Chapter **52**

Pain Control for People with Cancer and AIDS

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The undertreatment of chronic pain is a global problem, especially for people in the final stages of cancer and, increasingly, AIDS. The pain of dying is often severe, but it can be controlled for most people by a simple and inexpensive intervention: oral analgesic drugs, including morphine and other opioids. Although it was long known that opioid drugs were essential for the relief of moderate to severe pain, even in the 1980s the amounts being used globally were so low that only a minority of those dying could have had adequate pain relief. Since then progress has been made, mainly in resource-rich countries, widening the gap between rich and poor. The absence of opioids in developing countries is not merely a problem of supply or costs, however. This chapter lays out the institutional and political barriers that restrict their availability in most low- and middle-income countries.

BURDEN OF PAIN FROM CANCER AND AIDS

Pain is "an unpleasant sensory and emotional experience associated with either actual or potential tissue damage or described in terms of such damage" (Task Force on Taxonomy 2004). Pain, in its various manifestations, is the most common symptom leading patients to seek medical assistance (box 52.1).

Measurement of Pain

Pain is a subjective experience, but it can be described by patients and assessed using validated questionnaires and scales (Cleeland 1990). In *categorical scales,* the patient describes the pain using specific words, for example, mild, moderate, severe, or excruciating. With *numerical scales,* patients rate their pain by choosing a number—for example, from 0 (no pain) to 10 (worst pain). *Visual analog scales* often take the form of a ruled line, anchored on the left by the words *no pain* and on the right by *worst possible pain.*

Pain measurement instruments have been validated in clinical trials of analgesic therapies and subsequently used in national and international surveys, repeatedly demonstrating sensitivity and reliability for both cancer and AIDS patients. These instruments include the Brief Pain Inventory (Bernabei and others 1998; Cleeland and others 1996; Daut, Cleeland, and Flanery 1983), the Memorial Pain Assessment Card (Fishman and others 1987), the Memorial Symptom Assessment Scale (Portenoy and others 1994), and the Edmonton Symptom Assessment Scale (Chang, Hwang, and Feuerman 2000).

Effects of Pain

Pain dramatically affects quality of life. Patients with persistent serious pain cease participating in social activities and may be unable to work or care for their families (Daut, Cleeland, and Flanery 1983). Psychological effects, including depression and anxiety, increase with pain intensity (Rosenfeld and others 1996).

The suffering of an individual radiates throughout households, neighborhoods, and villages. Caregivers suffer distress, anxiety, and depression. They may have to give up their own employment to care for a dying relative. The loss of income of the patient and the caregiver may dramatically lower the family's social status (Murray and others 2003).

Box 52.1

Classification of Pain

Pain is classified according to two main characteristics: temporal and physiologic. *Temporal* categories are

- acute pain
  - characterized by a well-defined onset and self-limited end
  - allows clear description of location, character, and timing
  - shows signs of autonomic nervous system hyperactivity—for example, tachycardia, hypertension, profuse sweating (diaphoresis), dilated pupils (mydriasis), or pallor
- chronic or persistent pain
  - long lasting, usually defined as at least three months
  - characterized by a localization, character, and timing that is often more vague than with acute pain
  - characterized by adaptation of the autonomic nervous system, so signs of hyperactivity disappear
  - results in significant changes in psychological, functional, and social status.

Physiologic pain categories are

- somatic pain
  - originates in ligaments, tendons, bones, blood vessels, and nerves
  - sharp or dull, but typically well localized and intermittent
- visceral pain
  - originates in body organs and results from activation of nociceptive receptors and efferent nerves
  - characterized by deep aching and cramping, often referred to cutaneous sites
- neuropathic pain
  - results from direct injury to peripheral receptors, nerves, or the central nervous system
  - typically burning and dysesthetic (abnormal and unpleasant), often in area of sensory loss.

Source: Authors.

Pain in Patients with Cancer and AIDS

Several well-defined acute and chronic pain syndromes are associated with cancer, with HIV/AIDS, and with their treatment (Breitbart 2003; Foley 1979). In low-income countries, where patients usually present late in the course of illness, pain from the disease itself is more common than treatment-related pain.

Researchers consistently report that 60 to 90 percent of patients with advanced cancer experience moderate to severe pain, regardless of age and gender and whether ambulatory or hospitalized (Cleeland and others 1988; Cleeland and others 1996; Daut and Cleeland 1982; Foley 1979, 1999; Stjernsward and Clark 2003). The intensity, degree of pain relief, and effect of pain vary according to the type of cancer, treatment, and personal characteristics, but prevalence and severity of pain usually increase with disease progression. No population-based studies of AIDS-related pain have been published, but several researchers report that up to 80 percent of patients in the last phase of illness experience significant pain requiring analgesics (Larue, Fontaine, and Colleau 1997; Schofferman and Brody 1990; Singer and others 1993).

Pain Days

No standard metric has been developed to describe the pain burden for people at the end of life. We have adopted a transparent and direct measure—the *pain day*—defined as a day of moderate or severe pain requiring an opioid drug for relief. The elements that determine the number of cancer and AIDS pain days in a population are the numbers dying from each condition and the average prevalence and duration of severe pain associated with dying.

Patterns of pain from specific cancers and from AIDS at given stages appear to be similar everywhere. However, because different cancers produce different symptoms, the mix of cancers in a country will influence the overall pattern and burden of pain reflected in the total number of pain days.

About 2.1 million deaths from cancer and about 3 million from AIDS occur annually in low- and middle-income countries (LMICs) worldwide, and these numbers are increasing. Using expert opinion, we estimate that about 80 percent of people dying from cancer and 50 percent of those dying from AIDS experience moderate or severe pain, lasting for an average of 90 days.

INTERVENTIONS FOR PAIN RELIEF

The goal of pain control is not to cure disease, but to allow patients to function as effectively as possible and to minimize pain. Interventions for pain relief include drugs, radiotherapy, and anesthetic, neurosurgical, psychological, and behavioral approaches (see table 52.1). However, analgesic drugs are the mainstay of treatment and the focus of this chapter. According

Table 52.1 Procedures Used to Control Specific Types of Cancer Pain

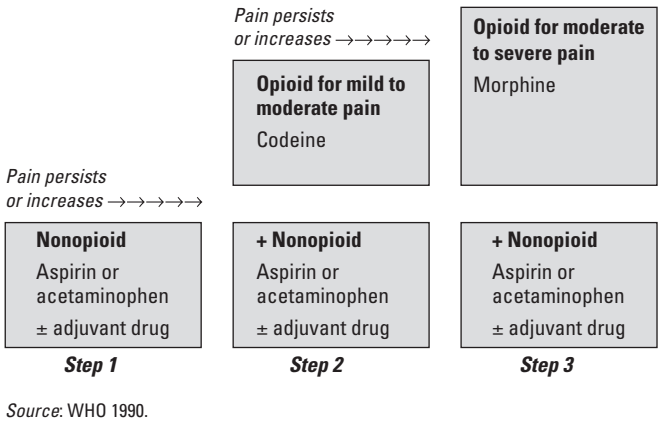
Type of procedure	Most common indications
Anesthetic	
Inhalation therapy with nitrous oxide	Breakthrough pain, incidental pain in patients with diffuse, poorly controlled pain
Intravenous barbiturates (for example, sodium pentobarbital)	Diffuse body pain and suffering inadequately controlled by systemic opioids
Local anesthetic by intravenous, subcutaneous, or transdermal application	Neuropathic pain in any site with local application to the area of hyperesthesia or allodynia
Trigger point injections	Focal muscle pain
Nerve block	
Peripheral	Pain in discrete dermatomes in chest and abdomen or in distal extremities
Epidural	Unilateral lumbar or sacral pain
	Midline perineal pain
	Bilateral lumbosacral pain
Intrathecal	Midline perineal pain
	Bilateral lumbosacral pain
Autonomic	
Stellate ganglion	Reflex sympathetic dystrophy
Lumbar sympathetic	Reflex sympathetic dystrophy of the lower extremities
	Lumbosacral plexopathy
	Vascular insufficiency of lower extremity
Celiac plexus	Midabdominal pain from tumor infiltration
Intermittent or continuous epidural infusion with local anesthetics	Unilateral and bilateral lumbosacral pain
	Midline perineal pain
	Neuropathic pain from the midthoracic region down
Intermittent or continuous epidural or intrathecal with local opioid analgesics	Unilateral and bilateral pain below the midthoracic region; often combined with local anesthetics
Intermittent or continuous intraventrical infusions with opioid analgesics	Head and neck pain and upper chest
Chemical hypophysectomy	Diffuse bone pain
Neuroablative	
Nerve root: rhizotomy	Somatic and neuropathic pain from tumor infiltration of the cranial and intercostal nerves
Spinal cord: dorsal root entry zone lesion	Unilateral neuropathic pain from brachial, intercostal, and lumbosacral plexopathy and postherpetic neuralgia
Spinal cord: cordotomy	Unilateral pain below the waist; often combined with local neurolytic blocks in perineal and bilateral lumbosacral plexopathy; may be performed bilaterally
Spinal cord: myelotomy	Midline pain below the waist, but rarely used because it involves extensive surgery
Brain stem: mesencephalic tractomy	Pain in the nasopharynx and trigeminal region
Thalamus: thalamotomy	Unilateral neuropathic pain in the chest and lower extremity
Cortex: cingulotomy	Useful through a stereotactic approach for diffuse pain
Pituitary: transsphenoidal hypophysectomy	Bone metastases in endocrine-dependent tumors, breast, and prostate
Neurostimulatory	
Peripheral nerve: transcutaneous and percutaneous electrical nerve stimulation	Dysesthesias from tumor infiltration of nerve or trauma
Spinal cord: dorsal column stimulation	Of limited use in neuropathic pain in the chest, midline, and lower extremities
Thalamus: thalamic stimulation	Of rare use in neuropathic pain in the chest, midline, or lower extremity
Radiotherapy	
External beam	Bone and brain metastases
	Nerve and spinal cord compression

(Continues on the following page.)

Table 52.1 Continued

Type of procedure	Most common indications
Physical	
Cutaneous stimulation (superficial heat, cold, massage)	Dysesthesias from tumor infiltration of nerve or trauma
Transcutaneous electrical nerve stimulation	Cutaneous nerve injury pain
Acupuncture	For focal or diffuse pain syndrome
Bed rest	Reduced movement–related pain syndrome
Psychological	
Hypnosis	Provides distraction and cognitive approach to reduce pain
Relaxation, imagery, biofeedback, distraction, reframing	Provides distraction and cognitive approach to reduce pain
Patient education	

Source: Breitbart 2003; Authors.



Source: WHO 1990.

Figure 52.1 The Three-Step Analgesic Ladder

to the World Health Organization (WHO), "A palliative care programme cannot exist unless it is based on a rational national drug policy," and this includes "regulations that allow ready access of suffering patients to opioids" (WHO 2002, 87).

WHO Three-Step Analgesic Ladder and Its Effectiveness

WHO has developed a "three-step analgesic ladder" (figure 52.1) for cancer pain and its treatment (WHO 1986), which includes a strong opioid (morphine) (table 52.2). The ladder is equally appropriate for patients with HIV/AIDS (O'Neill, Selwyn, and Schietinger 2003).

The steps in the ladder represent increasing pain severity and the drugs that should be used in each case:

- Step 1 is limited to nonopioids, including drugs that are widely available (for example, acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs, or NSAIDs).
- Step 2 describes moderate pain that requires a combination of a nonopioid and opioid for relief.
- Step 3 is for pain requiring a strong opioid. No specific dosages are recommended for opioid drugs because the concept of a standard dose does not apply: effective doses of oral morphine range from as little as 5 mg to more than 1,000 mg every four hours. Adjuvant drugs are also essential to treat side effects of analgesics or to provide additive analgesia (table 52.2).

Controlled field testing and clinical experience has demonstrated that 70 to 90 percent of cancer patients can achieve pain control using the ladder (Goudas, Carr, and Bloch 2001). Although the ladder has not been validated in formal studies for patients with AIDS, recent clinical reports describe its successful application (Anand, Carmosino, and Glatt 1994; Kimball and McCormick 1996; McCormack and others 1993; Newshan and Lefkowitz 2001; Newshan and Wainapel 1993; Schofferman and Brody 1990).

In an ideal world, a trained professional would prescribe pain medication throughout the course of illness, in accordance with the ladder. However, most patients self-medicate pain with analgesics and traditional medicines that they buy over the counter until they have late-stage disease and severe pain that can be treated only with a strong opioid. That is when they are most likely to seek formal medical care, which would start on step 3 of the ladder. Unfortunately, the opioid they need is unlikely to be unavailable in LMICs, even from health professionals.

Adequacy of and Barriers to Pain Control and Palliative Care in Developing Countries

The adequacy of pain control in populations is not easily measured. A useful and available surrogate is the per capita consumption of morphine (Joranson 1993), a figure based on mandatory annual reports by national governments to the International Narcotics Control Board (INCB). Of the 27 million grams of morphine used legally in 2002, 78 percent went to six countries—Australia, Canada, France, Germany,

Table 52.2 Basic Drug List for Cancer and AIDS Pain Relief: Analgesics and Adjuvant Drugs

Category Analgesics	Basic drugs	Alternatives
Nonopioids	Acetylsalicylic acid (aspirin)	Choline magnesium trisalicylate
	Acetaminophen	Diflunisal
	Ibuprofen	Naproxen
	Indomethacin	Diclofenac
Opioids for mild to moderate pain	Codeine	Dihydrocodeine
		Hydrocodone
		Tramadol
Opioids for moderate to severe pain	Morphine	Methadone
		Hydromorphone
		Oxycodone
		Pethidine
		Buprenorphine
		Fentanyl
Opioid antagonists	Naloxone	Nalorphine
Adjuvant drugs for analgesia and symptom control		
Antiemetics	Prochlorperazine	Metoclopramide
		Ondansetron
Laxatives	Senna	Cisacodyl
	Sodium docusate	Bran
	Mineral oil	Dantron
	Lactulose	Sorbitol
	Magnesium hydroxide	
Antidiarrheal agents	Loperamide	Paregoric
	Diphenoxylate hydrochloride and atropine sulfate	
Antidepressants (adjuvant analgesics)	Amitriptyline	Imipramine
		Paroxetine
Antipsychotic	Haloperidol	Thorazine
Anticonvulsants (adjuvant analgesics)	Gabapentin	Valproic acid
	Carbamazepine	
Corticosteroids	Prednisone	Prednisolone
	Dexamethasone	
Anxiolytics	Diazepam	Clonazepam
	Lorazepam	
	Midazolam	
Psychostimulants	Methylphenidate	Pemoline

Source: Foley, Aulino, and Stjernsward 2003.

the United Kingdom, and the United States. The rest went to the other 142 countries that reported. Morphine is largely unavailable in Africa, the eastern Mediterranean, and Southeast Asia (figure 52.2).

The major barriers to palliative care in LMICs are scarce resources, lack of national policies or low priority for pain relief, lack of awareness by health professionals and the public that cancer and AIDS pain can be relieved, concern that medical use of opioids will lead to drug abuse and addiction, and legal restrictions on opioids. Medical, religious, gender, social, and cultural factors also present barriers (see box 52.2). With AIDS, social and self-stigmatization work against adequate care of any kind. In addition, most of the emphasis in poor countries has been on prevention and, more recently, on antiretroviral drugs. In all cases, even less care is in place for children than for adults (Joranson, Rajagopal, and Gilson 2002).

Box 52.2

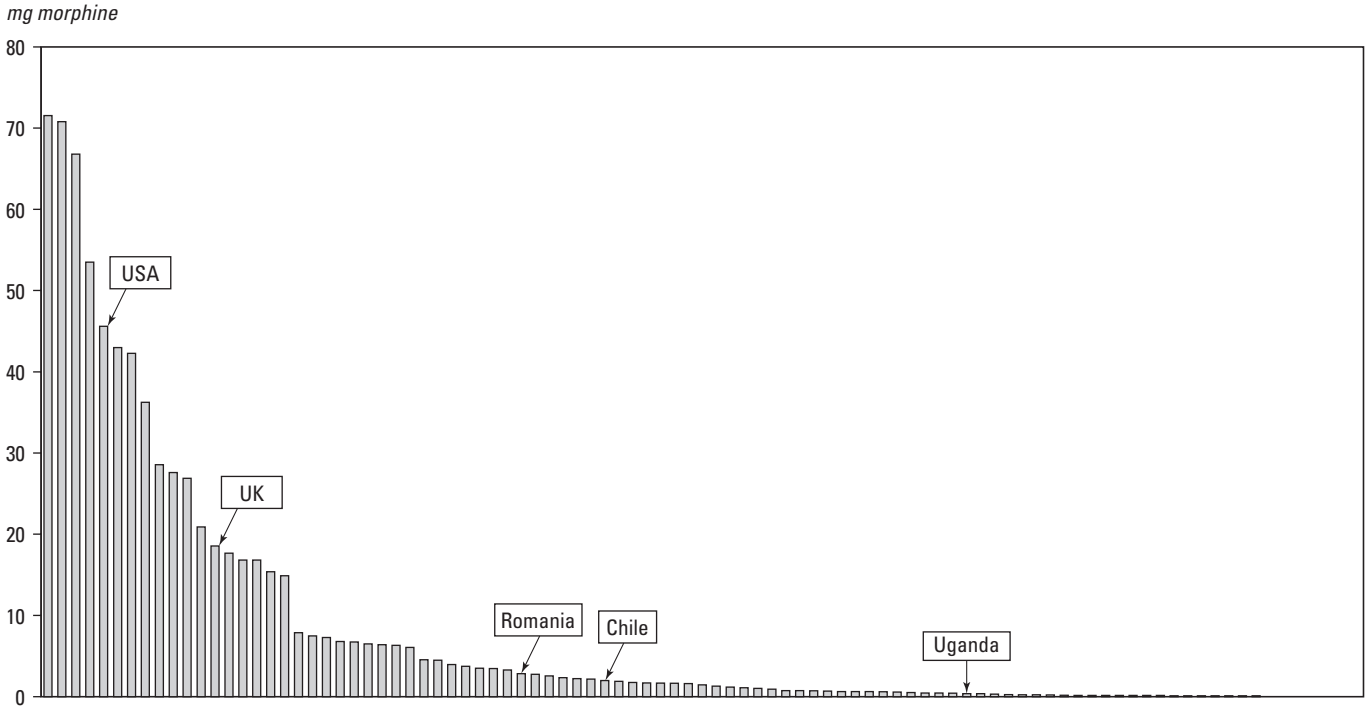
Living with and Dying from Cancer in Scotland and Kenya

Physical suffering dominates the lives of people with advanced cancer in rural Kenya. In contrast, the concerns of cancer patients in Scotland, whose physical needs are met, focus on the prospect of death. A recent study compared these two groups.

The suffering in Kenya stems largely from poverty and the high cost of basic health care. Hospital care is limited, and patients feel happier at home. Families care for patients without drugs or supplies or even the knowledge of what to expect and how to help the patient. Patients are concerned about the physical and financial burden on their families. They are comforted and inspired by religious beliefs and by the support of their communities. They accept their fate.

In Scotland, health care is free and of high quality. Patients are able to get primary treatment for the cancer and, when needed, palliative care. They are likely to be angry about their illness rather than accepting, and many feel isolated from family and friends. Although patients' physical needs are met routinely, psychosocial needs are met only for some.

Source: Murray and others 2003.



Source: INCB 2003 and authors' calculations.

Figure 52.2 Global Morphine Consumption, by Country (Per Capita, 2002)

Legal Controls on Opioid Drugs

The Single Convention on Narcotic Drugs of 1961, amended by the 1972 Protocol (United Nations 1961), is an international treaty that aims both to prevent the illicit production of, trafficking in, and use of narcotic drugs and to ensure their availability for medical and scientific needs. The INCB, established in 1968 by the Single Convention, is the independent, quasi-judicial organization that implements the Single Convention.

The Single Convention requires that all countries (even nonsignatories) intending to make opioids available for medical use estimate national opioid needs and report annually on imports, exports, and distribution to the retail level. It also

Box 52.3

Pain Control in Romania and Chile

Palliative care has developed in Romania since the early 1990s, largely through the Romanian Association for Palliative Care. Support has come predominantly from U.K. charities and from the Open Society Institute. Services are provided throughout the country by paid staff and volunteers in 10 hospital-based inpatient services, 9 hospice home care teams, 2 day care services, and 1 palliative care training center that provides services. Coverage is still low: only 15 percent of cancer patients are treated with opioid analgesics. Morphine is available (paid for by the government) only for terminally ill cancer patients. Prescription restrictions and extra authorization needed for releasing morphine to each patient are still so burdensome that patients may die before the paperwork is completed. The situation is improving gradually, however.

Palliative care has developed in Chile over the past 15 years, largely through nongovernmental organizations. The Ministry of Health's cancer program has also played a role by including palliative care in its National Cancer Control Program initiative and by moving to reform drug laws. As a result, morphine consumption increased from less than 5 kg in 1990 to 55 kg in 2000. Despite these efforts, only a minority of patients have access to oral morphine for chronic pain related to cancer or AIDS. The remaining barriers include inadequately trained clinicians, a lack of national standards and guidelines, cure-oriented cancer treatment policies, fear of addiction on the part of both professionals and the public, and a lack of resources to improve the health care infrastructure.

Sources: International Observatory on End of Life Care 2005.

sets out the following principles on which countries can develop their own policies and regulations:

- Individuals must be authorized to dispense opioids by virtue of their professional license or be specially licensed to do so.
- Opioids may be transferred only between authorized parties.
- Opioids may be dispensed only with a medical prescription.

Many governments have imposed even tighter restrictions, such as limiting the number of days for which an opioid prescription can be written.

COSTS AND COST-EFFECTIVENESS

This section describes the costs and benefits of providing oral morphine and essential adjuvant drugs to terminally ill cancer and AIDS patients who require it. It assumes the drugs are used according to the WHO analgesic ladder. We recognize that other analgesics can also contribute significantly to patients' costs and pain relief, but at least some such drugs (acetaminophen, for example) are available relatively cheaply in most places. Although not everyone has access to such drugs, we are unaware of any data that could be used to estimate that proportion. Costs are estimated for three countries at differing income levels and with different patterns of cancer and AIDS deaths: Chile, Romania, and Uganda (see box 52.3).

Costs Included in the Estimates

The quantitative analysis presented here is restricted to the costs, before such drugs reach the patient, of oral morphine and the adjuvant drugs needed to treat its side effects. We mention other costs associated with delivering oral morphine to terminal AIDS and cancer patients later in this section, but for reasons we discuss, we have not assigned dollar values to them.

Costs of Oral Morphine. The appropriate measure of drug cost is the sum of costs to all payers—governments, insurers, charities, and patients—for the drug itself, but that sum does not include the costs of personnel to administer the drug or otherwise care for the patient.

Oral morphine can be purchased in bulk powder or finished form and administered as a tablet or liquid (De Lima and others 2004; Rajagopal and Venkateswaran 2003). The cost to the final payer is influenced by import taxes, if any; requirements to document the chain of custody of the product; costs to local manufacturers of excipients, salts, diluents, and other materials required to produce finished forms; and price markups. The actual cost of oral morphine in LMICs is difficult to document because it is unavailable in so many places or is manufactured for finished use at different points in the distribution chain. The price of a 30-day supply of immediate-release oral morphine in 2003 ranged from US$10 in India to US$254 in Argentina, among the few countries for which prices were reported (De Lima and others 2004).

Morphine is likely to cost less where it is produced locally and used in easy-to-reach, urban locations. Liquid preparations made by mixing morphine powder will cost less than tablets. Even with these variations, if barriers to access to oral morphine are removed, a total drug cost of 1 cent per milligram or less for immediate-release oral morphine should be achievable for most countries. A realistic and conservative estimate of the cost of oral morphine is 0.5 cent to 1.0 cent per milligram in the countries in our analysis.

The cost of morphine per patient depends on the number of days that opioids are required and the average daily dose, recognizing that the required dosage typically increases with increasing pain nearer to death. An average daily dose in palliative care programs in developing countries is roughly 60 to 75 mg per day, and patients require this dose for an average of three months. (Merriman 2002; personal communication, L. De Lima, International Association for Hospice and Palliative Care, June 2004; personal communication, M. R. Rajagopal, Amrita Institute of Medical Sciences, Kochi, Kerala, India, June 2004).

Using the inputs above, we estimate the cost of oral morphine for a cancer or AIDS patient with severe pain near the end of life at about 30 to 75 cents per day, or US$9.00 to US$22.50 per month, which is needed for an average of three months.

Costs of Other Necessary Drugs. Morphine's most common side effects are constipation, nausea, and (less frequently) psychosis. Representative drugs to treat these conditions are senna, a laxative, available to some government purchasers for

Table 52.3 Background Data, Assumptions, and Results of Cost Analysis

Item	Uganda	Chile	Romania
Economic, demographic, and health characteristics			
Population, 2001	22,800,000	15,400,000	22,400,000
Gross national income per capita, 2001 (US$)	260	4,590	1,720
World Bank income designation	Low	Upper middle	Lower middle
Percentage of the population living in rural areas	85	14	45
Number of cancer deaths, 2000	10,504	18,315	38,360
Number of AIDS deaths, 2001	84,000	220	350
Prevalence of cancer and AIDS deaths (per million population)	4,145	1,204	1,728
Morphine use per capita, 2001 (mg)	0.1	2.1	2.2
Total morphine use, 2001 (mg millions)	2.191	31.770	48.809
Assumptions and estimates used to determine the costs of oral morphine			
Percentage of cancer patients requiring end-of-life care with oral morphine	80	80	80
Average number of days of oral morphine required for cancer patients	90	90	90
Average daily dose of oral morphine for cancer patients (mg)	60–75	60–75	60–75
Effectiveness of intervention, cancer (percentage of pain days averted per day of therapy)	80	80	80
Percentage of patients with cancer already receiving adequate end-of-life pain care	0.5	20.0	15.0
Percentage of AIDS patients requiring end-of-life care with oral morphine	50	50	50
Average number of days of oral morphine required for AIDS patients	90	90	90
Average daily dose of oral morphine for AIDS patients (mg)	60–75	60–75	60–75
Effectiveness of intervention, AIDS (percentage of pain days averted per day of therapy)	80	80	80
Percentage of patients with AIDS already receiving adequate end-of-life pain care	0.5	20.0	15.0
Average daily cost of related drugs for cancer and AIDS patients (US$)	0.18–0.33	0.18–0.33	0.18–0.33
Cost analysis results (all costs in 2002 US$)			
Total incremental annual cost of oral morphine (US$ millions)	2.2–4.9	0.6–1.2	1.1–2.6
Incremental annual cost per capita (US$)	0.10–0.21	0.03–0.07	0.05–0.11
Incremental number of pain days per year avoided with use of oral morphine (millions)	3.6	0.9	1.9
Incremental cost per person per day of pain avoided (US$)	0.60–1.35	0.60–1.35	0.60–1.35
Incremental cost per year of pain-free life added (US$)	216–420	216–420	216–420

Sources: Income and demographic data, World Bank 2003; cancer deaths, Ferlay and others 2001; AIDS deaths, UNAIDS and WHO 2002a, 2002b, 2002c; per capita morphine use, INCB 2003; authors' calculations.

about 3 cents per day; prochlorperazine, an antiemetic, about 8 cents per day; and haloperidol, an antipsychotic, about 15 cents per day (Management Sciences for Health 2003). Retail prices after markups would add 20 to 30 percent.

Under the assumptions of this analysis, oral morphine for all dying cancer and AIDS patients would cost between 3 cents and 21 cents per capita per year (table 52.3) in Chile, Romania, and Uganda. The cost per pain day avoided by oral morphine is the same in all three countries, assuming that each country can acquire and dispense morphine equally efficiently.

Cost-Effectiveness

The analysis indicates that the drug costs of oral morphine come to about US$216 to US$420 per year of pain-free life gained in the three sample countries. The next question is whether the pain relief that could be achieved would be worth the cost. We know that patients value pain-free days highly. A day lived with the certainty of experiencing severe pain is of very low value, perhaps even lower than death itself (Furlong and others 2001; Le Gales and others 2002). Bryce and others (2004) find that people are willing to give up several months of healthy life for access to good end-of-life care. Patients in low-income countries place as great or even greater value on pain relief as patients in high-income countries (Cleeland and others 1988; Murray and others 2003).

Costs Not Included in the Analysis

The analysis presented includes only the most basic costs—the costs of oral opioids and associated drugs—that would be incurred in a pain control program. Clearly, there are many other costs, ranging from the costs of services at the individual patient level to the costs of changing drug laws and policies at the national level. The most significant additional costs are discussed below.

Incremental Costs of Care Delivery. In addition to requiring the drugs themselves, implementation of the three-step ladder requires trained individuals to assess and monitor patients. Where health care systems are well developed, the incremental cost of adding oral morphine will be low. If it involved one additional health center visit, the cost per patient would increase by about US$8 in Chile, US$6 in Romania, and US$4 in Uganda, amounting to less than 1 cent per capita in all three countries.

Where primary health care is weak, widespread access to oral opioids depends on the development of new systems, such as community- or hospital-based palliative care networks. Clearly, allocating the full cost of upgrading the health care system, or even the development of new palliative care programs, to oral morphine alone, would be inappropriate.

Other Costs. Security and recordkeeping related to stocking and distributing opioids, required by the Single Convention, entail additional fixed and ongoing costs. Because most hospitals handle injectable opioids (for example, pethidine), these costs would be less for hospital-based programs than for community-based programs.

Professional training and education is required for all personnel involved in the use of opioids for dying patients, in part to overcome fears and in part to ensure proper use. These costs are likely to be highest where the health care system is most deficient.

The costs of changing national policy toward opioids is substantial in terms of cost, time, expertise, and leadership (see, for example, Pain and Policy Studies Group 2003 and 2004 and other annual reports at http://www.medsch.wisc.edu/painpolicy/publicat/annrepts.htm). The time expended is an opportunity cost, but it may be amortized over a long time if the effort succeeds.

Potential Cost Savings. In some circumstances, making oral morphine available through a palliative care system could actually save money—for example, if it enabled some terminally ill patients who would otherwise be admitted to the hospital for pain control to die at home, or if it shortened their period of hospitalization. This outcome is more likely in places with good medical infrastructure, but even in low-income countries, patients in unbearable pain are often brought to hospitals by distressed relatives who are willing go into debt to ease the suffering.

IMPLEMENTATION OF STRATEGIES TO IMPROVE PAIN CONTROL

Providing adequate oral morphine involves medical, political, legal, and societal change. Model programs, such as Hospice Uganda and efforts in India, have demonstrated the feasibility of providing good palliative care, including oral morphine, even for poor rural dwellers. WHO and the INCB have supported these efforts.

WHO Guidance on Palliative Care and Pain Relief

WHO has affirmed the need for palliative care and has defined the elements of model programs in several reports. In 2002, WHO's executive board called for the integration of pain and palliative care into national cancer control programs (box 52.4; WHO 2002). The Joint United Nations Programme on HIV/AIDS and the WHO AIDS Program consider pain and palliative care to be essential and pain management to be integral to AIDS care (Foley, Aulino, and Stjernsward 2003). WHO, in collaboration with the INCB and the WHO

Box 52.4

WHO Pain Relief and Palliative Care Recommendations Based on Resource Level

WHO's recommendations are as follows:

- Countries with low levels of resources should ensure that minimum standards for pain relief and palliative care are progressively adopted at all levels of care throughout the country. Countries also should ensure that patient coverage is high through services provided mainly by home-based care. Home-based care is generally the best way to achieve good-quality care and coverage in countries with strong family support and poor health care infrastructure. However, many patients are cared for in large cancer hospitals, and these institutions should have pain relief and palliative care available to all patients.
- Countries with medium levels of resources should ensure that minimum standards for pain relief and palliative care are progressively adopted at all levels of care and that, nationwide, coverage of patients is increasing through services provided by health care workers and home-based care.
- Countries with high levels of resources should ensure that national pain relief and palliative care guidelines are adopted by all levels of care and that, nationwide, patient coverage is high through a variety of options, including home-based care.

Source: WHO 2002.

Collaborating Center (WHOCC), has developed guidelines for national authorities to self-diagnose their regulatory systems for problems that might lead to a lack of access to needed drugs (WHO 2000). These organizations also sponsor national and international workshops to help national authorities evaluate their policies, develop action plans, implement policy change, and evaluate outcomes. In addition to WHO and the INCB, a number of programs and organizations are making resources and expertise available to assist countries in various ways (box 52.5).

Hospice Uganda. Hospice Uganda began in 1993 with an old Land Rover, a grant to last three months, and a mandate to become Africa's model home-based hospice for dying cancer and AIDS patients (Ramsay 2001). By July 2004, the original Kampala location had served about 4,500 nearby patients. Two additional sites—Mobile Hospice Mbarara and Little Hospice Hoima—had served about 2,500 patients (Merriman 2004). Hospice Uganda's influence has spread across Africa through its reputation and the training programs it runs (Merriman 2004).

At the beginning, morphine was largely unavailable, and the law required that a physician prescribe it. Hospice Uganda's founder, Anne Merriman, convinced the government to amend the law to allow specialist palliative care nurses and clinical officers to prescribe morphine (Merriman 2003). Now, morphine, paid for by the government, is available for dying patients in about 15 of Uganda's 56 districts (Merriman 2003). In 1998, Uganda became the first nation in Africa to list palliative care as an essential clinical service.

The cost of treating a patient in Kampala and Mbarara is about US$7 per week, including one home visit. For patients who come to the hospice, the cost is about US$4 per week (personal communication, A. Merriman, Hospice Uganda, February 2003). Even at those prices, most patients cannot afford even the medicines, which are subsidized by contributions.

India. For decades, the only morphine available in India was injectable and used for postoperative pain. The enactment of a strict, national narcotics law caused morphine use to decline even further, from a high of 573 kilograms in 1985 to 18 kilograms in 1997, among the lowest per capita in the world. During the period of declining use, international efforts to promote pain control and palliative care programs began to reach India. In 1992, pain relief and the availability of morphine were designated priorities in the National Cancer Control Programme (Joranson, Rajagopal, and Gilson 2002; Rajagopal, Joranson, and Gilson 2001; Rajagopal and Venkateswaran 2003).

The Ministry of Health convened national workshops from 1992 to 1994 to ascertain why morphine use continued to decline. The following experience from a referral hospital, recounted by a former narcotics commissioner of India, is instructive:

> the Institute has not been able to procure a single tablet [to] date, primarily due to the stringent state laws and multiplicity of licenses. After a lot of effort, the Institute had been able to obtain the licenses in 1994 and had approached [a manufacturer] for a supply of tablets . . . [but] by the time the tablets

Box 52.5

Selected Resources for Developing National Palliative Care Programs

Resources available to countries include the following:

- The WHOCC for Policy and Communications in Cancer Care at the University of Wisconsin serves as a critical resource for palliative care education and country policy makers interested in assessing their opioid drug regulations and developing strategies for change. Its Web site links to WHO guidelines in several languages and provides articles and reports on efforts to improve national policy and opioid availability in Africa, Asia, Eastern Europe, and Latin America. See http://www.medsch.wisc.edu/painpolicy/.
- The WHOCC publishes *Cancer Pain Release* every quarter. The journal includes topical analysis of current issues in cancer pain management and palliative care and reviews recent international research and educational resources. See http://www.whocancerpain.wisc.edu/.
- The Open Society Institute sponsored workshops in cooperation with WHO's Essential Drug and Cancer units to bring together pain and palliative care experts and drug policy makers from Central and Eastern Europe and the former Soviet Union to develop strategies for implementing regulatory change to improve opioid availability. The Open Society Institute also supports the development of implementation strategies in 12 of these countries. That effort involves experts in pain and palliative care, cancer, and AIDS and representatives from ministries of health and financing and health insurance programs. See http://www.soros.org/initiatives/health/focus_areas/international.
- The *Journal of Pain and Symptom Management* has published three special supplements over the past nine years in association with the International Association for the Study of Pain. The supplements describe countries' efforts to advance opioid availability and palliative care. See http://www.elsevier.com/wps/find/journaldescription.cws_home/505775/description#description.
- The International Observatory on End of Life Care is a clearinghouse on palliative care in resource-poor countries that is aimed particularly at policy makers. The initial focus has been on Eastern and Central Europe, but the intent is to cover all resource-poor countries. See http://www.eolc-observatory.net/global_analysis/index.htm.

Source: Authors.

> could be arranged, the licenses had expired. The doctors at the Institute and the associated pain clinic have stopped prescribing morphine tablets. (Joranson, Rajagopal, and Gilson 2002, 153).

In 1999, the INCB called on the government of India to take measures to make morphine available for medical uses. In 1994, an initiative begun by the WHOCC, the Indian Association of Palliative Care, and the Pain and Palliative Care Society systematically studied the reasons for the lack of morphine. In 1997, the WHOCC developed a proposal to reduce the number of licenses and extend their period of validity, and the following year all state governments were instructed to adopt a model rule based on the proposal. Gradually, rules have begun to change. By 2002, 7 of 28 states or territories had adopted the model rule, but it has been implemented successfully only in Kerala.

The success in Kerala can be attributed to three things: (a) the state government simplified the licensing process and stipulated that for oral morphine to be available from a center, it must have at least one doctor with at least one month of practical experience in palliative care; (b) the national drugs controller exempted palliative care programs from needing a drug license, thereby eliminating the need for a pharmacist; and (c) a palliative care network was established, which consists of about 50 small programs. Statewide, coverage has increased to about 20 percent of those needing palliative care.

RECOMMENDATIONS FOR RESEARCH AND DEVELOPMENT

Policy makers and program implementers need practical tools to improve pain control and palliative care. They need survey instruments, guidance on how to effect policy and legal changes, and palliative care models for resource-poor settings. Many tools exist, but those could be made more accessible through the use of toolkits, distance learning, Web sites, and so on. Each country also should gather information to assess its own capabilities and needs, such as the following:

- In relation to the national level:
  - Study the incidence and prevalence of pain related to major causes of illness and death using methodologies

adapted from developed countries (Breivik, Collett, and Ventafridda forthcoming).

- Survey existing pain and palliative care programs to identify national and local leaders in pain control and palliative care and to catalog national guidelines and standards for acute and chronic pain. For hospice and palliative care services, assess the extent of available care, service delivery models, national and local policies, and professional and public knowledge about pain control and palliative care.
- Assess national and local regulatory barriers to opioid availability using WHO (2000) guidelines and needs assessment protocols (Higginson 1997) to help countries identify the patient-related, physician-related, and institutional issues that impede drug distribution.
- Study costs that affect opioid availability in several countries to document the costs of licensing, obtaining, storing, keeping records for, and dispensing opioid drugs.
- Study the costs of alternative delivery models for pain control medications in LMICs.
- Assess the offsetting savings achievable by reducing hospital days by means of better outpatient access to oral morphine, to document potential savings in representative countries, which might help reduce barriers to access.

- In relation to model programs:
  - Construct an inventory of model programs for pain control and palliative care. Include their infrastructure and personnel needs, their operating costs, and so on, in easy-to-use formats such as toolkits and education and training programs for policy makers and implementers. Regularly add new information from ongoing and new initiatives.
  - Devise additional models, particularly for poor rural communities, for providing palliative care and pain control practically, efficiently, and sustainably.

CONCLUSIONS

Unrelieved acute and chronic pain is a serious public health problem worldwide, and 80 percent of cancer patients and 50 percent of AIDS patients experience severe pain during the last months of life. Relief for these patients is possible only with oral morphine or another opioid, but developing countries face many barriers in this respect. Nevertheless, model pain and palliative care programs have demonstrated the feasibility of providing opioid treatment safely, effectively, and inexpensively in resource-poor settings. To this end, national governments must resolve the legal and regulatory barriers to opioid availability, but they need the expertise and support of the global community to make pain relief a reality.

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