot be prosecuted. Pragmatic approaches on the opioid agonists supply side involved the formulation of a national protocol for opioid dependence treatment, a system for training, licensing and monitoring doctors to operate methadone maintenance centres, and the concurrent formulation and endorsement of the necessary regulations. The authorities are also pursuing the inclusion of methadone syrup in the national pharmacopoeia as the recommended formulation for opioid dependence treatment in the country (10,11).

Sources: UNAIDS Second Independent Evaluation 2002-2008. Country visit to the Islamic Republic of Iran Summary Report, 2009. [http://data.unaids.org/pub/BaseDocument/2009/20090515\\_sie\\_countrysummaryreport\\_iran\\_en.pdf](http://data.unaids.org/pub/BaseDocument/2009/20090515_sie_countrysummaryreport_iran_en.pdf)  
HIV prevention and care among injecting drug users in the Islamic Republic of Iran, WHO Regional Office for the Eastern Mediterranean Region, 2008. [http://www.emro.who.int/asd/pdf/hiv\\_review\\_iran.pdf](http://www.emro.who.int/asd/pdf/hiv_review_iran.pdf)

## BOX 1.8

**CASE STUDY: Malaysia**

Malaysia, where 76% of all HIV infections were among injecting drug users, started a pilot project for treatment of opioid dependence with methadone in 2003. The country subsequently endorsed methadone maintenance programmes as part of a harm reduction programme in 2005, to operate beyond the pilot phase. Opioid agonists could be prescribed in a range of settings, including Government hospitals, community clinics and general practitioners' clinics. The programme has also relied on the support of NGOs. At the end of 2007, the country reached the target of 5000 people on methadone. Price negotiations between the Government and suppliers resulted in a decrease in the retail price of methadone from US\$10 to US\$0.80 for 40 mg in the same year. By 2015, the country aims to reach 25 000 injecting drug users with opioid dependence treatment and to extend the provision of methadone in prisons, following the Iranian example (10,11).

Sources: Reid G. Malaysia and harm reduction: the challenges and responses. *International Journal of Drug Policy*. 2007 Mar;18(2):136-140.  
Noordin N. Substitution treatment in Malaysia. *Lancet*. 2008 Sep;372(9644):1149-1150.

## **1.5 CHALLENGES AND PRIORITIES**

Substantial work is needed to reverse the current situation of limited access to pain relief and treatment of opioid dependence and to remove the attitudinal, knowledge, supply, legal and administrative barriers to essential medicines at national and global levels. For opioid analgesics and opioid agonists, the key challenges have been identified and action is now required to overcome these and meet patients' needs. However, the extent and causes of access problems for other controlled medicines have not generally been analysed to the same degree, for example for antiepileptics.

The availability of essential controlled medicines and the specificity of barriers to adequate treatment may vary from country to country, as the different barriers listed below can be more or less acute according to the different categories of essential controlled medicines (e.g. opioid analgesics, benzodiazepines). These barrier categories are interrelated, the availability of essential controlled medicines requires a holistic approach to address problems in each of these broad areas.

### **1.5.1 Educational needs and strategies**

There is a need for greater awareness among policy-makers, health professionals and the general public to dispel the belief that medical use of opioid analgesics can do harm to patients and cause dependence. Treatment guidelines and training curricula for health workers on rational medicine use have been identified as priorities to overcome educational and attitudinal barriers to adequate pain management. Similarly, the dissemination of guidance and evidence on the effectiveness of opioid agonists in treating injecting drug users is a crucial factor in mobilizing government support and initiating and scaling up national programmes. Education for effective pain relief and treatment of opioid dependence is urgently needed in all countries where the consumption of opioid analgesics and coverage of dependence treatment services is low.

Assessment of the availability of, and knowledge about rational medical use of, antiepileptics, anticonvulsants and medicines for emergency obstetric care would be the first step in order to understand the extent of country-specific barriers to these categories of controlled medicines.

### **1.5.2 Balancing national drug control policy and regulations**

National drug control policies should be balanced to meet public health needs and the right to attain the highest possible standard of health, and the right to be free from torture, cruel, inhuman and degrading treatment or punishment. The international drug conventions state the imperative of making controlled pharmaceuticals available for medical and scientific use, but often signatory countries have implemented the conventions into national laws and regulations in a way that does not ensure, and even limits, the availability of essential medicines classified as narcotic and psychotropic substances. Assessing the current policy bottlenecks, operating changes in national policies, regulations and laws, and disseminating these changes among regulators, procurement officials and health workers are crucial steps in ensuring the availability of essential controlled medicines to patients.

Changing policies, however, will not result in enhanced availability of controlled medicines unless laws and regulations are amended accordingly. For example, if a policy is introduced to allow trained nurses to prescribe opioid analgesics, it will require amending or changing

a number of national regulations about dispensing of narcotic drugs and the professional role of nurses in the health system. There are several layers of regulations in countries that need to be considered throughout the supply chain, from procurement to prescription and dispensing. Failure to amend one single layer of regulation may compromise the final objective of making essential controlled medicines available. In this context, it could be useful for WHO to provide and disseminate model laws to guide countries in meeting their obligations under the conventions to provide adequate availability of controlled essential medicines.

### 1.5.3

#### Overcoming supply barriers

Price surveys at country and global levels are needed to enlighten production and supply barriers both for opioid analgesics and for oral formulations of methadone and buprenorphine. Currently, limited information is available for analysing how the manufacturing and retail prices further impact on access to these medicines.

One of the major problems acknowledged with the procurement of these and other medicines is the formulation of adequate need forecasting that take into account the epidemiological figures as well as the absorptive capacities of health systems. This will be a challenge, especially for countries that increase their absorption capacity by tackling the educational, policy and regulatory barriers. The requirement to submit annual estimates for medicines listed under Schedule I of the Single Convention on Narcotic Drugs, such as morphine and methadone, and the formalities for importation and exportation of these pharmaceuticals can indeed become a barrier if procurement and programme managers in countries do not plan adequately. Supply barriers may also be reduced by simplifying existing national regulations related to procurement, distribution and dispensing of controlled medicines while ensuring no diversion to the illicit market.

Meeting Millennium Development Goal 8E to ensure access to affordable essential medicines implies commitment to address these barriers for opioid medicines at national and global levels. It also requires analysis of the extent to which the status of other controlled medicine impacts on their availability for medical use. Life-saving and essential medicines, such as general obstetric emergency treatments, general anaesthetics and antiepileptics, cannot be withheld from health systems purely on the grounds that they are listed in the international drug conventions.

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## ABBREVIATIONS

ACMP	Access to Controlled Medications Programme
DFID	Department for International Development
ECOSOC	Economic, Cultural and Social Council
INCB	International Narcotics Board
HIV	Human Immunodeficiency Virus
UK	United Kingdom
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization