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THE WORLD MEDICINES SITUATION 2011

ACCESS TO CONTROLLED MEDICINES

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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[1] 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

[1] 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 μ-opioid receptor, while buprenorphine is a partial agonist for the μ-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 *Schedule II and III*	Codeine	15, 30 mg tablet	Opioid analgesic, antidiarrhoeal
1961 United Nations Single Convention on Narcotic Drugs *Schedule 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 *Schedule III*	Buprenorphine	2 mg, 8 mg sublingual tablets[a]	
1971 United Nations Convention on Psychotropic Substances *Schedule IV*	Diazepam[b]	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 *Table I*	Ergometrine	200 microgr/1ml ampoule	Obstetric emergency (oxytocics)
	Ephedrine	30 mg/1 ml ampoule	Obstetric emergency (used in spinal anaesthesia to prevent hypotension)

[a] 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. 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

[b] 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.[1]

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

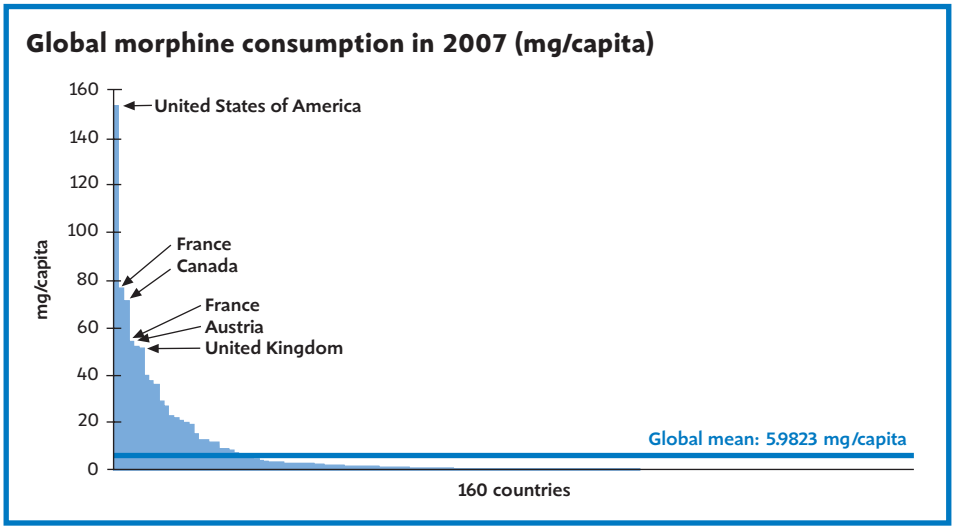
Globally, only 8% of injecting drug users are treated with methadone and buprenorphine.

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

[1] 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 opiod 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 opiod 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