Medicine and Society

Opioid: Plenitude versus pittance

BIDHU KALYAN MOHANTI

ABSTRACT

The opioid crisis in the USA and in other developed countries can potentially affect low- and middle-income countries (LMICs). The licit medical use of opioids has two sides. The USA and high-income countries maintain abundant supply for medical prescription. Between 1990 and 2010, the use of opioids for cancer pain relief was overtaken by a dramatic rise in the opioid prescriptions for non-cancer acute or chronic pain. The surge led to the opioid epidemic, recognized as social catastrophe in the USA, Canada and in some countries in Europe. From 2016, the medical community, health policy regulators and law-makers have taken actions to tackle this opioid crisis. On the other side, formulary deficiency and low opioid availability exists for three-fourths of the global population living in LMICs. Physicians and nurses in Asia and Africa engaged in cancer pain relief and palliative care face a constant paucity of opioids. Millions of patients in LMICs, suffering from life-modifying cancer pain, do not have access to morphine and other essential opioids, due to restrictive opioid policies. Attention will be needed to improve opioid availability in large parts of the world, even though the opioid crisis has led to control the licit medical use in the USA.

Natl Med J India 2022;35:303–7

> 'It is a shame that we possess such insufficient knowledge concerning the character of pain—those symptoms which represent the essential part of all bodily suffering of man.'
>
> ALFRED GOLDSCHEIDER, 1894

INTRODUCTION

'Something isn't quite right.' This is most often an expression which should draw medical attention to the individual's pain experiences.[1] Pain is considered the oldest and most recognized of all symptom burdens associated with both acute and chronic diseases. Pain intensity can vary from mild to severe, and different analgesics are prescribed according to different pain levels. Human suffering is conspicuous when the pain intensity is moderate-to-severe and is chronic in nature.

The history of analgesia in medical practice records the use of poppy (*Papaver somniferum*) and its derivatives in different forms since 1500 BC. The medicinal use of poppy juice gained acceptance in Europe, during the middle ages. Many influential European doctors prescribed it for pain relief and observed both soporific and euphoric effects. Towards the second-half of the 17th century, *laudanum*, a cocktail of opium mixed with sherry was introduced by Thomas Sydenham, an English physician.[2] Between the 18th and 19th centuries, India became the largest producer and exporter of poppy latex.[3] Worldwide, the use of opioids, with or without medical advice, has witnessed an unabating rise in the past 400 years.

In 1986, a structured approach to cancer pain relief was designed as the 'analgesic ladder' by the WHO.[4] Over the next 15 years, the medical community adopted this ladder to treat pain in most non-cancer conditions and strong opioids in step-3 of the WHO ladder became the cornerstone for management of chronic pain.

Yet, like Janus, the two-faced Roman god, opioids exhibit high benefits and hazardous consequences for the patients.[5] Nevertheless, medical practitioners prescribe these drugs as the panacea for all types of pain and often ignore the scientific basis of the analgesic ladder, monitoring and early warning signals. In the past 10 years, long-term prescriptions for medical use and the large quantities of illicit supply are two factors that have created an epidemic of opioid-related deaths, emergency visits and adverse health issues as reported in the medical literature and public media, mainly emanating from the USA and Canada.[6]

One BBC news feature on 26 March 2019 with the headline, 'Sackler-owned Purdue pharma settles opioid lawsuit for $2790 million'[7] brought society face to face with the opioid crisis. This has led to stricter guidelines,[8] punitive actions and a political urgency for control of opioid use through policies in the USA.

On the other side, in most countries in Asia and Africa, there is widespread unrelieved pain experienced by millions due to neglect and lack of recognition within the health system.[9] The WHO's access to controlled medications programme, in consultation with the International Narcotics Control Board, has identified that medical use of opioids is dismally low or non-existent in low- and middle-income countries (LMICs).[10] Despite advances in cancer management, the provision of palliative care in these two continents, with nearly 5.9 billion out of 7.7 billion inhabitants globally (76% of world population), continues to be highly inconsistent.

The return of opiophobia, as a possible consequence of the epidemic in the USA, can influence health policy-makers and law-enforcing agencies in Asia and Africa to further restrict the medical use of opioids for cancer and chronic pain management.

I discuss the two sides of the licit medical use of opioids, not necessarily as the USA and Canada versus Asia and Africa, to reduce the formulary deficiency and improve opioid prescription for nearly three-fourths of the global population.

KIMS Cancer Centre, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar 751024, Odisha, India; *drbkmohanti@gmail.com*

[**To cite:** Mohanti BK. Opioid: Plenitude versus pittance. *Natl Med J India* 2022;**35:**303–7.]

PART A

The genesis

The scourge of opioid addiction, in the 21st century, has impacted every sociodemographic community in the USA leading to severe healthcare and societal burden of epidemic proportions with an economic cost of over US$ 500 billion per year.[11] Opioid-related deaths have increased every year for the past two decades, resulting in a drug overdose epidemic that killed more than 64 000 Americans in 2017.

The historical context of the present menace could be traced back to the 1970s and 1980s. A few influential studies and reports, published by palliative care and pain specialists, articulated the perception that the use of morphine and its derivatives for pain relief were not addictive. Hence, the following became the guiding policies for health professionals.[12]

1. Chronic pain, both malignant and non-malignant in origin, and certain forms of severe acute pain can be relieved by opioids only.
2. Badly under-treated pain can cause high levels of emotional and physical stress.
3. Long-term use of opioids carries a low-risk of addiction, overuse or misuse.

In 1995, the American Pain Society (APS) introduced a campaign entitled 'Pain is the fifth vital sign'. This urged a more aggressive use of opioids, and was included in the subsequent consensus statement that endorsed opioid prescription for persistent pain unrelated to cancer.[13]

The medical world is known to show an assembly approach towards a new drug, biomedical device, or therapeutic intervention until the negative and harmful effects are substantially proven. The widespread enthusiasm to use COX-2 inhibitors, as the magic non-steroidal anti-inflammatory drug (NSAID) and the subsequent realization of adverse effects, is a classic recent example.[14]

From the early 1980s till the beginning of the 21st century, the pro-opioid cultural and regulatory approvals created a simple message: Pain must be treated adequately with opioids, and without the fear of iatrogenic addiction.[15] Thus, assertive recommendations paved the way for pain management as a pillar of human rights and urged the doctors, hospitals and health system providers in the USA and Canada to refrain from withholding opioid prescriptions.[2,7,12] Any repudiation or evidence showing the harms of opioid use were dismissed, in good faith, towards a humanitarian cause.

The foundation shaken

The appropriate opioid use at the end of life and in advanced cancer continues to remain invaluable.[8,10,12] However, since 2002, it has been reported that the most prescribed drug in the USA is an opioid: Hydrocodone in combination with acetaminophen (paracetamol). More than 200 million such prescriptions were signed and dispensed annually. The rise in opioid prescriptions is attributable to their increased long-term use for chronic nociceptive pain not related to cancer in spite of limited or no evidence of effectiveness.[6,7,12,13] Osteoarthritis, low back pain, knee/hip replacement pain, post-surgery and/or, poly-trauma pain, etc. are some of the conditions for which the evidence of effectiveness and the safety of long-term opioid use is weak or non-existent. Studies have identified substantial risk, as high as 50%, of opioid misuse or iatrogenic addiction among patients who are prescribed opioids for non-cancer pain relief.[15]

Table I. Pain intensity-based opioid prescription

Pain intensity	Opioids prescribed globally
Severe	Morphine, pethidine, methadone, hydromorphone, fentanyl
Moderate-to-severe	Buprenorphine, oxycodone
Mild-to-moderate	Codeine, hydrocodeine, dextroprpoxyphene

The understanding of the pathophysiology of pain, for cancer and non-cancer diseases, is fairly recent and the drug measures for pain relief are limited.[2,6,8,12] The biological and physiological components of pain demand judicious medical practice. In terms of their analgesic action, opioids are broadly classified as shown in Table I.

Unfortunately, adherence to such a distinction in analgesic prescription practice has remained a challenge. For example, transdermal opioids, fentanyl and buprenorphine, are frequently used for both malignant and non-malignant chronic pain. Fentanyl is 100 times more potent than morphine. The medical use of transdermal opioids requires a combination of factors to be weighed carefully, such as equivalence of morphine dose, pharmacokinetics and suitable indications.[5,6,15]

How has the licit opioid prescription in the USA evolved into an epidemic?[16] Pain management has created a complex new regime, attributable to three factors: (i) enthusiastic prescription of opioids; (ii) overdrive from the pharmaceutical industry; and (iii) transition from the licit market to illicit drug peddling in society.[6,7,12,15] Opioids constitute an important class of neurotransmitters that are involved in pain control, and are well known to enhance pleasure and addiction.[2,5,6] As illicit psychoactive drugs, fentanyl and heroin its precursor, account for a huge trade through traffickers and dark web for recreational use and/or abuse.[6,15]

It is universally accepted that a profit motive is the underlying driver of all business activities. Much before black tar heroin and Purdue Pharma's miracle drug oxycontin; the British rulers throughout the 19th century, under the sanctimonious argument of free trade, had pushed opium cultivation in India and its trade between India and China. Amitav Ghosh, the author of *Sea of poppies*, in his well-researched and nuanced depiction, brings out the trade–war tragedy, 'Does it not trouble you, Mr Burnham, to invoke God in the service of opium?' Ghosh's narrative may be tantamount to historical fiction surrounding the system of colonization, yet the gains of the opium trade were at the cost of the lives of millions.[3] A similar template was used by Purdue Pharma and the larger pharmaceutical industry to push physicians to address the 'fifth vital sign' and to actuate a pain-free society.[7,12,16]

Facing the crisis

The SUPPORT for Patients and Communities Act, 2018 was enacted as a federal law, in a timely need for society.[17] This Act is specifically aimed at US citizens: (i) to address substance use disorders; (ii) to promote opioid recovery; and (iii) to extend treatment provisions for patients and communities. Earlier in 2016, the Centers for Disease Control and Prevention (CDC) issued, 'CDC Guideline for Prescribing Opioids for Chronic Pain-United States, 2016', aimed at physicians and medical establishments treating pain conditions for more than 3 months and on long term.[8]

Since 2016, the opioid crisis is a major issue within the health systems, mainly in the USA and spilling over to Canada and Europe. The US millennials are dying at high rates leading to a decline in the country's life expectancy curve. The death rate for the age group of 15–24 years rose by 19.75% from 2006 to 2015. The explanation correlates with opioid overdose deaths among the young.[18]

Health researchers are identifying more harms than benefits of prolonged opioid therapy, both for non-cancer as well as for cancer pain.[19,20] Pain relief or comfort from opioid therapy does not necessarily lead to improvements in other aspects of health. On the contrary, adverse effects can lead to significant physical deterioration and unintended respiratory depression, and early death can occur when opioid therapy is poorly monitored.[5,6,8,12,13,16] Long-term prescription of strong opioids and the subsequent surge in seekers from the illicit routes are well documented in the USA.[8,12,15,18]

According to the International Narcotics Control Board (INCB) Report, 2018, one can find large variations in the types of opioids that are used in different countries. For example, of the five countries (USA, Canada, Germany, Denmark, Austria) with the highest prescription rates, German physicians are more likely to prescribe fentanyl, while hydrocodone is widely used in the USA but barely prescribed elsewhere.[21] Till 2014, persons with hydrocodone prescriptions could get refilled easily at the local pharmacy as it was a Schedule III drug. Subsequently, it has been classified as a Schedule II drug with more stringent medical use. There is little clinical justification for hydrocodone in long-term pain relief practice. Similarly, fentanyl preferred as a dermal patch in Germany or abused for pleasure-seeking through the illicit market in the USA, is 50–100 times more potent than oral morphine, with unclear understanding about its dosage and pharmacokinetics.[6]

The APS has endorsed aggressive action by the National Institutes of Health to accelerate scientific solutions to help resolve the nation's opioid crisis, and to fund for research on opioid misuse and pain management. Health professionals are learning not to equate chronic non-cancer pain with cancer pain suitable for an opioid prescription. Moreover, the recommendation for the 'fifth vital sign' has been retracted in 2016, and the APS has amended its advocacy for pain relief in the past few years.[13] Underpinning our knowledge, the existing analgesia prescription may not be always efficacious to completely eliminate pain in all the treated patients.

PART B

Continuing with pain

There exists the other side of our dystopian palliative care world in the continents of Asia and Africa. Every year, nearly 6 million persons die from cancer without sufficient analgesics or often without any treatment of their pain.[9,10] Seventy to eighty per cent of patients diagnosed with cancer in these countries have a survival expectancy of 1 to 2 years. Medically and rightfully, 30%–50% of these patients need opioid prescription for their intractable pain. Historically, global policy-makers have paid little attention or have undertaken insufficient measures towards this huge gap in health system delivery.[22]

Since the advocacy for cancer pain management in 1986 under the WHO's analgesic ladder,[2,4] the persisting under treatment of cancer pain in Asia and Africa is a result of inadequate availability of strong opioids.[9,10,21,22] Several predisposing circumstances are the reasons, namely, (i) excessively restrictive policies and complex procedures that govern the licence for medical use; (ii) limited duration of opioid prescription; (iii) burdensome procedures to report and document opioid prescriptions; and (iv) limited number of physicians and nurses with adequate training and exposure to manage moderate-to-severe pain.[10,22,23]

Pain specialists, palliative care physicians and the public in Asia and Africa have struggled in the past 30 years to improve access for medical use of opioids. The geographical, political, social and cultural contexts have not been easy to negotiate. To protect themselves against the harms of drug dependence, policy-makers and governments in many countries introduced drug control measures, but in doing so adversely impacted the availability and use of controlled medicines for medical use.[9,10] It is estimated that because of the low supply and poor access to palliative care, although 75% of cancer deaths occur in LMICs, <15% of those dying with cancer pain receive an opioid prescription.[9,10,23]

Progress and pittance

The global supply of legal opioids, similar to its Janus disposition,[5] has the two sides of plenitude versus pittance.

Since the introduction of the 'gate control theory of pain' in 1965,[24] steady scientific progress towards better understanding of pain mechanisms, and improved management of pain disabilities have occurred within the health system.[2,15] Cancer-related pain, from time of diagnosis, till the end-of-life is experienced by more than 50% of patients. The alleviation of moderate-to-severe pain improves the quality of life and survival trajectory.[2,4,9] This focus has led the western world to improve the availability of cancer pain medication, opioids in particular.

The 7th World Health Assembly in its resolution WHA 70.12 of 2017 reiterated and urged the Member States, 'to provide pain relief and palliative care in line with resolution WHA 67.19 (2014) on the strengthening of palliative care as a component of comprehensive care throughout the life course'.[25] However, the continued shortfall in the supply of and access to opioids in Asia and Africa proves to be the hurdle in affordable services.[9,10,22,23] The opium poppy plant (*Papaver somniferum*) is the source from which alkaloids such as morphine, thebaine, oripavine and codeine are extracted for manufacturing the medicinal drugs. According to the INCB report,[21] in 2017, India was the leading licit agricultural producer and exporter of raw opium, accounting for 98.4% of global production, with a manufacturing capacity of 380.4 tonnes of morphine. Of the total morphine produced, only 10.8% of the product was sourced for palliative care use. In LMICs, 13.6% of morphine for pain relief was prescribed, which amounted to 1.6% of the total manufacture of morphine globally.[21] Moreover, India does not figure in the top 10 countries as a manufacturer or consumer of licit morphine. Indian farmers hold on to non-remunerative lands, the quality of poppy straw has declined in the past 5 years, and the two government-owned opium and alkaloid factories are in financial distress. These combined factors have led to a situation, in India, of importing 20 000 kg of codeine phosphate. The striding 'Make in India' approach has the unique opportunity to give a qualitative focus to the entire chain of opium cultivation, land allocation and monitoring, support price to farmers, manufacturing of opium alkaloids, and licensing to drug companies for the production of codeine, morphine and other opioids. This will give a big boost to affordable palliative care in India and can support the palliative

care services in Asia and Africa, where India is a major supplier of generic drugs. In addition, this can improve the recommendations from INCB and WHO, because the country-wise use of morphine for cancer pain relief, remains far from optimal in LMICs.[8,9,21–23]

Caution and improvement

The real and potential hazards including dependence, addiction, emergency visits, respiratory depression and deaths related to prescription opioids in the USA and the western world are widely recognized. Health system personnel who prescribe opioids in LMICs should acknowledge the emerging information, 'the well intentioned efforts to treat cancer pain can inadvertently lead to opioid use disorder, even if the patients follow medical direction precisely'.[18]

While prescribing opioids, it was advocated within the WHO cancer pain relief ladder,[4] to monitor and record all adverse effects in a timely manner. However, the different settings of most patients, in LMICs, who are on long-term morphine or other opioid therapy make it impractical for any supervised documentation of toxicities and addiction. Often, the refilling of prescription at the palliative care facility or hospital is done on the statement of family caregivers. This poses several challenges. Unlike awareness in western countries to record and analyse opioid-related adverse drug events (ORADEs), which occur in 10%–15% of patients,[12,15] such reporting is not routine in LMICs. In fact, the literature search of published studies, reports and papers from Asia and Africa lack any substantive findings related to iatrogenic dependence, ORADEs, opioid overdose-related emergency visits or death rates; whereas the safe use of opiates or no evidence of diversion in these regions have been adequately highlighted.[9,23]

The open-ended and liberal long-term prescription of opioids has caused enormous burden on the health system in the USA. In recent years, several predisposing factors for ORADEs are identified, such as elderly age, woman gender, comorbid conditions, habitual alcohol or drug abuse, depression or psychosis, and organ failure. To improve the prescription practice and reduce the harms, these factors should not be ignored.[12,17] Thus, there is a timely need for the medical community in LMICs to learn from the opioid crisis in the USA, mainly the salient cautionary points reported from the long-term opioid therapy for chronic non-cancer pain.[6-8,11-13,15]

The health systems and policy-makers in LMICs should engage with renewed knowledge to increase the establishment and spread of palliative care facilities and pain relief measures.[26]

1. Patients with cancer pain need provision of opioid therapy.
2. Medical units for pain and palliative care should be started for the ease of access to millions of suffering patients.
3. Palliative care facilities for a defined population or geographical region should be considered a quality indicator of the health system.
4. Doctors, nurses and paramedics should be imparted special training on pain management and medical use of opioids; including dosage, duration, refill, adverse effect record; and how or when it can be withdrawn/stopped.
5. Long-term opioid prescription, and cancer survivors receiving opioid therapy for more than 1 year, should form a group for special attention towards documentation and research.

The CDC guidelines,[8] and the subsequent regulatory Act[17] were implemented in recent years to mitigate the serious effects on people's health. With mounting evidences of ORADEs, the cancer pain relief guidelines of 1986[4] have been revised by WHO in 2019. The new recommendation of the WHO recognizes the lack of level-1 evidence, in human subjects, for long-term safety and efficacy of opioid therapy in reducing chronic pain and improving function.[27] Simultaneously, the non-opioid methods and interventions, such as psychological, anaesthetic/neurosurgical and radiotherapy, should be focussed on in clinical trials.

CONCLUSION

The 'art of medicine' demands to respect the science and struggle along the way in pain relief measures; more importantly the licit use of opioid therapy for every section of society. Every year, the affluent American, per capita, consumes opioid derivatives 2000 times higher than an adult from India. The low quantity of medicinal morphine and other opiates consumed in Asia and Africa, despite abundant production of raw materials, is linked to the restrictions and health system deficits in LMICs. Palliative care and cancer pain management improves dramatically when policy changes enable access to essential pain medicines including opioids for these deprived population in the world.

It will be prudent to recognize that the opioid crisis could also spread to LMICs, where physicians can inappropriately start and incorrectly continue long-term opioid therapy. The knowledge, training and skill sets, with adequate safeguards for and reporting of ORADEs, can further improve the confidence of the public and increase the policy accessibility from government agencies. Palliative care in LMICs will need trustful approaches from all stakeholders within the global health system, despite the ongoing opioid crisis in the developed world.

Conflicts of interest. None declared

REFERENCES

1 Chapman CR, Beach WA. Patient-initiated pain expressions: Interactional asymmetries and consequences for cancer care. *Health Commun* 2020;**35:** 1643–55.
2 Meldrum ML. A capsule history of pain management. *JAMA* 2003;**290:**2470–5.
3 Ghosh A. *Sea of poppies*. New York:Farrar, Straus and Giroux; 2008.
4 World Health Organization. Cancer Pain Relief. Geneva:WHO; ý1986. Available at *www.who.int/iris/handle/10665/43944* (accessed on 3 May 2019).
5 Ahlbeck K. Opioids: A two-faced Janus. *Curr Med Res Opin* 2011;**27:**439–48.
6 Helmerhorst GT, Teunis T, Janssen SJ, Ring D. An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada: Is Europe next? *Bone Joint J* 2017;**99-B:**856–64.
7 BBC News Feature. Sackler-owned Purdue Pharma settles opioid lawsuit for $2790m. 26 March 2019.
8 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. *JAMA* 2016;**315:**1624–45.
9 Knaul FM, Farmer PE, Krakauer EL, De Lima L, Bhadelia A, Jiang Kwete X, *et al*. Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: The Lancet Commission Report. *Lancet* 2018;**391:** 1391–454.
10 Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. *J Pain Symptom Manage* 2014;**47:**283–97.
11 The Council of Economic Advisers, Executive Office of the President of the United States. The Underestimated Costs of the Opioid Crisis; 2017. Available at *www.whitehouse.gov/sites/whitehouse.gov/files/images/The Underestimated Cost of the Opioid Crisis.pdf* (accessed on 17 Jun 2019).
12 Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. *Pain Ther* 2018;**7:**13–21.
13 Levy N, Sturgess J, Mills P. "Pain as the fifth vital sign" and dependence on the "numerical pain scale" is being abandoned in the US: Why? *Br J Anaesth* 2018; **120:**435–8.

14 Sanghi S, MacLaughlin EJ, Jewell CW, Chaffer S, Naus PJ, Watson LE, *et al*. Cyclooxygenase-2 inhibitors: A painful lesson. *Cardiovasc Hematol Disord Drug Targets* 2006;**6:**85–100.
15 Beauchamp GA, Winstanley EL, Ryan SA, Lyons MS. Moving beyond misuse and diversion: The urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health* 2014;**104:**2023–9.
16 DeWeerdt S. Tracing the US opioid crisis to its roots. *Nature* 2019;**573:**S10–S12.
17 SUPPORT for Patients and Communities Act; 2018. Available at *https://docs.house.gov/Billsthisweek/20180924/HR6.pdf* (accessed on 11 Jun 2019).
18 Castaneda R. Millennials hit hard by opioids. *US News*; 12 Mar 2018.
19 Novy DM, Nelson DV, Koyyalagunta D, Cata JP, Gupta P, Gupta K. Pain, opioid therapy, and survival: A needed discussion. *Pain* 2020;**161:**496–501.
20 Cohen SP, Hooten WM. Balancing the risks and benefits of opioid therapy: The pill and the pendulum. *Mayo Clin Proc* 2019;**94:**2385–9.
21 Report of the International Narcotics Control Board for 2018. Available at *www.incb.org/.../AnnualReports/AR2018/...Report/Annual_Report_2018_E_.pdf* (accessed on 20 Jun 2019).
22 Prager GW, Braga S, Bystricky B, Qvortrup C, Criscitiello C, Esin E, *et al*. Global cancer control: Responding to the growing burden, rising costs and inequalities in access. *ESMO Open* 2018;**3:**e000285.
23 Thinh DH, Sriraj W, Mansor M, Tan KH, Irawan C, Kurnianda J, *et al*. Analgesic prescription patterns and pain outcomes in Southeast Asia: Findings from the analgesic treatment of cancer pain in Southeast Asia study. *J Glob Oncol* 2018;**4:**1–10.
24 Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965;**150:**971–9.
25 Seventieth World Assembly. WHA 70.12. Cancer Prevention and Control in the Context of an Integrated Approach. Available at *https://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R12-en.pdf* (accessed on 9 Jul 2020).
26 Bhadelia A, De Lima L, Arreola-Ornelas H, Kwete XJ, Rodriguez NM, Knaul FM. Solving the global crisis in access to pain relief: Lessons from country actions. *Am J Public Health* 2019;**109:**58–60.
27 World Health Organization. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. Geneva:WHO; 2018. Available at *www.who.int/ncds/management/palliative-care/cancer-pain-guidelines/en/* (accessed on 16 Mar 2020).