Chapter 16

▪ Opioid Policy, Availability, and Access in Developing and Nonindustrialized Countries

David E. Joranson

Karen M. Ryan

Martha A. Maurer

INTRODUCTION

More than two decades ago, an expert committee of the World Health Organization (WHO) concluded that most pain due to cancer could be relieved if health professionals would use a relatively simple analgesic method and if patients could have access to opioids such as oral morphine.1 The WHO analgesic method also has been endorsed for relief of pain due to HIV/AIDS.2

United Nations (UN) health and regulatory agencies repeatedly have appealed to health professionals, their organizations, and governments to cooperate in order to implement the WHO analgesic method and remove barriers that block patient access to opioid pain medications.3, 4, 5, 6, 7 Although drug regulations and opioid availability have improved in some countries, the vast majority of cancer and AIDS patients in the developing world, and many in developed countries, still lack access to these essential medications. This chapter focuses on opioids that are indicated for moderate to severe pain associated with cancer and AIDS, such as morphine, oxycodone, and fentanyl.

A further disparity exists in reported medical consumption of opioid analgesics between developed nations with a small proportion of the global population and the large and growing population of developing countries. With the shifting burden of cancer and AIDS to developing countries, the public health problem of inadequate availability of pain medications is deepening.8,9

Health professionals who manage pain must know about the regulation of opioid analgesics. Just as effective clinical management of pain rests on a body of knowledge, treatment methods, and communication between the clinician and patient, so the task of ensuring access to pain medications in any country depends on knowing the role and responsibilities of national governments and on communication between drug regulators and health professionals.

This chapter outlines the body of knowledge about government drug control policy and the methods that are being developed to assist health professionals and governments to improve opioid analgesic availability and access. “Opioid availability” refers to whether a country has stocks of opioid analgesics either at the manufacturer or retail level of the drug distribution system. The term may be used in referring to the presence of opioids within a country, or at any point throughout the drug distribution system, including in the health care facilities that provide medical care for patients. Alternatively, “opioid accessibility” refers to patients' ability to obtain the opioid pain medications they need for pain relief. Clearly, patient access is not possible unless opioids are available in a country. Therefore opioids may be legally available within a country or even a health care facility, but patients may not be able to access them for a variety of reasons. Cooperation of governments with pain and palliative care experts and their national and international organizations is emphasized.

PAIN RELIEF IS PART OF CANCER AND AIDS CONTROL

The global incidence and prevalence of cancer and HIV/AIDS is a public health problem of great concern. The WHO estimates that there are 22 million people with cancer in the world. Each year approximately 10 million individuals are diagnosed with cancer, and more than 6 million die from this noncommunicable disease. Experts predict that these numbers will double by 2020, with major impacts on developing countries where it is estimated that the majority of new cases and deaths from cancer, including children, will occur.8,9 The global occurrence of HIV/AIDS is also a critical public health problem. The Joint United Nations Programme on HIV/AIDS (UNAIDS) indicated that in 2007, 33.2 million people were living with HIV/AIDS, a communicable disease, and 2.1 million people died from AIDS.10

During the course of their disease, people living with AIDS and cancer survivors experience pain as well as a variety of other symptoms that will negatively impact the quality of their lives.11 Those nearing the end of life are likely to experience even more severe symptoms.2,12, 13, 14, 15 Common symptoms of cancer include pain, fatigue, anxiety, constipation, cough, depression, dyspnea, and nausea.1 Patients with cancer or AIDS often have severe pain, particularly during the late stages of the

disease.13,15, 16, 17, 18, 19 In the developing world, most cancers are diagnosed in late stage.16,17 Pain can be due to the disease itself, the treatment of the disease, or another concurrent disorder.

Pain and Palliative Care

Palliative care, including the critically important component of pain management, is a model of care aimed at relieving symptoms of disease and its treatment and improving the patient and family's quality of life throughout the course of the disease. The WHO has long recognized that relieving pain and other symptoms in cancer1 and AIDS2,20 is a necessary part of palliative care, including for children.21

Palliative care and pain relief medicines should be available and accessible to all individuals who have pain and other symptoms.2,12 In 200222 and 2003,9 the WHO emphasized that palliative care be part of any national program aimed at reducing the overall burden of cancer, and that it is the government's public health responsibility to develop a policy and program to address palliative care needs in the country. The WHO has expanded its recommendations to include HIV/AIDS control programs: “Palliative care is an essential component of a comprehensive package of care for people living with HIV/AIDS because of the variety of symptoms they can experience—such as pain …”2

There is a strong international imperative that palliative care, including pain management, should be included in national cancer and HIV/AIDS control efforts. The WHO has reaffirmed the necessity of including palliative care as a critical component of

cancer or AIDS control efforts in a country.23,24 At the country level, national policies should provide a policy framework for developing and expanding health care services to reach patients who need disease treatment as well as relief of pain and other symptoms.

In 2007, the WHO published a guide for developing effective national cancer control programs that include palliative care. This guide reiterated that national palliative care plans must include policy to provide for the medications necessary to manage symptoms associated with cancer, including opioid analgesics for pain.25

OPIOIDS ARE ESSENTIAL MEDICINES

There are many useful therapies for treating cancer pain, including pharmacological and nonpharmacological approaches. Opioid analgesics, and in particular orally administered morphine, are regarded by international health experts as the gold standard for relieving moderate to severe pain due to cancer or AIDS. The WHO Expert Committee on the Selection and Use of Essential Medicines has designated morphine and other opioid analgesics as *essential medicines,* which are those medicines that “… satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.”26

The first WHO essential medicines list, issued in 1977, identified 208 essential medicines for treating the global disease burden, and included morphine to treat pain, thereby recognizing its benefit to public health.27 In 2007, the 15th edition celebrated the 30th anniversary of the Model Essential Medicines List.28 This list identified 340 essential medicines and included only morphine, immediate and sustained release, as an opioid analgesic appropriate for the treatment of moderate to severe pain. Currently, 156 of 193 WHO member states have official essential medicines lists.

In 2005, the WHO Cancer Control Program requested that the International Association for Hospice and Palliative Care (IAHPC) recommend a list of essential medicines specifically for palliative care. In 2006, a committee of the International Association for Hospice and Palliative Care Board members and external advisors from 29 pain and palliative care organizations guided the process of identifying the medications to treat the most prevalent symptoms in palliative care. The effort focused on efficacy and safety of medications, with the presumption that cost considerations will be made at the national level. The committee recommended 33 essential medicines (14 are also on the WHO list of essential medicines); the list can be online accessed at http://www.hospicecare.com/resources/pdf-docs/iahpc-list-em.pdf. The list includes four opioid analgesics to treat moderate to severe pain: transdermal fentanyl, methadone, morphine (both immediate and sustained release preparations), and oxycodone. If accepted, this list would expand WHO's list of essential medicines to treat moderate to severe pain, which presently includes only morphine (both immediate and extended release). The WHO will be conducting cost effectiveness analyses and evidence-based reviews of the recommended medications to determine whether it will adopt this list of essential medicines for inclusion in its list for palliative care. Meanwhile, the IAHPC encourages countries to use the list as a model when developing their own lists of essential

medicines according to resources and needs.

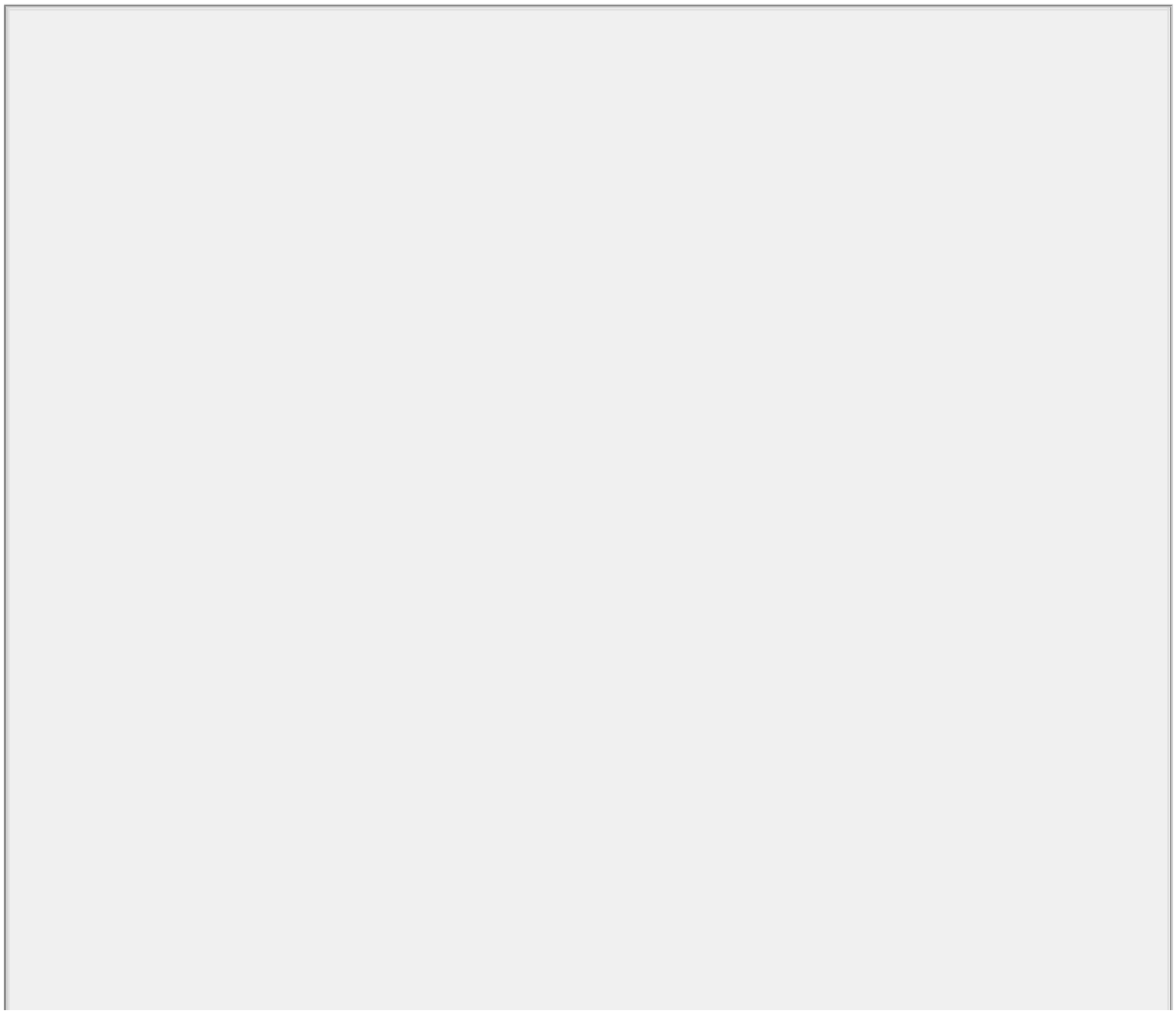
OPIOID ANALGESICS ARE CONTROLLED DRUGS

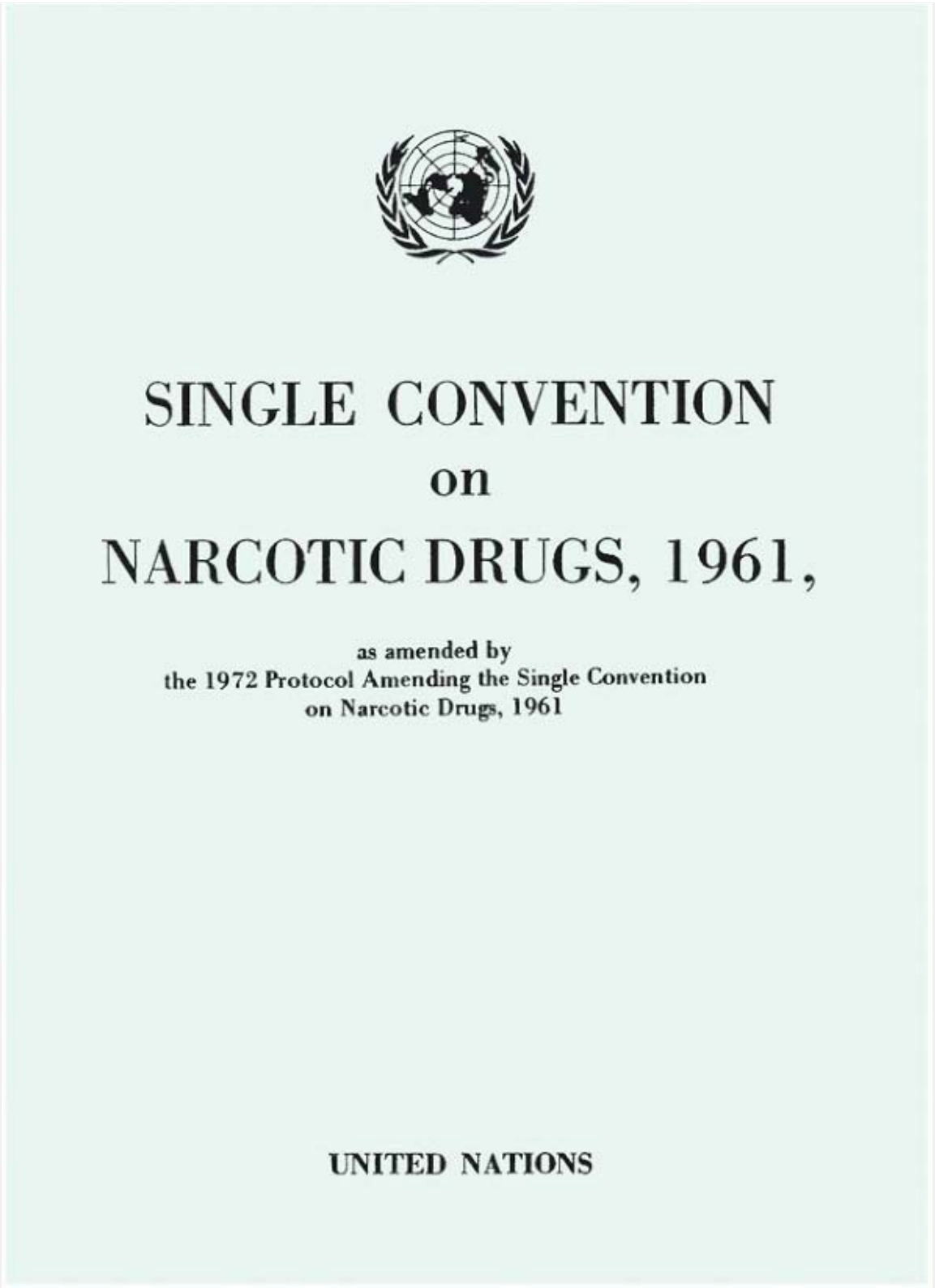
Opioid analgesics, in addition to being medicines that are essential for relieving pain, have a potential for abuse and drug dependence. They are “controlled” by an international law called the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol Amending the Single Convention on Narcotic Drugs, 1961 (Single Convention) (see Fig. 16.1)29 as “narcotic drugs,” a legal term that will be used where the context requires. This chapter addresses opioid analgesics that are agonists with no ceiling effect that can relieve moderate to severe pain, such as morphine, fentanyl, oxycodone, and hydromorphone. This chapter does not address codeine, which is not a pure agonist, or other partial or mixed agonists, such as buprenorphine and pentazocine, which are controlled under the Convention on Psychotropic Substances, 1971.30

Nearly every government, or party, in the world has formally acceded to the Single Convention. As of 2006, 181 countries were Parties to the Single Convention, representing 99.6% of the world's population. In so doing, each has agreed to adopt laws, regulations, and administrative procedures to carry out the aims of the Single Convention. The Single Convention establishes obligations to which national governments have acceded, to control opioids and also to make them available for medical purposes.

The premise of the Single Convention rests on the recognition that the consequences of addiction to narcotic drugs pose a threat to society that governments must address: “… addiction

to narcotic drugs constitutes a serious evil for the individual and is fraught with social and economic danger to mankind.”28 The Single Convention establishes an international government framework of prohibitions and requirements concerning the legitimate production, manufacture, and distribution that is intended to prevent illicit trafficking, nonmedical use of narcotic drugs, and diversion, which is the illegal movement of controlled medications from the licit distribution system into the illicit market. The most restrictive category under the Single Convention is Schedule I, which includes narcotic drugs considered to be highly addictive and liable to abuse. Morphine and other opioids such as fentanyl, oxycodone, and pethidine are controlled in Schedule I.





SINGLE CONVENTION
on
NARCOTIC DRUGS, 1961,

as amended by
the 1972 Protocol Amending the Single Convention
on Narcotic Drugs, 1961

UNITED NATIONS

FIGURE 16.1 The United Nations Single Convention on Narcotic Drugs, 1961.

According to the Single Convention, several UN organizations have roles in the procedure to schedule drugs. The WHO Expert Committee on Drug Dependence has the responsibility of providing recommendations to the Commission on Narcotic Drugs regarding scheduling drugs.31 This role is critically important as scheduling decisions can have major implications for the availability of drugs for medical care.

The principal *international* requirement is that legitimate trade in narcotic drugs is regulated, including the cultivation of opium and manufacture of medicinal opioids such as codeine and morphine. To prevent diversion, an import-export system is established to limit trade to the amounts necessary for medical use; trade is regulated by the International Narcotics Control Board (INCB) in Vienna, Austria.

The INCB was established in 1968 as an independent and quasi-judicial monitoring body to implement UN international drug control conventions.31 The 13 members of the INCB are elected by the Economic and Social Council of the UN and serve as individuals rather than representatives of their governments. The WHO nominates three members who have medical, pharmacological, or pharmaceutical experience. The INCB's responsibilities in regard to opioids include: (1) to ensure, in cooperation with governments, that adequate supplies of drugs are available for medical and scientific uses and to prevent diversion of drugs from licit sources to illicit channels; (2) to administer the system whereby governments must estimate the amounts of narcotic drugs required for medical and scientific purposes; (3) to monitor licit distribution of narcotic drugs using governments' reports of amounts consumed, in an effort to coordinate a supply sufficient to meet, but not exceed, demand; (4) to analyze information provided by governments, UN bodies, and other international organizations to ensure that governments adequately implement the provisions of the treaty; (5) to maintain a “permanent dialogue” with governments, working closely with them to comply with their obligations under the international drug control treaty; (6) to recommend, when appropriate, additional technical and/or financial assistance for those countries needing support in carrying out obligations of this treaty; (7) to ask for explanations of apparent violations of the treaty, propose corrective measures to governments that are not fully adhering to the treaties, and assist governments to overcome difficulties. If the INCB determines a government has not taken measures to remedy a serious situation, it may call the matter to the attention of the Commission on Narcotic Drugs and the Economic and Social Council of the UN. As a last resort, the treaty empowers the INCB to recommend that governments stop trade with a defaulting country.31

The Single Convention establishes several *national* obligations, among them that governments must regulate all entities that handle controlled drugs. The goal is to create a closed distribution system, including security and record keeping. Prescribing and dispensing to individuals must be done only for medical purposes by medical professionals authorized under national law, using “medical prescriptions.” Distribution outside of the regulated system is prohibited in order to prevent diversion of controlled drugs from medical to nonmedical uses. There is little if any diversion of narcotic drugs from the licit international trade, despite the large number of transactions involved; most diversion of narcotic drugs occurs within domestic circuits.32 Efforts to prevent diversion should be balanced so as not to interfere in medical practice and patient care.33,34

Examples of efforts to lessen the risks of abuse and diversion include risk management plans before marketing of new controlled drugs35,36; guidance for clinicians on how to safeguard controlled drugs37; education for clinicians about how to assess patients for abuse and drug dependence as well as for pain; and ethics guidelines for how pain medicine specialists can balance the benefits and risks of opioid treatment.38

CONTROLLED MEDICINES SHOULD BE AVAILABLE

In addition to controlling drugs to prevent their diversion and nonmedical use, the Single Convention stipulates a second obligation to ensure adequate availability of narcotic drugs for medical and scientific purposes. The Single Convention clearly recognizes the importance of narcotic drugs as analgesic medications, and asserts that medical access to opioids for relief of pain is to be assured by governments, since they are obligated to conform their laws to the Single Convention, “… the 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.”39

The drug availability obligation is no less important than drug control, but it is poorly understood and implemented by health professionals and governments. There is no indication that the medical value of controlled drugs is lessened as a result of scheduling under the Single Convention. Scholars of international narcotic drug policy have concluded that the Single Convention, as amended, recognizes that the basic purpose of international drug control is to reduce the availability of drugs for nonmedical purposes, but “that this should not affect or limit their therapeutic use.”40

Government Mechanisms to Ensure Adequate Drug Availability

The INCB recognizes *both* drug control and drug availability obligations of governments:

One of the objectives of the Single Convention on Narcotic Drugs, 1961 … is to ensure the availability of opiates, such as codeine and morphine, that are indispensable for the relief of pain and suffering, while minimizing the possibility of their abuse or diversion.3

To accomplish this objective, the Single Convention requires that governments adopt laws, regulations, and administrative procedures to implement two specific mechanisms that are intended to ensure adequate availability of opioid analgesics in

countries, while preventing nonmedical use. First, governments must annually establish an estimate of the amounts of opioids that will be required for all medical and scientific needs for the coming year. Licit trade in narcotic drugs can be lawfully conducted only within this amount. If imports exceed a country's estimated requirements, exporters are obligated to refrain from further trade with the country. Governments are encouraged to develop valid estimation methods, to establish estimates that take increasing demand into consideration, to cooperate with health professionals to obtain information about unmet needs, and to increase the estimate whenever necessary to always satisfy medical needs. Second, governments must report the amounts of each narcotic drug consumed (i.e., distributed to the retail level), to allow identification of consumption that either exceeds or falls short of the estimate.

Implementation of Drug Availability: The Competent National Authority

Each Party to the Single Convention is expected to establish a drug control program not only to prevent illicit trafficking and diversion, but also to ensure the adequate availability of narcotic drugs for medical and scientific purposes5 and to designate an agency called the Competent National Authority (CNA) to implement the functions required by the Single Convention. This office is usually located in the pharmaceutical department of the Ministry of Health, the national drug control or public security agency, or the functions may be divided between agencies. The CNA is the principal national administrative authority for carrying out the estimation and statistical reporting procedures that are necessary for ensuring that opioid analgesics are adequately available for medical and scientific purposes. Guidelines for estimating the amounts of opioids required for medical and scientific use and for reporting consumption statistics are useful for those who want to understand the administrative procedures to be followed by CNAs.41,42 The INCB provides guidelines for CNAs to comply with the Single Convention, including the administration of effective mechanisms to ensure opioid availability.43

DISPARITIES IN OPIOID CONSUMPTION

The Single Convention requirement that national governments report annual consumption statistics provides a unique source of data to describe global and national opioid consumption trends and to study disparities. Consumption means the amounts of opioid analgesics distributed for medical purposes to the “retail” level in a country (i.e., to those institutions and programs that are licensed to dispense to patients, such as hospitals, nursing homes, pharmacies, hospices, and palliative care programs). The INCB uses consumption statistics to: (1) monitor compliance of governments with the provisions of the Single Convention; (2) identify trade discrepancies between importing and exporting countries, (3) detect imbalances between quantities of medications available and disposed within a country; (4) identify trends in the worldwide availability of opioids and other drugs for medical needs; and (5) monitor and maintain a global balance of supply and demand of opioids for medical and scientific needs.42

Opioid consumption statistics have several useful applications for those who study and improve opioid availability to: (1) identify whether a country has available opioids that can relieve moderate to severe pain, (2) learn whether the amounts indicate any substantial current consumption or progress over time,14 and (3) evaluate the outcome of efforts to improve opioid availability.

Consumption statistics provided in INCB reports have several limitations that should be considered when using them as an indicator of opioid availability:

1. Some governments report late, do not report for a particular year or period, or make inaccurate reports, which results in incomplete or invalid information for that year. Consequently, the amounts for the most recent year may be underreported; these deficiencies may be corrected in subsequent years.
2. The INCB's published reports do not provide data on small quantities; instead, the symbol “<<” signifies that a country reported between 0 and 0.499 kg, and also rounds up to 1 kg reported amounts that were reported between 0.5-0.999.32 Although not available from the INCB's published reports, consumption of small amounts can nevertheless be important, especially in countries with small populations or in those which are just beginning to address their needs.
3. Consumption statistics do not distinguish between clinical uses for opioids, as in methadone for treatment of pain or drug dependence, or fentanyl for analgesia or anesthesia.
4. Consumption statistics do not distinguish between programs that use opioid analgesics such as hospitals and hospices.
5. Consumption statistics do not indicate which products or dosage forms of an opioid are available within a country (i.e., whether an opioid is in oral, parenteral, or transdermal form).
6. Consumption statistics are not a valid clinical indicator of the quality of pain control in a country.

Morphine Equivalence Metric

The WHO has considered a country's annual consumption of morphine to be an indicator of the extent that opioids are used to treat severe cancer pain and an index to evaluate improvements in pain management.13,14 The WHO and the INCB have long recognized that pain is inadequately treated owing to low consumption of morphine in most countries, and great disparities between countries.44,45 Additional opioid analgesic medications and formulations such as fentanyl, hydromorphone, and oxycodone have been introduced in global and national markets over the past 20 years and should be taken into consideration when studying opioid consumption in a country, region, and globally. To what extent does consumption of morphine alone compared with other opioids adequately describe a country's medical use of opioids?

To address this question, the Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care (PPSG/WHOCC) developed a metric called morphine equivalence (ME) for each principal opioid used to treat moderate to severe pain that is expressed in terms of morphine equivalence and adjusted for population. The ME allows an equianalgesic comparison of the consumption of morphine with other opioid medications at the national, regional, and global levels.45 A total ME statistic combines consumption of several principal opioid analgesics into one metric. The following study drugs were selected to calculate the total ME because they are the opioids that are indicated for severe pain: fentanyl, hydromorphone, methadone, morphine, oxycodone, and pethidine. We used conversion formulas established by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway.46 These data were obtained directly from the INCB, thereby eliminating the small quantity limitation; the other limitations of opioid consumption statistics apply to ME data.

Global Trends

The 30-year trend ending in 2005 in Figure 16.2 shows that prior to 1986, morphine ME was very low and stable throughout the world; it was paralleled by total ME. After WHO announced its cancer pain relief three-step analgesic ladder in 1986 and encouraged use of oral morphine, morphine ME began to increase; total ME increased more rapidly and diverged from morphine ME. With the emergence of additional opioids and dosage forms in the mid-1990s, total ME increased even more, so that morphine ME became less and less of a valid indicator of global opioid consumption. In 1986, global morphine ME was 50% of total ME, compared to 14% in 2005. In recent years, fentanyl, methadone, oxycodone, and hydromorphone, respectively, accounted for the greatest portion of opioid consumption, at least for the global aggregate data.

Of interest is the long-term decline in consumption of pethidine (meperidine), likely due to increasing recognition of the potential risks associated with accumulation of the toxic metabolite norpethidine. Pethidine has been used in many countries mainly by injection for postoperative pain because of a perception that its very short duration of action reduces the risk of dependence. Pethidine is no longer recommended by the WHO for the treatment

of pain28 although it continues to be used. Programs that move away from pethidine should ensure that other suitable opioids are accessible; if pethidine is available, there should be no regulatory barrier to this transition, as pethidine and other opioids such as morphine are controlled in the same schedule and should be subject to the same international and national controls.

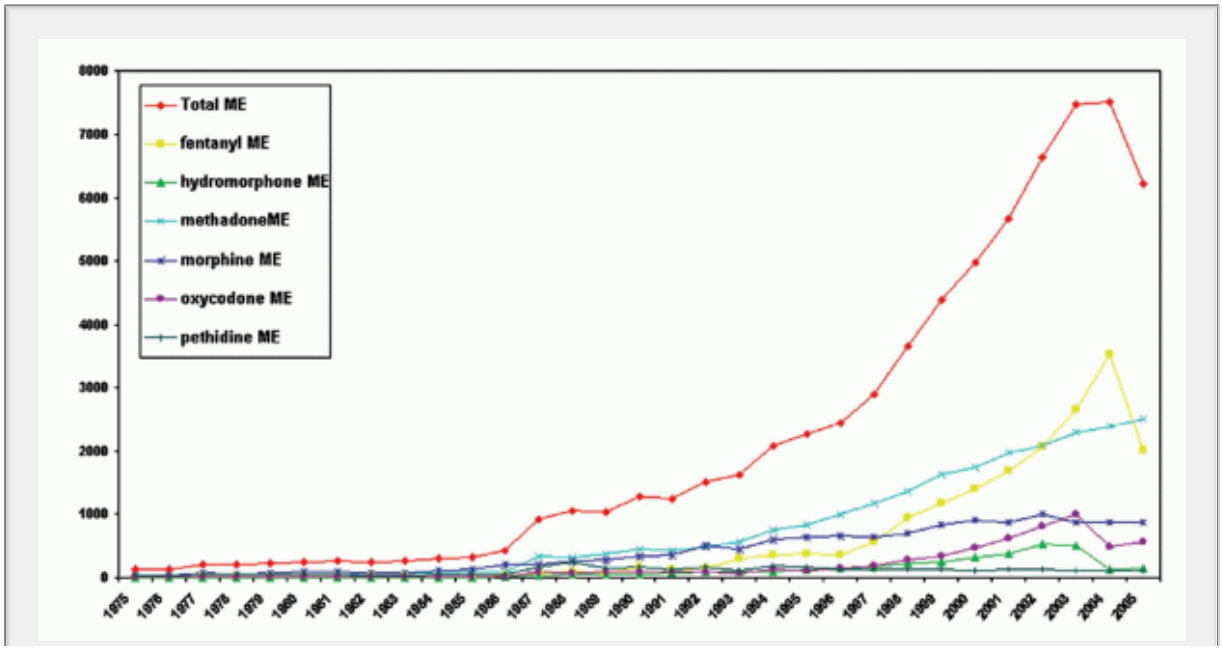


FIGURE 16.2 Global opioid consumption, ME by drug and total ME, mg/capita.

Disparities in Consumption Among High- and Low-Income Countries

At the national and regional level, there are great disparities in the amount of morphine consumed between high- and low-income countries. The INCB has consistently reported that a small number of high-income countries consume most of the morphine in the world, while the remaining countries, which have over 80% of the world's population, consume a small fraction.47 Is this striking disparity unique to morphine consumption, or are there similar disparities for total ME?

Major disparities in ME are also evident when geographic regions are compared. Table 16.1 shows the milligram per capita total ME for six regions compared to the global total ME for 1975, 1986, and 2005. Global total ME increased fourfold between 1975 and 1986 and 14-fold from 1986 to 2005. Similarly, each of the regions experienced increases in total ME during the 30-year period; however, there were striking disparities between the regional total ME as a percentage of the global total ME. The total ME for Africa, a region with mostly low-income countries, was consistently the smallest percent age of total global ME and experienced a slight decrease between 1986 and 2005. The regional total ME for Asia, Central and South America, and the Middle East, also regions with predominantly low-income countries, were similar to Africa, representing relatively small percentages of the global total ME and experiencing decreases in the percentage of total global ME between 1986 and 2005. In contrast, Europe, a region with a number of high-income countries, had the largest percentage of total global ME throughout the 30-year period, with a substantial increase in the last 20 years. In 2005, these data showed that Europe and the four high-income countries of Australia, Canada, New Zealand, and the United States represented over 85% of the global total ME.

TABLE 16.1 GLOBAL AND REGIONAL TRENDS IN TOTAL ME (MG/CAPITA)

Year	Africa Total ME	Middle East Total ME	Central and South America Total ME	Asia Total ME	Australia, Canada, New Zealand, U.S. Total ME	Europe Total ME	Global Total ME
1975	3.21 (2%)	7.66 (6%)	8.29 (6%)	10.08 (8%)	41.58 (34%)	53.10 (43%)	123.92
1986	8.99 (2%)	23.05 (5%)	72.63 (16%)	50.16 (12%)	99.6 (23%)	175.38 (41%)	430.93
2005	31.46 (1%)	141.717 (2%)	97.41 (2%)	212.95 (3%)	1551.66 (25%)	4189.31 (67%)	6218.61

Values in parentheses indicate the region's percentage of the global total ME for that year. Percentages added across rows may not total 100% due to rounding.

Country Comparisons

In some countries, morphine alone continues to be a valid indicator of total ME but not in others. Two European countries are compared: the Russian Federation and Belgium. In the Russian Federation, the low and relatively stable consumption of morphine ME has paralleled that of total ME. In Belgium, fentanyl ME has always accounted for the increasing trend in total ME. These

differences are interesting and no doubt related to social, cultural, or economic differences between the countries.

Additional studies using the ME statistic are needed to further examine the role of opioid consumption as an indicator of treating pain over the past 20 years. What other events in the pain management/palliative care field may have influenced the changes in the consumption of strong opioids? What are the countries

for which morphine consumption alone was the most and least accurate, and what might this signify? What are the strong opioids that account for most of the global and regional increase in consumption? The ME statistic may be a useful tool to examine these types of questions at the global, regional, and national levels.

Finally, we identified an important contribution for fentanyl and methadone in the total ME increase over time. Future studies should correct for these medications' other clinical indications to focus solely on their use for pain relief, especially methadone's use for addiction treatment. This procedure will ultimately provide a much more precise measure of national opioid consumption for pain treatment.

BARRIERS: HEALTH PROFESSIONALS AND GOVERNMENTS

A number of factors, or barriers, contribute to inadequate availability of opioid analgesics49; their presence and severity vary from country to country. Weakness of health care infrastructure and problems in access to basic services is a typical constraint to obtaining pain relief and palliative care that is found especially, but not only, in developing countries, and in countries with remote areas and challenging geography. This chapter concentrates on the opioid-related barriers involving health professionals, government drug regulatory policies, and drug distribution systems.

Since national laws control drug availability and access, it is useful to know how government drug regulators perceive the issues relating to opioid availability. The INCB surveyed government drug control authorities about barriers in their countries; Table 16.2 lists these barriers.5 Although the survey was conducted in 1995, the barriers are similar to those of today. Approximately 10 years later, Help the Hospices surveyed health care professionals and hospice or palliative care staff from Asia, Africa, and Latin America about barriers to accessing pain relieving medications and, in particular, oral morphine.50 Sixty-nine surveys were returned, representing 31 countries and all 3 regions. The barriers to accessing oral morphine can be summarized by the following: (1) excessively strict national laws and regulations; (2) fear of addiction, tolerance, and side effects; (3) poorly developed health care systems and supply; and (4) lack of knowledge on the part of health care professionals, the public, and policy makers.

TABLE 16.2 BARRIERS IDENTIFIED BY 1995 INCB SURVEY

- Fear of addiction to opioids
- Lack of training of health care professionals about the use of opioids
- Laws or regulations that restrict the manufacturing, distribution, prescribing, or dispensing of opioids
- Reluctance to prescribe or stock opioids stemming from fear of legal consequences
- Overly burdensome administrative requirements related to opioids
- Insufficient amount of opioids imported or manufactured in the country
- Fear of diversion
- Cost of opioids
- Inadequate health care resources, such as facilities and health care professionals
- Lack of national policy or guidelines related to opioids

It is important to identify the barriers in a country, distinguish between them, and choose intervention strategies that can be effective. For example, it would be ineffective to use professional education to change strict prescription regulations; changing strict regulations could be part of an effort to alleviate physicians' fears of addiction and of being investigated, but would not do much to change the low priority of pain management or address reimbursement issues. A survey has been developed to gather information about barriers.51 Once identified, for example, using a convenience survey of participants at a conference, barriers can be studied, prioritized, and categorized: (1) knowledge and attitudes about pain, opioids, and addiction; (2) opioid regulatory policy; (3) the drug distribution system; and (4) cost of opioid analgesics.

Knowledge and Attitudes About Pain, Opioids, and Addiction

Incorrect knowledge about pain, opioids, and addiction often underlies attitudes and can result in medical and institutional practices that block access to opioid analgesics. If professionals who are responsible for regulating drugs are misinformed about addiction, now referred to as *dependence syndrome* in the WHO International Classification of Diseases-10,52 or have outdated attitudes about the benefits and risks of opioids, they may not be able to accept that there is an unmet need for opioid analgesics and be reluctant to examine regulatory policies for barriers.1 The International Association for Pain and Chemical Dependency (IAPCD) provides an international forum for considering the relationship between pain and addiction.53 IAPCD is an international organization with the objective of fostering communication and cooperation among professionals in health care, law enforcement, policy, and regulation in an effort to improve pain management for all patients, including those with a history of, or current, addictive disorders.

Inadequate Education of Health Professionals

The governments who responded to the 1995 INCB survey frequently identified insufficient education of health professionals as a barrier to opioid availability.5 If health care professionals do not understand the importance of pain management, or how to assess and treat pain, they may be reluctant to care for pain patients or lack the confidence to prescribe medications like morphine. Indeed, given the major advances in knowledge about pain, opioids, and addiction, it is likely that what health professionals and the public learned 20 years ago is inaccurate by today's standards.

Exaggerated Fears of Opioid Dependence Syndrome

The barrier identified most frequently by government narcotic regulators in the 1995 INCB survey was concern about addiction to opioids.5 Overstated concerns about the risk of dependence syndrome and side effects preventing adequate treatment of pain or regulatory reform is a phenomenon that has been called “opiophobia.”54,55 Early definitions of dependence syndrome were developed by experts in addiction before opioid pain management became a priority. These experts believed that mere exposure to morphine produced dependence syndrome,56 and that physical dependence, expected in extended use of opioids, was the principal characteristic of dependence syndrome and therefore to be prevented.52 New knowledge about pain and dependence syndrome has led to official recognition that diagnosis of drug dependence depends on the principal characteristics of compulsive behavior and continued use despite harm, whether or not physical dependence or tolerance is present.57 Despite evidence that addiction or dependence syndrome—when defined and applied correctly —is not inevitable or even common when opioids are used

to relieve pain in patients without a history of substance abuse, fears of addiction continue to impact the treatment decisions of health care professionals resulting in suboptimal pain relief.58 There is no question that some individuals are susceptible to addiction/dependence syndrome, so a competent assessment of the patient including substance abuse history is indicated, as well as monitoring for warning signs.

Misunderstanding of Side Effects

Patients and families sometimes fear that using opioids to manage pain will result in side effects that cannot be managed.58 Several side effects are associated with the medical use of opioids, including constipation, fatigue, nausea, vomiting, itching, drowsiness, confusion, and sedation.13 Health care professionals and patients should realize that side effects are predictable and should be anticipated and treated.59 Most patients will experience a reduction in many of the side effects, such as sedation and nausea, within the first week of opioid therapy. Constipation does not diminish so clinicians should always advise patients to begin a bowel regimen with opioid therapy.59 When side effects persist despite treatment, adjustment of the dose and trials of other opioids are indicated.

Fear That Opioids Will Hasten Death

Some fear that the use of opioids for pain at the end of life in terminally ill patients will hasten death owing to the side effect of respiratory depression. This has been shown to be more a myth than reality.60 Respiratory depression can be a concern when opioids are administered by poorly trained physicians, when the patient has not used opioids previously and the starting dose is too high, when the dose exceeds what is necessary to relieve a patient's pain, when the dose is increased too rapidly, or when the patient does not adhere to the directions for use. However, studies have found that incremental dose increases to relieve pain are safe when pain is severe.61 If respiratory depression occurs during treatment, it can be reversed by the administration of an opioid antagonist medication such as naloxone, which should be available. Rather than shortening patient survival, some studies suggest that adequate relief from pain can improve quality of life and possibly survival.61,62

Health Care Professionals Fear Legal Sanction

The INCB survey showed that governments realize that health care professionals fear legal sanctions. This is a significant barrier leading to reluctance to prescribe opioid analgesics. The WHO has also recognized that health care professionals may be reluctant to prescribe or stock opioid medications if they make a mistake or perceive a risk of losing their professional license, or even criminal prosecution based on misunderstanding of pain, opioids, and addiction.13 Consequently, it is important that the WHO13,63 and the INCB5 have recognized that overly restrictive laws and regulations impede adequate opioid availability in some countries.

Government Regulatory Policy

Clearly, governments' main responsibility is to protect public health and safety; so it is reasonable and necessary for governments to take steps to prevent harm caused by diversion of opioid analgesics to nonmedical uses. But the relevant policies and activities should not interfere in medical practice and patient care. The Single Convention establishes a number of basic requirements for national laws and regulations to establish a “closed” distribution system to prevent diversion:

- everyone involved in the industrial production and medical distribution of narcotic drugs must be authorized to do so by the government;
- medical prescriptions, the format to be decided by governments, must be used to provide opioids to legitimate patients, and only for medical purposes;
- “counterfoil” prescription forms with several copies may be used but they are not required; and
- security, record keeping, and reporting requirements must be observed.39

A lack of understanding about how international law intends there to be a balance between controlling diversion and drug availability can lead to overly restrictive regulation of opioid medications. Pain and palliative care advocates should also avoid making opioids available *without* a control system; this would also be unbalanced and could lead to public health and safety consequences.

It should be noted that the systems established by governments to regulate prescription and distribution of opioids were designed before the value of the oral use of opioid drugs for cancer pain management was recognized. These systems were developed to prevent the diversion and abuse of opioids and not to prevent the use of opioids for pain relief.1

It is clear that some countries have gone beyond the minimum control measures required by the Single Convention and have established very stringent controls, especially in relation to drug prescription and distribution.1 The INCB has recognized that some legislators and administrators have overreacted to drug abuse and have enacted laws, regulations, and administrative policies that impede the availability of opiates for medical purposes.3 These include complex prescription forms and prescription books that must be obtained from the government with considerable difficulty, restrictions that limit the diagnoses of eligible patients, limitations on prescription amount to a few days, limitations on daily dose, and elaborate licensing requirements for palliative care programs. In countries with states, as in India and the U.S., some states have enacted restrictive laws and regulations that interfere with opioid distribution and patient access to opioid pain medications.64,65

The Single Convention clearly recognizes that governments have the right to regulate narcotic drugs more strictly than required by the Single Convention. The 34th WHO Expert Committee on Drug Dependence (ECDD) discussed the impact of unduly strict national laws on the medical availability of controlled medications, acknowledging there are countries where stricter measures are applied than are required by the Conventions. While recognizing that this is permissible, the ECDD said that governments should bear in mind that the aims of the Single Convention are to ensure availability for medical use as well as to prevent abuse. The ECDD called on national authorities to carefully consider whether “… .any such measure currently in force could be modified to permit access for patients in need.”66

Drug Distribution Systems

In any country, opioid medications must first be approved and then procured by importation or domestic manufacture from narcotic raw materials or drugs seized by law enforcement. A system of government-regulated distributors then distributes to the retail level of pharmacies, hospitals, clinics, nursing homes, hospices, and palliative care programs, where registered health care professionals prescribe and dispense them to patients. The entire system of medication acquisition and disbursement is referred to as the drug distribution system. Figure 16.3 illustrates the key components of a drug distribution system and Table 16.3 presents examples of drug distribution system barriers.

Cost of Opioid Analgesics

The cost of opioid analgesic products has been identified by international organizations and researchers as a barrier to opioid availability and access.67, 68, 69 Comparative studies have reported

wide variability in the cost of opioids analgesics throughout the world. One study of developed and developing countries found the cost of opioids relative to income was significantly higher in developing countries than in developed countries.69 Another comparative study of codeine, fentanyl, morphine, and tramadol in nine developed Western European countries found great variability in the cost of opioids. The wholesale price of morphine was consistently the lowest of all the opioids in each of nine countries over the 3-year study period.69 A recent survey of cancer pain treatment in Latin American countries revealed that a patient's inability to pay for opioid medications was one of the central reasons they are not prescribed.68

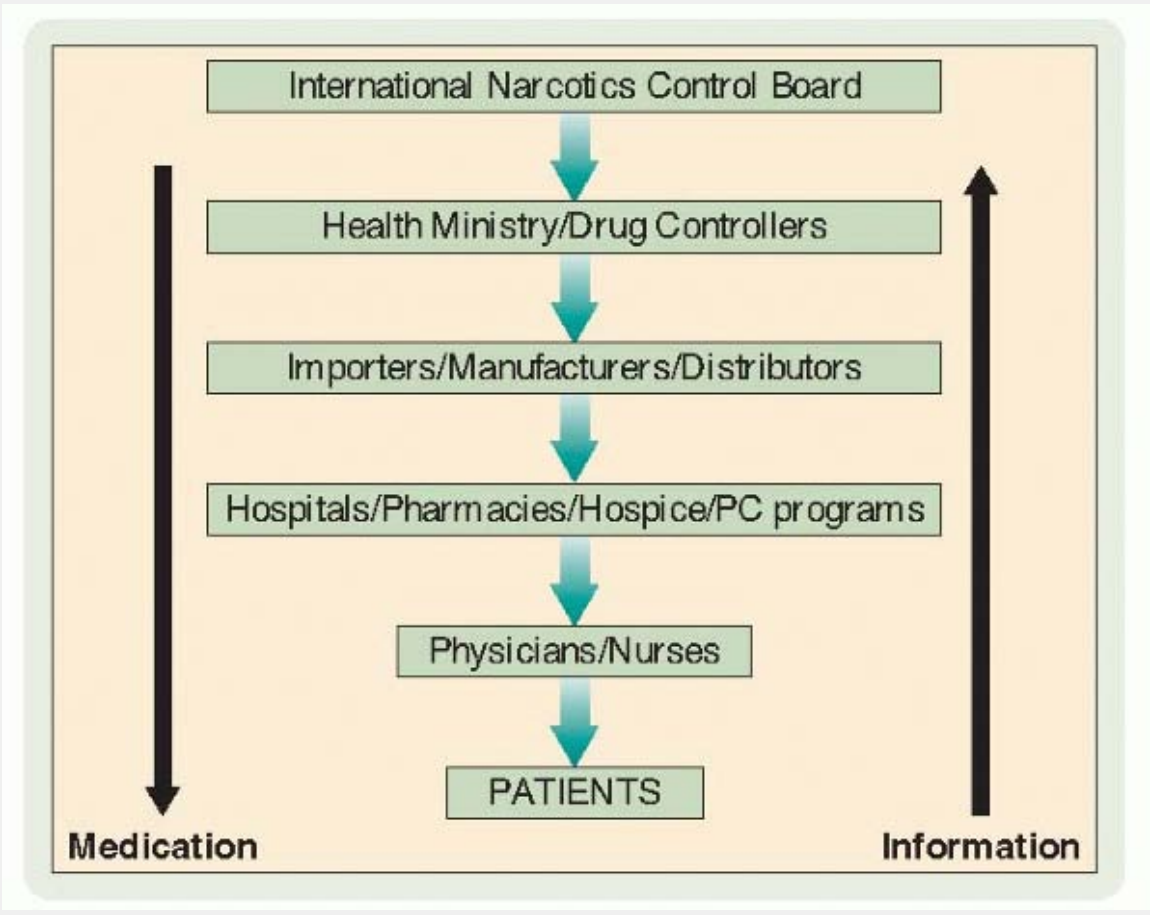


FIGURE 16.3 Drug distribution system.

UNITED NATIONS' RECOMMENDATIONS

Although there have been efforts to inform health professionals and their organizations about the need to work with government,50,70 this subject is not well understood among most health care professionals and their organizations because it is not ordinarily included in medical education. A brief historical review of the recommendations of UN bodies shows they have made a number of useful observations and recommendations to governments and health professionals, including that they should cooperate with each other to ensure adequate availability of opioids for medical purposes including pain relief throughout the world. Indeed, representatives of national governments, acting through their membership in UN bodies such as the Economic and Social Council and its Commission on Narcotic Drugs, and the World Health Assembly, have for a number of years requested governments to evaluate their national drug control policies for impediments and to improve the availability of opioid analgesics for medical purposes.

TABLE 16.3 EXAMPLES OF DRUG DISTRIBUTION SYSTEM BARRIERS

- Government has not made procurement arrangements for the importation or domestic manufacture of needed opioids.
- There are delays in government decision making about procurement.
- Government's official estimate of type and quantity of opioids required is insufficient.
- The government's method for estimating opioid requirements does not take into consideration the actual needs.
- Manufacturers and distributors do not distribute opioids in a timely way.
- The number of health professionals, pharmacies, and patient care facilities authorized to procure and dispense opioids to patients who need them is insufficient.
- Governments do not have the systems in place to guarantee a safe and effective transfer of medications from wholesalers to retailers.

Beginning in 1989, a consultation between the INCB and the WHO Cancer Unit, then led by Dr. Jan Stjernsward, produced an authoritative recognition of the opioid availability problem and a strong recommendation that governments should act to evaluate their national laws. The INCB requested governments throughout the world to “examine the extent to which their health-care systems and laws and regulations permit the use of opiates for medical purposes, identify possible impediments to such use and develop plans of action to facilitate the supply and availability of opiates for all appropriate indications.”3

In 1990, the WHO Expert Committee on Cancer Pain Relief and Active Supportive Care made a recommendation similar to that of the INCB, requesting that national governments should conduct a “regular review [of legislation], with the aim of permitting importation, manufacture, prescribing, stocking, dispensing and administration of opioids for medical reasons, … [and] review of the controls governing opioid use, with a view to simplification, so that drugs are available in the necessary quantities for legitimate use.”4

In 1995, the INCB returned to the subject of opioid availability for pain relief and conducted a survey to determine whether governments had responded to its 1989 recommendations. The responses of the 65 responding governments were analyzed and published along with several pointed conclusions and recommendations including that “governments that have not done so should determine whether there are undue restrictions in national narcotics laws, regulations or administrative policies that impede prescribing, dispensing or needed treatment of patients with narcotic drugs, or their availability and distribution for such purposes, and should make the necessary adjustments.”5 The INCB outlined its expectations for governments under the Single Convention: “A national drug control programme should have legislative authority reflecting the provisions of the 1961 Convention, delegation of responsibility for implementation, including administrative responsibility for managing import and export licenses, estimating medical requirements, reporting required statistics and supervising adequate controls over distribution. Controls over the professionals and medical facilities that distribute narcotic drugs should ensure accountability and prevent diversion while making narcotic drugs

available to the patients who need them. Controls should not be such that for all practical purposes they eliminate the availability of narcotic drugs for medical purposes."5

The INCB called specific attention to the role of health professionals, recommending that their organizations, including the International Association for the Study of Pain (IASP), teach students and practitioners about the medical use of opioids, their adequate control, and the correct use of terms related to dependence.5 The INCB further recommended that IASP and other nongovernment organizations establish ongoing communication about national requirements, unmet medical needs, and impediments to availability with the CNAs in their countries. Such recommendations are consistent with the ethical responsibilities of physicians to comply with all laws and regulations but also to work toward changing them if they interfere in the practice of medicine and patient care.38

The INCB requested and received a number of comments from

national chapters of the IASP including from Canada, Chile, Colombia, Hungary, Japan, Kenya, Malaysia, New Zealand, the Philippines, Republic of Korea, Russian Federation, Singapore, Slovakia, the United Kingdom, and the U.S. Summaries of these comments were included in the INCB's report (see http://www.incb.org/pdf/e/ar/1995/suppl1en.pdf)

One INCB recommendation in particular was to the WHO to develop "methods that can be used by government and nongovernment organizations to identify impediments to the appropriate medical availability of narcotic drugs."5 Subsequently, the WHO revised its seminal publication *Cancer Pain Relief*1 to include a Guide to Opioid Availabilty13 and designated the Pain and Policy Studies Group (PPSG) at the University of Wisconsin to be a WHO Collaborating Center (WHOCC), with terms of reference to develop methods to improve opioid availability. The PPSG/WHOCC drafted international guidelines for evaluating national opioids control policy. In 2000, the WHO and the INCB approved them, emphasizing that governments should use the guidelines to examine their laws and regulations and health care systems to identify impediments and to ensure that opioid medications are always available to patients when they are needed.73 The WHO also proposed that governments encourage health care workers to report to the appropriate authorities any instance in which oral opioids are not available for cancer patients.1

In 2005, the UN Economic and Social Council adopted a resolution about the treatment of pain using opioids,6 found online at http://www.un.org/docs/ecosoc/documents/2005/resolutions/Resolution%202005-25.pdf. It recognizes that medical use of narcotic drugs is indispensable for the relief of pain and suffering, that low national consumption of opioids is a matter of great concern, and that opioids such as morphine should be available at all times in adequate amounts and appropriate dosage forms to relieve severe pain. A resolution by the World Health Assembly7 in the same year called for the development of a funding mechanism to facilitate the actions necessary to improve the availability of opioids for the treatment of pain.72 See online at http://www.who.int/gb/ebwha/pdf_files/WHA58-REC1/english/A58_2005_REC1-en.pdf and http://www.who.int/medicines/areas/quality_safety/Framework_ACMP_withcover.pdf

Taken together, these findings and resolutions form an unmistakable and uncontroversial imperative from the highest level of international and national government health and regulatory authorities in the world that governments and health professionals should work together to identify and remove impediments to the adequate availability of opioids for medical purposes.

METHODS AND EXAMPLES

There are several approaches to consider when implementing the United Nations' recommendations to review drug control policies and address identified barriers to opioid availability. The following section outlines approaches, methods, tools, and resources that national governments or palliative care advocates can use to develop and implement a national project to improve opioid availability.

The specific activities and the order in which they are carried out may not be the same in every country because of differing national situations. We discuss a general approach for a national project, but the activities outlined should be considered flexible and be adapted to a country's situation. Some of the activities may already have occurred, or may need to be repeated to garner broader support and new steps or stakeholders may emerge as the project develops. A national project usually begins as a result of leadership of one or more professionals in pain management, palliative care, or drug regulation.

TABLE 16.4 LEARNING ABOUT OPIOID AVAILABILITY EFFORTS IN YOUR COUNTRY

Regional and National Organizations:

International Association for Hospice and Palliative Care Worldwide hospice and palliative care directory: hospicecare.com/
Regional Hospice and Palliative Care Associations:
African Palliative Care Association: apca.co.ug/
Asia Pacific Hospice Palliative Care Network: aphn.org/
European Association for Palliative Care: eapcnet.org/about/about.html
Latin American Palliative Care Association: cuidadospaliativos.org/
International Association for the Study of Pain Chapters: iasp-pain.org
International Observatory on End-of-Life Care Country Reports:
The Observatory provides “Clear and accessible research-based information about hospice and palliative care provision in the international context. We present public health and policy data relating to hospice and palliative care services. This is complemented by material drawn from the social and cultural analysis of end of life issues, including ethnographic, historical and ethical perspectives. You will find data here for over 61 countries in Eastern Europe, Central Asia, Africa, South America and the Middle East in ways which facilitate cross-national and regional comparison and analysis.” eolc-observatory.net/global_analysis/index.htm

Assessing the Country Opioid Availability Situation

An important initial step when beginning an effort to improve opioid availability is to collect and review available information about a country's pain and palliative care situation, such as how much opioid medication is currently being used, and if there are activities underway to improve opioid availability. There are a number of resources that can provide this type of information, such as the Country Profiles on the PPSG/WHOCC website, which will be discussed in greater depth in the next section. Sometimes a more formal needs assessment has been accomplished,72 however, it is very important to assess those factors that relate directly to the unmet needs for opioid analgesics and how they are controlled and distributed. Table 16.4 offers suggestions for identifying the extent and nature of existing efforts by regional or national organizations toward improving palliative care or opioid availability in a particular country. With increasing interest in opioid availability in many parts of the world, it is important for the planners to identify those who are interested or already involved in order to exchange information and coordinate activities.

Identification of Barriers to Opioid Availability

After an assessment of the situation and stakeholders in a country, the next step in the process may be to identify the regulatory barriers to adequate opioid availability. The WHO Achieving Balance Guidelines is the central resource; it offers a framework for understanding and specific criteria for assessing regulatory barriers. The criteria are recommended by international authorities.74 The Guidelines were approved by a group of international experts in pain management and drug regulation and were reviewed and endorsed by the INCB, so they constitute the highest level of international health and drug regulatory consensus.

The WHO Guidelines are based on the principle of “Balance” which is derived from the Single Convention. This principle asserts that

governments' obligation to control narcotic drugs is not only to prevent drug abuse, but also to ensure the availability of opioid analgesics for medical purposes. Controls aimed at preventing drug abuse and diversion must not interfere with the adequate availability of opioid analgesics for patients' pain relief; drug abuse controls that interfere in opioid availability and patient access to effective pain care would be considered out of balance and should be identified and corrected.

Sixteen guidelines are recommended for use in assessing the adequacy of national drug control policy and administration, and encourage governments and health care professionals to cooperate in a study process using the guidelines. Each guideline or criteria is explained and documented; the guidelines should be used to evaluate the adequacy of: (1) policy language in laws and regulations, (2) administration of the estimates and statistics system, and (3) the functioning of the system that distributes opioid pain medications.

The Guidelines contain a Self Assessment Checklist (SAC) that can be used to familiarize the planners with the nature of the evaluation criteria, to guide an assessment activity within a group of interested parties, and to summarize findings.74 Once barriers are identified, additional information and review may be necessary to refine the analysis so that it is specific enough to discuss with regulators and to guide strategic planning of interventions.

Other methods to identify barriers may be used as well, such as interviews with key informants or focus groups with those who are familiar with patient care, unmet needs, and the national regulatory framework (e.g., clinicians, pharmacists, and regulators).45

Mechanisms of Change

Making change in national policy usually requires a government mechanism to allow the needs and action plans to be discussed and agreed upon. A direct dialogue between health professionals and government regulators can result in modifications to regulatory policy. Sometimes a more formal mechanism such as a task force or commission is needed to convene the stakeholders and guide a strategic planning process. A task force or commission appointed by the government can be a powerful mechanism, since government willingness to examine policy is a necessary component of changing government policy. Less formal methods such as a committee or task force of a nongovernment organization may be a good place to begin to study the problem, review relevant literature, raise awareness, and formulate a preliminary analysis. In any case, thoughtful fair leadership is always needed from one or more individuals who have the time, energy, credibility, communication ability, and willingness to listen and guide a process. The relevant body should prepare a report of its deliberations, including information about the needs, barriers, results of the policy evaluation, and recommended changes. The recommendations do not need to be limited to government regulations, and may include other aspects of national policy and program that are relevant to meeting the needs of people with cancer and HIV/AIDS. Needs assessments, such as the WHO Achieving Balance Guidelines, can provide a structure for the deliberations. The report should reflect a consensus so that points of disagreement, which could block later progress, are resolved early in the process. The following examples illustrate successful mechanisms that guided the policy change process in Italy and Uganda.

Italian Ministerial Workgroup

In 1998, health care organizations publicly requested the Italian Ministry of Health and other nongovernment organizations to address barriers to opioid availability by amending the opioid prescribing laws.75 The Drug Department of the Ministry of Health responded by appointing a multidisciplinary workgroup of physicians, pharmacists, and representatives of the Ministry of Health who had experience in cancer, pain management, palliative care, opioid legislation, and pharmacology. The objectives of the workgroup were: (1) to recommend changes to the Italian national opioid prescribing law, (2) to identify and make available the drugs necessary for pain relief, and (3) to develop educational information on cancer pain management to educate the public and health care professionals.76 Leadership was provided by leading palliative care physicians who reached out to the PPSG/WHOCC for technical assistance.

Ugandan Ministry of Health Study Group

In 1998, the Ugandan Ministry of Health invited staff from Hospice Africa Uganda, a nongovernment organization that had pioneered community-based palliative care in rural and urban Uganda, to be technical experts in a pilot study looking at the viability and safety of using morphine to treat chronic pain at the community level.77 The study involved semi-structured interviews with key informants, direct observation of morphine distribution throughout the country, and audits of clinical care quality. The Ministry's leadership and involvement with the study enhanced the government's awareness of the need to make policy change.

The Strategic Plan

Developing a strategic plan to address barriers to opioid availability is a critical phase in a national project. The strategic planning

process typically begins after the leaders have reviewed the literature, and used the BOAT and the SAC and/or other techniques to identify barriers.

In an effort to make a strategic plan realistic and achievable, the plan should focus on three to five of the most important opioid availability/access problems in a country which, if successfully addressed, would contribute to significant immediate and sustained improvements in patient access to pain medications. A strategic planning process requires some preparation, and can take place during a national event such as a workshop or commission, or in a regional workshop where country teams meet separately to develop and then share their strategic plans for comment.

Regional Workshops

Several workshops to improve opioid availability have been organized cooperatively between the WHO, PPSG/WHOCC, and national and/or regional nongovernment organizations that have an interest in relieving pain due to cancer and HIV/AIDS.[20,78, 79, 80, 81, 82, 83, 84] These 3-day regional workshops involved carefully selected teams of health care and regulatory professionals, including a representative of the CNA, from five or six countries in the same region. Drawing together countries in a particular region allows for participants to learn together about the methods to improve opioid availability, as well as common challenges and opportunities among the participating countries. These workshops culminate in a strategic planning process and specific action plans, and sometimes result in country teams working to implement a national project to address barriers to opioid availability. Leadership, availability of resources, and technical cooperation are critically important to successful follow-up implementation of strategic plans.

National or State Workshops

A national or state workshop involving the stakeholders (e.g., regulators, expert health care practitioners, and patient care programs)

can be a useful mechanism to initiate or continue the dialogue that is needed to improve opioid availability for medical needs. A workshop can be an opportunity to increase awareness by reviewing relevant literature, exchanging information among the stakeholders about pain management, palliative care, laws and regulations, and need for opioids leading to a report. Workshop participants can develop an action plan to submit to the government for its approval and action. The following example highlights a recent national workshop in Colombia.

Colombia

The CNA in Colombia is the Fondo Nacional de Estupefacientes (FNE) of the Ministry of Health. In cooperation with the PPSG/WHOCC and the WHO, the Fondo convened a national workshop of drug regulators and palliative care physicians in November 2007 to examine the procurement and distribution systems for opioid analgesics throughout the country. The goal was to improve these systems so that patients have better access to these essential pain medications from a well-functioning distribution system. The workshop, hosted by the Universidad de la Sabana, included representatives from the Ministry of Health (MOH), the WHO, the Pan American Health Organization (PAHO), the PPSG/WHOCC, the Colombian National Cancer Institute (INC), the International Association for Hospice and Palliative Care (IAHPC), the Colombian Chapter of the International Association for the Study of Pain (ACED), and the Colombian Association for Palliative Care. This workshop yielded excellent communication between health care practitioners and regulators from the 32 states in 6 national regions. Six regional break-out sessions were used to identify problems and obstacles as well as solutions. The six groups reported on their findings in a plenary session, where a strategy session was held to discuss possible solutions and to decide on recommendations to be presented to the FNE.

Implementation of Policy Changes

Improving national policy by itself is not sufficient to improve opioid availability and patient access. It is critically important to work with relevant government and nongovernment organizations to implement policy changes: this may include communication of policy changes to the public via the media (e.g., newspaper articles, radio announcements); for example, education of health care professionals, drug regulators, and law enforcement, including how the policy changes will impact their professional responsibilities. The following example from Kerala, India, illustrates the importance of translating policy changes into practice to positively affect patient care.

Kerala, India

In 1999, a task force appointed by the Kerala Health Secretary was successful in simplifying the state morphine rules, and a national policy was changed which exempted palliative care programs from the requirement to have a “drug license” to dispense

morphine (which requires employing a pharmacist, a substantial cost to the program).64 The policy improvements enhanced the efforts of the Pain and Palliative Care Society, a nongovernment organization based in Kerala, to expand greatly the number of palliative care clinics throughout the state to reach patients in rural and remote areas. The number of palliative care clinics in Kerala increased from 21 in 2000 to 68 in 2006.85

Case Example-Romania

The following example summarizes a recent national policy project to improve opioid availability and accessibility in Romania. This example highlights a series of activities and tools that were used by the Romanian leaders to achieve policy change and embark on implementation.

Regional Workshop

In 2002, the PPSG/WHOCC, the WHO European regional office (EURO), and the Open Society Institute (OSI) sponsored a 3-day regional workshop in Budapest, Hungary,45 entitled *Assuring Availability of Opioid Analgesics for Palliative Care.* The workshop was attended by teams of health are professionals and drug regulators from six Eastern European countries: Bulgaria, Croatia, Hungary, Lithuania, Poland, and Romania.

Strategic Planning

During the workshop, the six country teams used the WHO Guideline's SAC to identify barriers to opioid availability and develop an action plan for addressing those barriers. The team of Romanian health care professionals and drug regulators identified lack of morphine in most hospital pharmacies, severe restrictions on the out-patient use of opioids, and a complex regulatory system for prescribing opioids.45

Readiness for Policy Change

The workshop organizers had limited resources for follow-up and decided to choose one country on which to concentrate. Romania was identified as the country with the most potential for making policy changes because (1) it had many regulatory barriers that restricted patient access to opioids, (2) it had palliative care leaders who were highly motivated to work on making changes, and (3) the Ministry of Health, where the Competent Authority was located, was willing to establish a palliative care commission to evaluate national drug control policy and provide recommendations for change.45

Establishing a Mechanism: A Ministry of Health Commission

A Commission was a critical factor contributing to the successful policy change process in Romania. Following the regional workshop in 2002, the Romanian Ministry of Health appointed a Commission of Pain and Palliative Care specialists to study the narcotics control policies using the WHO Guidelines. The Commission requested assistance from the PPSG who assisted with the review and analysis of policies. A report of recommended policy changes was prepared and presented to the Minister of Health. This report became the basis for the changes in law and regulations that followed.45

Policy Change

The Minister of Health directed the Pharmaceutical Department to draft new legislation removing barriers that had been identified according to the Commission's recommendations. The proposed law was adopted by the Romanian Parliament in 2005. A team from the Ministry of Health CNA and the Commission came to the University of Wisconsin in 2004 to concentrate on drafting a regulation to implement the new law. The regulations, from which remaining barriers were removed, were approved in 2006 and became effective in 2007.86

Implementing Policy Changes

A process to implement the new law and regulations began with a meeting in Bucharest in 2006. All the major stakeholders, including representatives of palliative care, cancer, HIV/AIDS, the CNA, medical education, and the anti-drug law enforcement agency convened for a day to discuss how the new law and regulations would be successfully implemented. The meeting, titled “Implementing a modern and balanced opioid legislation in Romania,”

was attended by approximately 40 people, including the Vice Chair of the Parliament Commission for Health. The meeting provided an opportunity to educate all parties about opioids for treating pain under the new law and regulations. It was also an opportunity to

clarify any questions and to clear any doubts so there would be a consensus.

Educational Program

The Palliative Care Commission also recognized that it was necessary to develop a national education program and a curriculum to re-educate health care practitioners about how to prescribe opioid analgesics under the new regulations so as to improve pain management. A new Curriculum Planning Committee, including experts in palliative care and pharmacy from the University of Wisconsin, was developed to prepare a training of trainers program to reach physicians and pharmacists throughout the country. It consists of 20 hours of classroom teaching on two consecutive weekends and 6 hours of clinical practice in each participant's own setting. The courses include interactive case studies, are recognized by the Ministry of Health, and are nationally accredited for continuing medical education by the College of Physicians and Pharmacists.86 In the first year, approximately 2,200 physicians were trained (D. Mosoiu, personal communication, October 30, 2007).

NEW RESOURCES FOR NATIONAL POLICY PROJECTS

Several new resources are being developed to support policy reform activities and to accelerate the rate of change in the world.87

International Pain Policy Fellowship

The PPSG/WHOCC has learned that making policy and systems change in a country is more likely to be successful if three criteria are met:

1. A demonstrated unmet need for opioid analgesics for pain management due to regulatory barriers.
2. A committed pain or palliative care “champion” to work with the PPSG and also the government.
3. A demonstrated government commitment to address regulatory barriers.

In order to expand leadership for change in more countries, the PPSG/WHOCC developed an International Pain Policy Fellowship (IPPF), supported by a grant from the Open Society Institute's International Palliative Care Initiative. The IPPF seeks to provide candidates with the knowledge and skills necessary to develop and implement a project to improve the availability of pain medications for pain relief and palliative care in their respective countries. The 2-year Fellowship is intended for health professionals (for example pharmacists, oncologists, AIDS clinicians, pain and palliative care physicians), health care administrators, policy experts, or lawyers from low- or middle-income countries who have an interest in drug policy advocacy to improve availability of opioid analgesics for pain relief and palliative care.

The Fellowship consists of (1) education regarding the role of international drug control treaties, governments, health care professionals, and opioid analgesics in the treatment of pain; (2) a 1-week training session at the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center in Madison, Wisconsin; and (3) follow-up technical assistance to the Fellows for the duration of the 2-year Fellowship. The training curriculum covers the relationships between disease, pain, palliative care, inadequate opioid availability; examines the international legal framework for drug control, national government responsibilities to ensure drug availability, and examples of regulatory barriers; and provides resources for evaluating national policy as well as examples of their use. This specialized curriculum, based in large part on the WHO Guidelines, “Achieving Balance in National Opioids Control Policy,” addresses the dual, often competing, characteristics of opioid analgesics: their necessity for pain relief but also their potential for abuse.

The application process is competitive, based on demonstrated national leadership to develop pain management and/or palliative care; the strength of commitment to improving opioid availability in their country; position in national cancer, AIDS, pain, or palliative care association(s); and potential ability to develop a working relationship with government officials. Those selected as finalists are invited to a telephone interview for more in-depth discussions and examination of the potential for a successful Fellowship.

The inaugural IPPF was held in October 2006 with eight Fellows from Argentina, Colombia, Nigeria, Panama, Serbia, Sierra Leone, Uganda, and Vietnam. Additional funding provided by the United States Cancer Pain Relief Committee allowed seven members of an International Expert Collaboration in palliative care and opioid availability to attend the training session to assist PPSG/WHOCC staff to present the curriculum, guide the discussions, assist with country Action Planning, and follow up. These global experts have maintained follow-up communication and mentoring, in conjunction with PPSG/WHOCC staff, during the remainder of the 2-year Fellowship.

At the end of the week, the Fellows prepared detailed national Action Plans that will guide their activities to improve patient access

to opioid analgesics for the next 2 years, in collaboration with the PPSG/WHOCC.

In September 2007, the *New York Times* published a series about the global undertreatment of pain including in India87 and Sierra Leone.89 One article highlighted the situation in Sierra Leone, including the work of the International Pain Policy Fellow, who is the founder and Executive Director of Shepherd's Hospice in Freetown. He is implementing his action plan to improve patient access to pain medication. Working with the government, he is making progress to import oral morphine at the hospice to provide patients with appropriate pain management, he has trained his staff on the appropriate uses and handling of morphine, and he is taking part in a national Palliative Care Task Force.

These Action Plans are ambitious, each addressing unique and dynamic national environments characterized by political changes (such as national elections) and other unforeseen factors that impact national health care priorities. Consequently, the PPSG/WHOCC obtained funding from the Lance Armstrong Foundation to reconvene the 2006 class of fellows to discuss progress and challenges as they work toward the objectives outlined in their national Action Plan. The 3-day meeting allowed for (1) an update and discussion with each country on progress and barriers in the past 12 months; (2) break-out into small groups to revise the Action Plan, if necessary; (3) a report from each Fellow on their Action Plan revisions for the remainder of their Fellowship; and (4) preliminary exploration of the meaning of cancer survivorship in developing countries. This type of meeting can capitalize on the inevitable changes in national landscape that will occur during a 2-year period by providing a real-time forum to review and respond to both their achievements and challenges, and to utilize the collective experiences of the entire group that may allow Fellows to share methods for handling a particular obstacle that may be common among them.

IPPF Progress

Vietnam.

On 27 March 2007, a national workshop, “Workshop on Supply, Management and Use of Opioids in Palliative Care” was held in Hanoi, Vietnam. The workshop, which included a broad range of stakeholders from throughout the country, was

successful in accomplishing the following stated objectives: (1) to enhance understanding of the Principle of Balance in national narcotics control policies and the WHO- and INCB-supported narcotics policies, and (2) to agree on the action plan for 2007-2008 to ensure the availability of opioids used in palliative care. Participants divided into small working groups to discuss the action plan and to assign tasks. A consensus was reached that revisions and enhancements should be made to the current regulation on the supply, management, production, and use of opioids in palliative care. The following day, the Ministry of Health formally approved the new Action Plan. The Ministry of Health will now develop new prescribing regulations for opioids to improve availability which include the following policies aimed at improving availability as well as control:

1. The prescription length for opioids for terminal cancer and AIDS patients will be increased from 7 to 30 days.
2. The maximum dose of opioid prescriptions which was 30 mg will be eliminated.
3. The requirement for physicians and pharmacies to maintain opioid prescription records will be reduced from 5 to 2 years.
4. Opioids will be available in all districts throughout the country. If a district has no pharmacy that stocks opioids, the pharmacy of the district hospital will be required to stock opioids.
5. The Drug Administration of Vietnam (DAV) within the MoH revised its regulations on Procurement, Purchase, Distribution, Storage & Dispensing of Narcotic and Psychotropic Drugs following WHO, INCB guidelines.
6. The DAV will regulate conditions for production, importation, exportation, storage, distribution, and retailing of opioids and psychotropic drugs.
7. Any pharmacy that meets the standards of “Good Pharmacy Practice” (GPP) and “Good Store Practice” (GSP) will be able to sell opioids and psychotropic drugs. (In the past, only very few pharmacies could do this.)
8. Requirements for reporting of controlled medication supply and distribution and of estimated need will be revised in line with a newly designed, decentralized supply chain.
9. Templates for reporting, estimation, and bookkeeping will be revised to be in line with the improved management system.

Planning is underway for the second class of International Pain Policy Fellows in 2008.

Internet Course

Another way to accelerate change is to make the body of knowledge and experience more easily accessible to an international audience. Funded by the National Hospice and Palliative Care Organization (NHPCO), the PPSG/WHOCC developed a Web-based course about national drug control policies' impact on access to opioid analgesics for pain relief that will be available free of charge in 2008. The aim of the course is for learners to understand the body of knowledge encompassing the evaluation and improvement of national policies that govern the medical availability of opioid analgesics for cancer and AIDS patients. The course is intended for an international audience of health care professionals, local and national policy advocates, government drug regulatory personnel, national health policy advisors, and medical scholars. The course is accessible via the PPSG/WHOCC Web site (http://www.painpolicy.wisc.edu/on-line_course/welcome.htm).

Essential Elements of National Drug Control Policy

A question often encountered during the course of the PPSG/WHOCC's policy evaluation work in a number of countries is whether there exists a balanced model law that could be adopted or adapted to simplify drafting of new legislation. Although several model laws have been produced by UN agencies, PPSG/WHOCC has found none that address adequately the obligation to ensure drug availability. Further, our experience shows there is great variability among national laws. Each country has its own cultural history and health care systems. Their laws are so unique that wholesale replacement with a one-size-fits-all is not likely to be accepted. Consequently, the PPSG/WHOCC developed, in consultation with the WHO, the UN Office of Drugs and Crime, and the INCB, a report about the “essential elements” of a modern national opioids control policy that will present reasonable expectations for national policies, based on the obligations that were established in the Single Convention and the subsequent official interpretations of the drug control conventions and expert guidance from international health and regulatory bodies. See report at http://www.painpolicy.wisc.edu/internat/model_law_eval.pdf.

PPSG/WHOCC Web Site Resources

Some important parts of the body of knowledge regarding opioid availability are not easily accessible. The PPSG/WHOCC has established an international section of its website (http://www.painpolicy.wisc.edu) to provide worldwide public access to key resources and information. The international section contains most of PPSG/WHOCC's international publications and links to other important articles about opioid availability; monographs that present the opioid consumption trends globally, regionally, and nationally; as well as links to other relevant resources and organizations pertinent to specific countries. The 2000 WHO guidelines, “Achieving Balance in National Opioids Control Policy,” in 23 languages, are readily accessible from the home page and from each country page.

Country Profiles

A new and useful place to begin learning about the status of opioid consumption in a country is the Country Profile on the PPSG website. These profiles include: (1) the country population and a map, (2) the country's status of adherence to the Single Convention and whether the country has reported consumption statistics and submitted estimates to the INCB, (3) the contact information for the Competent National Authority, (4) opioid consumption statistics, and (5) links to relevant national resources regarding pain, palliative care, and opioid availability.

CONCLUSION

Deepening disparities between high-, low-, and middle income countries in the extent of availability of opioid pain medicines means that pain and suffering in the world is an increasing public health problem. This is cause for alarm and should precipitate concerted action by health professionals, their organizations, and their governments. Actions should be guided by an understanding not only of the need for pain medicines, but also the barriers, the drug control policy framework, and how to work with government drug regulators.

However, health care professionals from any country are not likely to know about these topics because they have not generally been included in basic professional education or continuing education about pain and palliative care. The purpose of this chapter is to outline the body of knowledge, methods, and experience that is relevant to understanding and improving national opioid availability and patient access to pain medicines.

How can this information be applied? Pain and palliative care specialists often are involved in the planning and delivery of training and education for colleagues in other countries, where availability

and access to opioid pain medicines is likely to be limited. Each of these occasions presents an opportunity, if not an ethical

imperative, for the visiting professional to learn about the national opioid situation and to address availability and access issues knowledgeably and appropriately.

This approach might result in presentations that include a discussion of the pharmacology of analgesics with emphasis on the opioids that are necessary to relieve severe pain, discussion of the types of barriers that may interfere in pain relief, explanation of national governments' obligation to ensure *adequate* opioid availability and the role of the Competent National Authority, encouragement to address the barriers, and where to find resources that can be used to improve opioid availability and access.

Although the body of knowledge about the control and availability of opioid analgesics may not be well known, the process of working with individual countries to improve opioid availability borrows from a method with which health professionals are very familiar. The elements of the medical model can be applied to solving problems in opioid availability: evaluation, diagnosis, and a treatment plan. Indeed, health care professionals and governments in India, Romania, and Uganda have worked together to diagnose opioid availability barriers and implement action plans to remove the barriers. New efforts to diagnose and treat barriers are being led by International Pain Policy Fellows in other lowand middle income countries.

There are hopeful signs of progress in some countries, but it is not likely that this progress—which is still in an early developmental phase—is sufficient to gain on the deepening global disparities in access to pain relief medications. Greater leadership will be needed from international drug control bodies, national governments, and from individual health professionals and their organizations.

References

1. World Health Organization. *Cancer Pain Relief.* Geneva, Switzerland: World Health Organization; 1986.

2. World Health Organization HIV-AIDS. *Palliative Care.* Geneva, Switzerland: World Health Organization; 2004.

3. International Narcotics Control Board. *Report of the International Narcotics Control Board for 1989: Demand for and supply of opiates for medical and scientific needs.* Vienna, Austria: United Nations; 1989:E.89 XI.5.

4. World Health Organization. *Cancer pain relief and palliative care: Report of the WHO Expert Committee on Cancer Pain Relief and Active Supportive Care.* Geneva, Switzerland: World Health Organization; 1990: WHO Technical Report Series, No. 804.

5. International Narcotics Control Board. *Report of the International Narcotics Control Board for 1995: Availability of opiates for medical needs.* New York: United Nations; 1996.

6. United Nations Economic and Social Council. *Treatment of pain using opioid analgesics; Resolution 2005-25.* Report on the forty-eighth session of the Commission on Narcotic Drugs E/2005/28; 19 March 2004 and 7-11 March 2005; Issued 22 July 2005. Available at: http://www.un.org/docs/ecosoc/documents/2005/resolutions/Resolution%202005-25.pdf.

7. World Health Assembly. *Cancer Prevention and Control.* Geneva, Switzerland: World Health Organization; 2005:WHA 58.22

8. Boyle P. The globalisation of cancer. *Lancet* 2006;368:629-630.

9. World Health Organization. *World Cancer Report.* Lyon, France: IARC Press; 2003.

10. United Nations Programme on HIV/AIDS, World Health Organization. *AIDS Epidemic Update.* Geneva, Switzerland: UNAIDS Information Centre; 2007.

11. Burton AW, Fanciullo GJ, Beasley RD, et al. Chronic pain in the cancer survivor: A new frontier. *Pain Med* 2007;8(2):189-198.

12. World Health Organization. *Symptom Relief in Terminal Illness.* England: Scientific Publishing/Clays; 1998.

13. World Health Organization. *Cancer Pain Relief: With a Guide to Opioid Availability.* 2nd ed. Geneva, Switzerland: World Health Organization; 1996.

14. Foley KM, Wagner JL, Joranson DE, et al. Pain control for people with cancer and AIDS. In: Jamison DT, Breman JG, Measham AR, et al., eds. *Disease Control Priorities in Developing Countries.* New York: Oxford University Press; 2006:981-993.

15. Frich LM, Borgbjerg FM. Pain and pain treatment in AIDS patients: A longitudinal study. *J Pain Symptom Manage* 2000;19(5):339-347.

16. Goudas LC, Bloch R, Gialeli-Goudas M, et al. The epidemiology of cancer pain. *Cancer Invest* 2005;23:182-190.

17. Davis MP, Walsh D. Epidemiology of cancer pain and factors influencing poor pain control. *Am J Hosp Palliat Care* 2004;21(2):137-142.

18. Breitbart W, Rosenfeld BD, Passik SD, et al. The undertreatment of pain in ambulatory AIDS patients. *Pain* 1996;65:243-249.

19. Larue F, Fontaine A, Colleau SM. Underestimation and undertreatment of pain in HIV disease: Multicentre study. *BMJ* 1997;314:23-28.

20. World Health Organization. *A community health approach to palliative care for HIV/AIDS and cancer patients in sub-Saharan Africa.* Geneva, Switzerland: World Health Organization; 2004.

21. World Health Organization. *Cancer Pain Relief and Palliative Care in Children.* Geneva, Switzerland: World Health Organization in collaboration with the International Association for the Study of Pain; 1998.

22. World Health Organization. *National Cancer Control Programmes: Policies and Managerial Guidelines.* 2nd ed. Geneva, Switzerland: World Health Organization; 2002.

23. World Health Organization Programme on Cancer Control. *Strategies to improve and strengthen cancer control programmes in Europe.* WHO Consultation held in Geneva, Switzerland; 25-28 November 2003.

24. World Health Organization, International Union Against Cancer. *Global Action Against Cancer.* Geneva, Switzerland: World Health Organization; 2005.

25. World Health Organization. *Cancer Control: Knowledge into Action-Palliative Care.* Geneva, Switzerland: World Health Organization; 2007

26. World Health Organization. *Essential medicines* (website). Geneva, Switzerland: World Health Organization; 2005.

27. World Health Organization. *Essential Medicines - WHO Model List.* 1st ed. Geneva, Switzerland: World Health Organization; 1977.

28. World Health Organization. *Essential Medicines - WHO Model List.* 15th ed. Geneva, Switzerland: World Health Organization; 2007.

29. United Nations. *Single convention on narcotic drugs, 1961, as amended by the 1972 protocol amending the single convention on narcotic drugs, 1975.* New York: United Nations; 1977.

30. United Nations. *Convention on Psychotropic Substances.* Geneva, Switzerland: United Nations; 1971.

31. International Narcotics Control Board. *1961 Single Convention on Narcotic Drugs: Part 1: The International Control System for Narcotic Drugs.* Vienna, Austria: International Narcotics Control Board; 2005.

32. International Narcotics Control Board. *Report of the International Narcotics Control Board for 2006.* New York: United Nations; 2007.

33. Joranson DE. Why is a balanced policy important, and do we have it now? In: Wilford BB, ed. *Balancing the response to prescription drug abuse, report of a national symposium on medicine and public policy.* Chicago, Ill: American Medical Association, Department of Substance Abuse; 1990:1-6.

34. Joranson DE. Guiding principles of international and federal laws pertaining to medical use and diversion of controlled substances. In: Cooper JR, Czechowicz DJ, Molinari SP, et al., eds. *Impact of prescription drug diversion control systems on medical practice and patient care: monograph 131.* Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Drug Abuse; 1993:18-34.

35. Katz NP, Adams EH, Benneyan JC, et al. Foundations of opioid risk management. *Clin J Pain* 2007;23(2):103-118.

36. Cicero TJ, Dart RC, Inciardi JA, et al. The development of a comprehensive risk-management program for prescription opioid analgesics: Researched abuse, diversion and addiction-related surveillance (RADARS). *Pain Med* 2007; 8(2):157-170.

37. Department of Health, Medicines Pal. *Safer management of controlled drugs: A guide to good practice in secondary care* England; 2007.

38. American Academy of Pain Medicine Council on Ethics. *Ethics Charter.* Glenview, IL: American Academy of Pain Medicine; 2005.

39. United Nations. *Single Convention on Narcotic Drugs, 1961.* Geneva, Switzerland: United Nations; 1973.

40. Bayer I, Ghodse H. Evolution of international drug control, 1945-1995. *Bull Narc* 1999; 51(1-2):1-17.

41. International Narcotics Control Board. *1961 Single Convention on Narcotic Drugs: Part 2: The Estimates System for Narcotic Drugs.* Vienna, Austria: International Narcotics Control Board; 2005.

42. International Narcotics Control Board. 1*961 Single Convention on Narcotic Drugs: Part 3: The Statistical Returns System for Narcotic Drugs.* Vienna, Austria: International Narcotics Control Board; 2005.

43. International Narcotics Control Board. *Guidelines for National Comptetent Authorities.* Vienna, Austria: International Narcotics Control Board; 2007.

44. International Narcotics Control Board. *Report of the International Narcotics Control Board for 2004.* New York: United Nations; 2005.

45. Mosoiu D, Ryan KM, Joranson DE, et al. Reform of drug control policy for palliative care in Romania. *Lancet* 2006;367(9528):2110-2117.

46. Ryan KM, Joranson DE, Gilson AM. Toward a more complete indicator of opioid consumption trends. Paper presented at: 7th International Conference on Pain & Chemical Dependency; New York; June 21-24 2007. Madison, WI, University of Wisconsin Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care; 2007.

47. World Health Organization Collaborating Centre for Drug Statistics Methodology. *Anatomical Therapeutic Chemical/Defined Daily Dose.* Oslo, Norway: Norwegian Institute of Public Health; 2007.

48. International Narcotics Control Board. *Report of the International Narcotics Control Board for 2003.* New York: United Nations; 2004.

49. Rhymes JA. Barriers to effective palliative care of terminal patients. An international perspective. *Clin Geriatr Med* 1996;12(2):407-416.

50. Adams V. *Access to pain relief: An essential human right.* London: Help the Hospices for the Worldwide Palliative Care Alliance; 2007.

51. Joranson DE. Availability of opioids for cancer pain: Recent trends, assessment of system barriers, new World Health Organization guidelines, and the risk of diversion. *J Pain Symptom Manage* 1993;8(6):353-360.

52. World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines.* Geneva, Switzerland: World Health Organization; 1992.

53. International Association of Pain and Chemical Dependency. International Association of Pain and Chemical Dependency website. Accessed January 29, 2008.

54. Morgan JP. American opiophobia: Customary underutilization of opioid analgesics. In: Hill CS, Fields WS, eds. *Advances in Pain Research and Therapy.* Vol 11. New York: Raven Press; 1989:181-189.

55. Bennett DS, Carr DB. Opiophobia as a barrier to the treatment of pain. *J Pain Palliat Care Pharmacother* 2002;16(1):105-109.

56. World Health Organization. *WHO expert committee on drugs liable to produce addiction: Third report.* Geneva,

Switzerland: World Health Organization; 1952:technical report series 57.

57. World Health Organization. *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines.* F1x.2 Dependence syndrome; Geneva, Switzerland; 2006 version.

58. Forbes K. Opioids: Beliefs and myths. *J Pain Palliat Care Pharmacother* 2006; 20(3):33-35.

59. Doyle D, Hanks GWC, Cherny N, et al. *Oxford Textbook of Palliative Medicine.* 3rd ed. New York: Oxford University Press; 2004.

60. Fohr SA. The double effect of pain medication: Separating myth from reality. *J Palliat Med* 1998;1(4):315-328.

61. Portenoy RK, Sibirceva U, Smout R, et al. Opioid use and survival at the end of life: A survey of a hospice population. *J Pain Symptom Manage* 2006;32(6): 532-540.

62. Bercovitch M, Adunsky A. Patterns of high-dose morphine use in a home-care hospice service. *Cancer* 2004;101:1473-1477.

63. World Health Organization. *Guiding principles for small national drug regulatory authorities. World Health Organ Drug Info* 1989;3(2):43-50.

64. Joranson DE, Rajagopal MR, Gilson AM. Improving access to opioid analgesics for palliative care in India. *J Pain Symptom Manage* 2002;24(2):152-159.

65. Gilson AM, Joranson DE, Maurer MA. Improving state pain policies: Recent progress and continuing opportunities. *CA Cancer J Clin* 2007;57(6):341-353.

66. World Health Organization. *WHO expert committee on drug dependence: thirty-fourth report.* Geneva, Switzerland: World Health Organization; 2006.

67. Mercadante S. Costs are a further barrier to cancer pain management. *J Pain Symptom Manage* 1999;18(1):3-4.

68. Moyano J, Ruiz F, Esser S, et al. Latin American survey on the treatment of cancer pain. *Eur J Palliat Care* 2006;13(6):236-240.

69. De Conno F, Ripamonti C, Brunelli C. Opioid purchases and expenditure in nine western European countries: 'Are we killing off morphine?' *Palliat Med* 2005;19:179-184.

70. De Lima L, Sweeney C, Palmer JL, et al. Potent analgesics are more expensive for patients in developing countries: A comparative study. *J Pain Palliat Care Pharmacother* 2004;18(1):59-70.

71. Colleau SM. Highlights of the INCB report. *Cancer Pain Release* 1996; 9(suppl):1-4.

72. World Health Organization. *Access to Controlled Medications Programme - Framework.* Geneva, Switzerland: World Health

Organization; 2007.

73. Green K, Kinh LN, Khue LN. *Palliative Care in Vietnam: Findings from a Rapid Situation Analysis in Five Provinces.* Hanoi, Vietnam; 2006.

74. World Health Organization. *Achieving balance in national opioids control policy: Guidelines for assessment.* Geneva, Switzerland: World Health Organization; 2000.

75. Federazione Nazionale Ordini dei Medici Chirurghi e Odontoiatri, Associazione Europea per le Cure Palliative, Associazione Italiana di Oncologia Medica, et al. *Proposta di modifica della legge sugli stupefacenti.* S I M G Rivista di Politica Professionale della Medicina Generale 1998;8(Ottobre):10-12.

76. Blengini C, Joranson DE, Ryan KM. Italy reforms national policy for cancer pain relief and opioids. *Eur J Cancer Care (Engl)* 2003;12(1):28-34.

77. Logie DE, Harding R. An evaluation of a morphine public health programme for cancer and AIDS pain relief in Sub-Saharan Africa. *BMC Public Health* 2005;5(82):1-7.

78. Joranson DE, Nischik JA, Gilson AM, et al. *Consumo de analgésicos opioides en el mundo y la región andina. Preparado para: Taller de Reguladores: Asegurando Disponibilidad de Analgésicos Opioides para Cuidados Paliativos*; Quito, Ecuador; 3-5 Diciembre de 2000. Madison, WI: University of Wisconsin Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care; 2000.

79. World Health Organization Regional Office for Europe. *Assuring availability of opioid analgesics for palliative care.* Meeting report of opioid availability workshop held in Budapest, Hungary; February 25-27, 2002. Copenhagen, Denmark, World Health Organization Regional Office for Europe; 2002.

80. Pain & Policy Studies Group. *Availability of opioid analgesics in Eastern Europe and the world.* Prepared for the Workshop on Assuring Availability of Opioid Analgesics for Palliative Care; Budapest, Hungary; February 25-27, 2002. Madison, WI: University of Wisconsin Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care; 2002.

81. Pain & Policy Studies Group. *Availability of opioid analgesics in Africa and the world.* Prepared for the WHO meeting, “A Community Health Approach to Palliative Care for HIV/AIDS and Cancer Patients in Africa”; Gaborone, Botswana; July 9-12, 2002. Madison, WI: University of Wisconsin Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care; 2002.

82. Pain & Policy Studies Group. *Availability of Morphine and Pethidine in the World and Africa, With a special focus on: Botswana, Ethiopia, Kenya, Malawi, Nigeria, Rwanda, Tanzania, Zambia.* Prepared for Advocacy for Palliative Care in Africa: A Focus on Essential Pain Medication Accessibility. Entebbe, Uganda; June 27-29, 2006. Madison, WI: University of Wisconsin Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care; 2006.

83. African Palliative Care Association. *Advocacy workshop for palliative care in Africa.* Kampala, Uganda: African Palliative Care Association; 2007.

84. Pain & Policy Studies Group. *Availability of morphine and pethidine in the world and Africa with a special focus on: Cameroon, Cote d'Ivoire, Ghana, Nigeria, Sierra Leone, The Gambia.* Prepared for Advocacy for Palliative Care in Africa: A

Focus on Essential Pain Medication Accessibility; May 9-11, 2007. Madison, WI: University of Wisconsin Pain & Policy Studies Group/WHO Collaborating Center for Policy and Communications in Cancer Care; 2007.

85. Kumar S. Kerala, India: A regional community-based palliative care model. *J Pain Symptom Manage* 2007;33(5):623-627.

86. Mosoiu D, Mungiu OC, Gigore B, et al. Romania: Changing the regulatory environment. *J Pain Symptom Manage* 2007;33(5):610-614.

87. Ryan KM. The Pain & Policy Studies Group. *J Pain Palliat Care Pharmacother* 2007;21(4):35-37.

88. McNeil DG. In India, a quest to ease the pain of the dying. *The New York Times.* September 11, 2007;D1-D5.

89. McNeil DG. Drugs banned, world's poor suffer in pain. *The New York Times.* September 10, 2007;A1-A12.