

## Chapter 9

# Cancer Pain Relief

James Cleary, Hellen Gelband, and Judith Wagner



## INTRODUCTION

Despite substantial effort and expenditure, at least one-third of patients diagnosed with cancer in high-income countries (HICs) die of their disease within a few years of diagnosis (National Cancer Institute 2009). In low- and middle-income countries (LMICs), two-thirds succumb, because the cancer types prevalent in LMICs tend to have poor prognoses, most cancers are advanced when diagnosed, and even for curable cancers few people have access to effective cancer treatment. For rich and poor everywhere, cancer can cause pain and severe distress, especially during the last few months of life. Cancer-related pain is not the exclusive domain of those who die of cancer. Even many who are cured of their disease live with the long-term effects of the disease and its treatment; many of them live with pain, as do people with a range of chronic conditions other than cancer.

For the majority of cancer patients in LMICs, the most effective and feasible intervention for pain control is medication. For mild pain, over-the-counter, inexpensive analgesic medicines can provide adequate relief. When these nonopioids no longer relieve pain, then weak opioids, such as codeine, may work. Cancer patients most often experience worsening pain as their cancer progresses; 70–80 percent progress to severe pain, which only strong opioid medicines can relieve.

Other approaches are effective for specific pain indications; the most widely applicable are palliative radiotherapy and surgery. Chemotherapy, neurologic, psychological, and other approaches also can be

effective (see Foley and others 2006 for a comprehensive listing). All but analgesic medications and psychological approaches require access to well-developed health care facilities; these are usually available in large urban areas of middle-income countries (MICs), although not necessarily in sufficient numbers, but they may not exist at all in low-income countries (LICs). For example, many countries have no radiotherapy centers, and many have only one center (International Atomic Energy Agency Directory of Radiotherapy Centres, <http://www-naweb.iaea.org/nahu/dirac/default.asp>). Palliative surgery and palliative radiotherapy are discussed further in chapters 13 and 14, respectively. The focus of this chapter is pain control medication, which can relieve most cancer pain and can be delivered at home, even in remote areas.

Since 1990, the World Health Organization (WHO) and other bodies have offered definitions of palliative care. These definitions differ in specifics but share a common vision of care that emphasizes effective pain relief and a team approach to care throughout the course of the illness (Cleary and Carbone 1997; Foley and Gelband 2001; Morrison and Meier 2011; WHO 1990). The primary goal of palliative care is improving the quality of life of patients and those around them; it is not the prolongation of life or the hastening of death. Access to pain relief has been declared a human right (Brennan, Carr, and Cousins 2007; Gwyther, Brennan, and Harding 2009; International Pain Summit of the International Association for the Study of Pain 2011; Lohman, Schleifer, and Amon 2010).

From a global perspective, the growth of palliative care has been largely limited to HICs, which also rank high on the Human Development Index (HDI). The availability of palliative care—using the availability of opioid medicines as a surrogate—is correlated with a country’s HDI. At the low end, the availability is almost nil, and repeated surveys have shown that this availability changed only marginally between 2006 and 2011 (Gilson and others 2013).

In the previous edition of *Disease Control Priorities in Developing Countries*, Foley and others (2006) documented the global problem of low access to adequate pain relief in LMICs. Since then, a few countries have improved access, but these accomplishments are sporadic; in many countries, the change is negligible. Now, there is both cause for optimism and the view of a long road ahead. Efforts to support leaders in reforming policy and clinical practice in LMICs have grown and provide a basis for improvements (Cherny and others 2013; Cleary, Radbruch, and others 2013).

This chapter describes the current state of pain relief in LMICs, consistent with WHO’s use of opioid consumption as a surrogate for access to palliative care in the Global Monitoring Framework for Noncommunicable Diseases (WHO 2013a). We describe the gaps in pain control access across countries, analyze the barriers to improving its delivery, and describe the costs and benefits that might accrue from removing the barriers.

Evidence summarized in this chapter focuses on the modest costs and substantial benefits of providing pain control, and it supports increased efforts in the short term. Pain control medication and other aspects of palliative care can lead, rather than follow, increased efforts in cancer treatment, relying on interventions that are part of a more advanced cancer control and treatment infrastructure.

## CANCER PATIENTS’ NEED FOR PAIN CONTROL MEDICATION

Patients with cancer usually experience pain at some points during their illness, increasingly toward the end. Mild and moderate pain often can be controlled with commonly available analgesics, such as acetaminophen and ibuprofen, but progressively stronger medications are needed to control cancer pain as the illness progresses and pain becomes more severe. Opioids—such as codeine and morphine—are invariably needed toward the end of life. This progression is embodied in WHO’s Three-Step Analgesic Ladder, developed in 1986 to guide clinicians (WHO 1986). More recently, the American

Pain Society has advocated an approach based on the mechanism of pain together with its severity, but this group also emphasized that all patients with cancer should have access to opioids, as needed (Miaskowski and others 2005).

How prevalent is the need for pain relief among cancer patients in LMICs? Cancer deaths are rising throughout the world as progress is made against infectious diseases and as the world’s population ages. In 2012, 5.3 million people died of cancer in LMICs, compared with 2.9 million in HICs. In Sub-Saharan Africa, 715,000 new cases and 542,000 cancer deaths occurred in 2008; these numbers are projected to nearly double by 2030 due to population growth and aging (Ferlay and others 2010). The consensus among researchers is that 60–90 percent of patients with advanced cancer experience moderate to severe pain (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 the progression of the disease.

Foley and others (2006) estimated that about 80 percent of people dying of cancer would experience moderate or severe pain that requires opioid medication for relief for an average of 90 days before death. This estimate amounts to 425 million days of cancer pain that could be relieved by opioids in LMICs each year currently.

## STATUS OF PAIN CONTROL IN LMICs

In an ideal world, palliative care and pain control would be one component of a cancer care system, but in nearly all LICs and for the rural poor in many MICs, palliative care—if it exists at all—is more likely to be independent of cancer services, and patients receive little or no primary cancer treatment. Unfortunately, despite the inclusion of morphine and codeine on WHO’s essential medicines list (WHO 2013b), the programs to deliver them are likely to be undeveloped, and patients go without relief.

In 2006, 66 percent of the world’s population lived in countries that had virtually no consumption of opioids, 10 percent in countries with very low consumption, 3 percent in countries with low consumption, and 4 percent in countries with moderate consumption (Seya and others 2011). Only 7.5 percent of the world’s population lived in countries with consumption levels defined as adequate. The level of adequacy of

access for a country was highly correlated with its HDI ( $R^2 = 0.7583$ ) (Seya and others 2011).

To what extent is the need for cancer pain relief met under these circumstances? Even with increases in certain areas, the starting levels are so low that the most recent levels are only a fraction of the per capita use in HICs (figure 9.1).

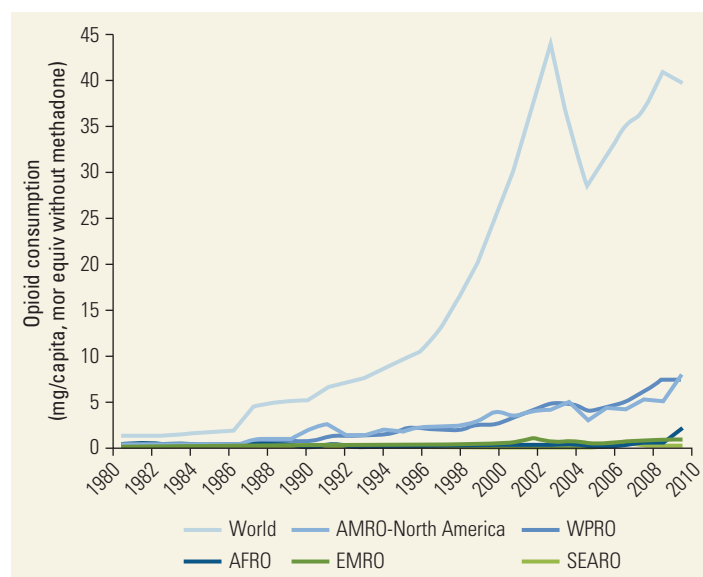
This global assessment is supported by new data from sites in 26 countries representing all World Bank income levels. The International Association for Hospice and Palliative Care (IAHPC) conducted its first round of the Opioid Price Watch (De Lima and others 2014), which reports on availability of opioids, as well as the prices that consumers pay for those medicines. The survey was conducted in the following manner: surveyors visited the pharmacy closest to a public health facility treating patients with life-threatening conditions. If that pharmacy had no opioids in stock, or if the chief pharmacist did not wish to participate, the surveyors visited the next closest pharmacy; this process continued until at least one opioid was found or the surveyor concluded that none would be available anywhere. At least one opioid was available in the first pharmacy sampled in all seven HICs. In three of the eight low-income sites in six countries (including three sites in Tanzania), no opioids were found, even after visiting an average of 4.5 pharmacies; where they were found, many fewer kinds were available than in HICs. In three of the sample countries—Moldova, Nepal, and Sudan—opioids for outpatients were available only from hospital pharmacies with permission to dispense them, limiting access geographically. No information was available on consumption in Moldova or Sudan, and very low consumption was reported per capita in Nepal, suggesting that most cancer patients have no access.

## AVAILABILITY OF BROADLY DEFINED PALLIATIVE CARE SERVICES

The level of palliative care services available to cancer patients was assessed in 2007 by the International Observatory of End of Life Care (Clark and others 2007) and again in 2011 (Lynch, Connor, and Clark 2013). Four categories were defined in 2007, and two subcategories were added in 2011 (designated 3b and 4b, following):

1. No known hospice-palliative care activity
2. Capacity-building activity
- 3a. Isolated palliative care provision
- 3b. Generalized palliative care provision

**Figure 9.1** Comparison of Opioid Consumption in Morphine Equivalents without Methadone (mg per capita)



Source: Cleary, Radbruch, and others 2013.

Note: AFRO = Africa; AMRO-North America = Latin America and Caribbean (America not including North America); EMRO = Middle East (Eastern Mediterranean); SEARO = Southeast Asia; WPRO = Western Pacific.

- 4a. Hospice-palliative care services at a stage of preliminary integration into mainstream service provision
- 4b. Hospice-palliative care services at a stage of advanced integration into mainstream service provision.

Palliative care was in stage 4a or 4b primarily in HICs, with only a handful of LMICs (mainly MICs) in the highest category. In 2011, most countries still had no services, were in a capacity-building mode, or had only isolated services.

## BARRIERS TO PAIN CONTROL IN LMICs

The near-total lack of access to opioid drugs for pain relief in most LICs and many MICs is best understood by examining the barriers to their supply (Cherny and others 2013; Foley and others 2006; Sloan and Gelband 2007). In HICs, modern palliative care, including access to opioid medicines and other methods of pain control, has often developed as an adjunct to cancer care programs. In LICs and many MICs, the same pattern has been difficult to follow because care programs simply do not exist in most places. However, cancer control programs are not the only things that

are absent, sparse, or overstretched. Medical and pharmacy resources are lacking in numbers and quality; medicines are costly and are most often paid for out of pocket. Patients in some places are reluctant to use addictive drugs, even in the last stages of illness, and clinicians who have received little training in appropriate prescribing for cancer patients may reinforce this reluctance.

The greatest and most widespread barrier, however—by far—comes from national regulations to control the nonmedical use of narcotics. These regulations make it difficult or impossible for clinicians to prescribe and patients to obtain opioids for relief of cancer pain. These regulations have been put in place in response to the Single Convention on Narcotic Drugs of 1961 (INCB 1961) and amended by the 1972 Protocol. The Single Convention is an international treaty to ensure the availability of opioids for medical and scientific needs while preventing the illicit production of, trafficking in, and nonmedical use of narcotic drugs. The Convention established the International Narcotics Control Board (INCB) in 1968 as an independent, quasi-judicial organization to implement the Single Convention.

The Single Convention requires that all governments, even nonsignatories, estimate the amounts of opioids needed for medical and scientific purposes and report annually on imports, exports, and consumption. It sets out the following principles on which countries can base 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.
- Security and records are required.

Despite the Convention's recognition of the need for opioid use in pain control—and the demonstration by organizations such as Hospice Africa Uganda that the needs of patients can be met even in remote areas while respecting these limits—the concern over illegal narcotics has tipped the scale against the legitimate medical needs of patients. Many countries have established regulations that go well beyond those required by the Convention. Overzealous drug controllers and poorly considered laws and regulations to restrict the diversion of medicinal opioids into illicit markets profoundly interfere with the medical

availability of opioids for the relief of pain. Often, the logistics of pain treatment with opioids is so burdensome or complex for physicians, nurses, and pharmacists that they assume it is an impossible task and do not pursue it. This problem has been recognized since the 1980s by INCB, WHO, the Council of Europe, and Human Rights Watch (Cherny and others 2010).

In 2000, WHO, in collaboration with INCB, developed guidelines for national authorities to scrutinize their regulatory systems for barriers that could impede access (WHO 2000). The movement to diagnose barriers to access has led to several exemplary national reforms. It appears that the very act of diagnosing regulatory impediments to opioids for cancer pain is a strong first step toward reform.

The international organizations that have collaborated in the Global Opioid Policy Initiative (GOPI)<sup>1</sup> have published a detailed country-specific analysis in five regions of the world of the availability and regulatory restrictions on seven opioid analgesic formulations (Cleary, De Lima, and others 2013; Cleary, Powell, and others 2013; Cleary, Radbruch, and others 2013):

- Codeine
- Immediate-release morphine (liquid or tablet)
- Controlled-release oral morphine
- Injectable morphine
- Oxycodone
- Transdermal fentanyl
- Immediate-release methadone

IAHPC deems these agents essential for treatment of pain in palliative care (De Lima and Doyle 2007).

Respondents commonly reported that these opioids were included in national formularies. The reality, however, was substantial variation in true availability and many regulatory barriers to access.

Although the picture we present is lack of progress on a broad scale, we can point to positive developments that have improved the availability or delivery of opioid medicines in particular situations (Gilson and others 2013). Cost has been reduced by the domestic manufacture of morphine tablets or solutions in Ethiopia (2010), Jordan (2004), and Vietnam (2009). In Kenya (2010), a tax on morphine powder was eliminated. In Ethiopia, India, Kenya, and Vietnam, providers and policy makers have been educated about the use of and need for opioids.

National cancer policies or palliative care policies have been created in a number of countries, laying the groundwork for greater opioid availability. This has

been the case in Ethiopia (2004), Kenya (2011), Nepal (2009), and Rwanda (2010). Jamaica took steps in 2010 and 2011 to clarify and facilitate opioid distribution through improved regulation. In Uganda (2004), the National Drug Policy and Authority statute was amended to allow specially trained palliative care nurses and clinical officers to prescribe morphine, greatly expanding the pool of providers and thus the population with access.

In Georgia (2008), Mongolia (2004), and Vietnam (2008), the number of days allowed for an opioid prescription was increased; in some cases, the eligible patient population was expanded, for example, from only patients with the most advanced cancers to those with certain types of acute and chronic pain.

## ECONOMICS OF PALLIATIVE CARE IN LMICs

We consider economics from two perspectives: that of the health care system and that of the patients. In countries with comprehensive, publicly funded health care, the governments pay for all or most of the services and commodities needed for palliative care. The patients pay either nothing or a predetermined copay.

In settings in which the public sector does not yet provide or subsidize the cost of services, patients may be responsible for all costs. The costs may be mainly market-driven, but they also may include taxes, tariffs, and other government add-ons. In the case of palliative care, the cost of pain control medications is most important. Patients everywhere inevitably bear other costs, including transportation and the opportunity costs of family caregivers who miss work. How high a barrier these costs impose varies with the economic situation of the families and the support available.

### Health System Perspective

Evaluating the costs and effectiveness of palliative care in LMICs presents challenges of the most basic kind. No single model of palliative care delivery can be implemented across all countries; each country presents with a unique constellation of health care resources and challenges.

Studies comparing the costs of organized palliative care programs for patients with cancer with care delivered in the absence of such programs are limited to HICs, where conventional cancer care is already well organized. Researchers reviewing such studies have concluded that organized palliative care tends to save health

care costs, compared with usual cancer care, because it lowers hospitalization rates for patients who are terminally ill (Simoens and others 2010). No specific model of palliative care appears to be superior to any other (García-Pérez and others 2009).

An important difference exists in the availability of pain relief in HICs and LMICs, however. Even when palliative care programs do not exist in HICs, medications for pain relief are usually available to patients with cancer through conventional medical care. Patients in LMICs are often unable to obtain such medications in any health care setting. Yet, it is telling that even when pain medications are readily available through conventional cancer care, organized programs for palliative care can enhance the effectiveness of pain control and lower the costs to the medical care system. Health care providers who focus on and are trained in cancer pain relief can reduce health care costs, at least in HICs, and improve the quality of life for patients and their caregivers (Amery and others 2009).

Most patients in LICs and many in MICs do not routinely receive care for cancer in hospitals; many receive no cancer-specific care at all. Where this is the case, improving access to pain relief at the end of life may increase health care costs, because adding care to a baseline of little or no care clearly involves new costs. For the minority of cancer patients who receive end-of-life care in hospitals, improving the availability of pain medicine through dismantling regulatory barriers, educating professionals, and integrating palliative care programs may reduce health care costs, as such measures have done in HICs.

A useful first step in assessing the cost of palliative care to a health system is to assess the cost of the most basic oral opioid medicine—oral morphine. Foley and colleagues estimated the cost of oral morphine, and medicines to treat side effects, sufficient for pain relief in the last three months of life in three countries—Chile, Romania, and Uganda—at between US\$0.48 and US\$0.98 per day (US\$ 2004) (Foley and others 2006).

In the United States, the average community pharmacy's acquisition cost of immediate-release oral morphine tablets sufficient for three days at 60 mcg per day was US\$1.20 in 2014. More sophisticated dosing forms may cost more to manufacture; new, patented formulations include in their price a premium for intellectual property. A fentanyl patch, for example, compares at US\$4.09 for similar pain relief.<sup>2</sup> Costs vary widely by country, depending on such factors as whether medicines can be produced within the country or must be imported, whether they face

import duties, and the nature of the existing medicine distribution system. An unfortunate circumstance is that the factors that make opioids more expensive tend to be prevalent in LMICs.

In some cases, making more effective pain relief medications available to patients with cancer by removing regulatory barriers would involve no costs other than the cost of the medicine itself. Where oral morphine is already available and affordable, for example, the additional cost of providing other medicines deemed essential for palliative care by IAHPC<sup>3</sup> would be limited largely to the drug costs alone, since the care delivery and narcotics control mechanisms would already be in place. The training for professional staff in the appropriate use of palliative medicines would be an ongoing cost, but that cost would be spread across the population of patients with cancer who are served.

In areas with no effective access to any opioids for these patients, getting the most appropriate medicine to patients is likely to involve additional clinic or home visits with trained personnel, as well as new controls to secure the medicines from theft or abuse.

Since 1993, Hospice Africa Uganda's (HAU) model program has offered palliative care to patients with cancer, AIDS, and, increasingly, other (mainly non-communicable) conditions. Most patients are seen at home, but HAU also provides hospice care at inpatient facilities (HAU 2013). The service is nurse-led, with physician backup. It includes basic needs support, including food, clothing, blankets, and transport costs; pain and symptom control, including morphine; and other support services. HAU estimated that the cost of adding a children's palliative care program at a hospital for children and at HAU's clinic was approximately US\$75 (US\$ 2007) per child per year. About one-third of that cost was for medicines and pharmacy consumables (Amery and others 2009).

### Patient Perspective

For patients, the most serious problem is that opioids are not available at any price, even if prescribed. Where they are available, price is the next consideration, but reliable information on the price of pain medicines to consumers has been lacking in LMICs. This deficit was the impetus for IAHPC to begin the Opioid Price Watch, an availability and price survey in a sample of 26 low-, lower-middle-, and upper-middle-income countries and HICs (De Lima and others 2014). The endpoints were the availability and price of opioids to the consumer on a single day in each site.

The survey included five opioids (13 formulations), including those on WHO's List of Essential Medicines

(17th edition, WHO 2011) and additional medicines on the IAHPC list of essential palliative care medicines:

- Fentanyl: transdermal patch
- Hydromorphone: injectable, oral liquid, oral solid immediate release, oral solid sustained release
- Methadone: oral liquid, oral solid
- Morphine: injectable, oral liquid, oral solid
- Oxycodone: oral solid immediate release, oral solid sustained release

The price of opioids, when available at all, was highest, in absolute terms, in the poorest countries, except in certain LMICs where they are free to patients; however, these are countries with extremely low consumption, meaning effectively no availability. In the Opioid Price Watch sample, these no-cost but no-availability countries were Nepal (LIC), Sudan (LMIC), and Romania (upper-middle income).

The least expensive drug globally, according to the international buyer reference price, was the immediate-release morphine oral solid; this was not the least expensive formulation (standardized to a 30-day average dose) in many countries. Fentanyl patches were less expensive in China (Chengdu), Germany, Guatemala, India, the Islamic Republic of Iran, Norway, Poland, Spain, the Philippines, and the United Kingdom, suggesting that these governments subsidize at least some of these medicines and do so differentially.

## CONCLUSIONS

There is no palliative care without pain control. The benefits of opioid medicines for pain relief to patients with cancer and their families, regardless of their whereabouts, are real and universally observable. These benefits have been known for decades, yet the vast majority of those dying in pain cannot get these medicines, even though the basic forms are inexpensive, oral, and relatively easy to administer at home. The movement to declare pain relief a human right reflects the recognition that its benefits extend to the core of human dignity. The question becomes not whether pain relief with opioids is worth its cost, but what steps will most quickly and efficiently facilitate access to these medications for those who need them, even in the absence of organized cancer control efforts.

It has taken the inspired efforts of pioneers to build palliative care capacity in LMICs, mainly in the private faith and philanthropic sectors, but involving, as it must, government. According to the GOPI report, many international and regional organizations are

focusing on palliative care, with efforts to find, train, and support the leaders in each country or area. The investment in leadership required to reform national and regional policies is a real cost that must be supported. The next steps identified by GOPI (Cleary, Radbruch, and others 2013), which they refer to as the “cornerstone trinity,” are medication availability, education, and policy reform. The costs of policy measures are front-loaded; once policies supporting the widespread availability of pain medications to patients with cancer are in place, they will need only routine monitoring.

These conclusions are robust even in the absence of large numbers of studies and supporting data about the extent of palliative care available in LMICs. The evidence supporting the effectiveness of pain control medicines is strong and applicable worldwide, but validation in LMICs would provide support to expanded efforts. Studies detailing the lack of services, the personal consequences of dying in pain, and the increasing burden of deaths from cancer and other noncommunicable diseases will help to persuade policy makers and funders of the importance of palliative care.

It is appropriate to note that progress has been made in the past few years, but the main message remains that very few of the increasing numbers of people dying from cancer in LMICs can expect to die without debilitating pain. Yet the interventions needed could be made available affordably everywhere, in a relatively short time, if given high enough priority and modest resources.

## NOTES

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries: US\$1,045 or less
- Middle-income countries:
  - Lower-middle-income: US\$1,046–US\$4,125
  - Upper-middle-income: US\$4,126–US\$12,745
- High-income countries: US\$12,746 or more

1. African Organisation for Research and Training in Cancer, African Palliative Care Association, Asia Pacific Hospice Palliative Care Network, Chinese Society of Clinical Oncology, Foundation Akbaraly, Madagascar, Help the Hospices, Indian Association of Palliative Care, International Association for Hospice & Palliative Care, Japanese Society of Medical Oncology, Latin American and Caribbean Society of Medical Oncology, Latin American Association for Palliative Care, Malaysian Oncology Society, Middle East Cancer

Consortium, Multinational Association of Supportive Care in Cancer, Myanmar Oncology Society, Open Society Foundations, Worldwide Palliative Care Alliance.

2. Sources: Prices obtained from the April 9, 2014, Survey of Drug Acquisition Costs Paid by Retail Community Pharmacies, <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Survey-of-Retail-Prices.html>. Equivalent daily doses are based on data provided by the Ventura County Health Care Agency, [http://www.vchca.org/docs/hospitals/fentanyl-patch-protocol-\(1\).pdf?sfvrsn=0](http://www.vchca.org/docs/hospitals/fentanyl-patch-protocol-(1).pdf?sfvrsn=0).
3. <http://hospicecare.com/resources/palliative-care-essentials/iahpc-essential-medicines-for-palliative-care>.

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