



The challenge of opioids in cancer care: balancing equity, safety, and access

Rebecca A. Rodin¹^, Cardinale B. Smith^{1,2}^

¹Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ²Division of Hematology and Oncology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Correspondence to: Rebecca A. Rodin, MD, MSc. Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029, USA. Email: rebecca.rodin@mssm.edu.

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Pain is a common and devastating symptom for people living with cancer, especially near the end of life, although opioids are highly effective analgesics that are supported as first-line treatment for moderate-to-severe pain in such individuals (1). For this reason, opioids have been classified as essential pain medications by the World Health Organization (WHO) since 1986, including in the most recent 2023 WHO Model List of Essential Medications. That list includes codeine and morphine (alternatively hydromorphone or oxycodone) for pain and transdermal fentanyl and methadone for cancer pain specifically (2). However, pain remains undertreated in a substantial proportion of people with cancer, even in high resource settings (3). There are multiple reasons for such undertreatment, including clinician, patient, and system level barriers. Healthcare clinicians often cite concerns about diversion and misuse, inadequate education about their appropriate use, and regulatory barriers (4). There is also perceived stigma by both patients and providers because of the association of opioids with addiction and their illicit use. Finally, system-level barriers, such as limited opioid availability and regulatory constraints, exacerbate disparities in pain management for individuals with cancer.

Current caution of healthcare clinicians about prescribing opioids is understandable in view of the ongoing opioid overdose epidemic that has killed over half a million Americans since 1999 (5). The risk of addiction and use

disorder was long unrecognized in the general population with chronic non-cancer pain, for whom opioids were aggressively marketed, and, to a lesser extent, in people with cancer (6). This blind spot allowed opioids of various kinds to be oversold and overprescribed, contributing to the paradox of excessive opioids for those who should not have received them and insufficient opioids for those most likely to benefit from them.

Commonly prescribed opioids, such as oxycodone, were responsible for the first wave of rising opioid overdose deaths in the United States (US) starting in the 1990s. This was followed in 2010 by a second wave of heroin overdoses and a third wave in 2013 of synthetic opioid overdoses, particularly illicit fentanyl (*Figure 1*). There have been numerous and varied efforts to mitigate this opioid epidemic in the general population, including litigation (e.g., lawsuits against opioid manufacturers and pharmacies), legislation (e.g., states' prescription drug monitoring programs), health policy (e.g., naloxone distribution initiatives), regulation [e.g., Drug Enforcement Agency (DEA) opioid production limits], and clinical guideline development [e.g., Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain] (7). These efforts have led to a reduction in overdose deaths due to commonly prescribed opioids, which declined by 17% in the general population from 2017 to 2019 (8). However, there is a growing body of evidence that suggests that these initiatives

^ ORCID: Rebecca A. Rodin, 0000-0003-2984-3514; Cardinale B. Smith, 0000-0003-3635-8701.

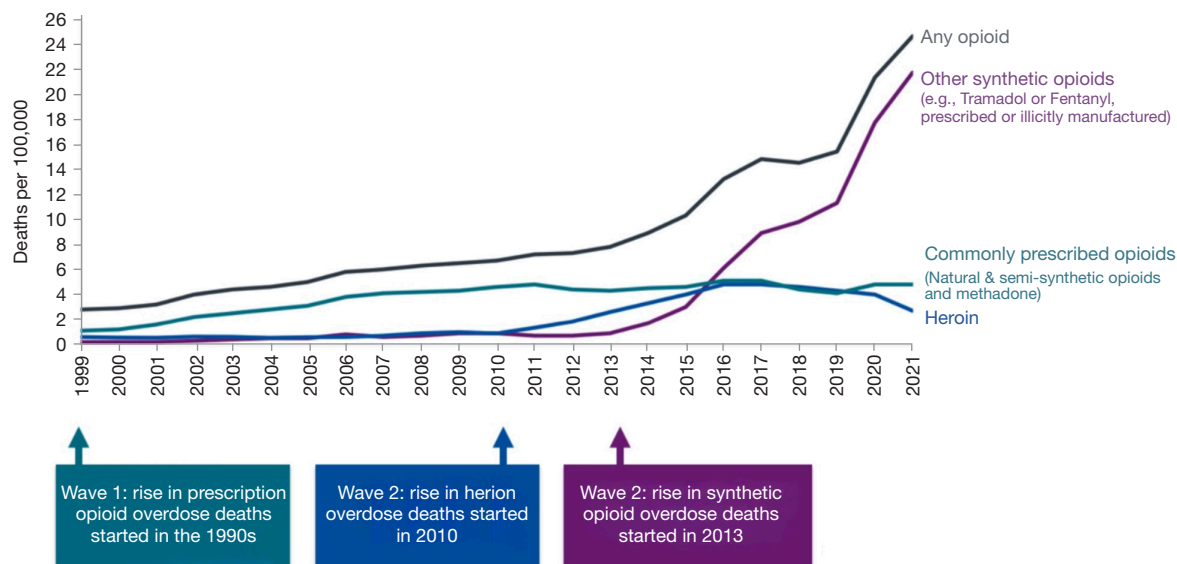


Figure 1 Three waves of the opioid overdose epidemic in the United States, 1999–2021 (source: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention).

have had the unintended effect of hindering access to opioids among those who clinically require them for pain, including people with cancer (9).

Recent data shows that oncologists' prescribing of opioids decreased by 20% in the US from 2013–2017 (10) and that the proportion of people with cancer who received any opioid in the last 3 months of life correspondingly declined from 43% in 2007 to 33% in 2019 (9). This reduction in opioid prescribing has been attributed in part to factors related to patients and prescribers. Barriers to opioid access that were identified by oncologists in a 2021 survey (4) included: (I) reluctance of patients with cancer to accept opioid therapy because of stigma they perceive from clinicians, pharmacists, and broader society; (II) patients' fear of becoming addicted to opioid medication; and (III) misinterpretation of guidelines for safe and effective use of opioids. However, there has been relatively little attention on the multiple and overlapping structural and systems-level barriers to clinically appropriate opioid use, including those operating at the level of public and private payers, pharmacies, manufacturers, and federal agencies (e.g., DEA).

At present, pharmacies across the US are reporting shortages of multiple essential opioid medications. This is consistent with the findings of a recent survey of 2,800 people with pain, 90% of whom reported delays or difficulties in their opioid prescription being filled at a pharmacy, largely due to opioids not being in stock (11). It is also aligned with

reports of the Food and Drug Administration (FDA) and American Society of Health Pharmacists of stock shortages for a range of essential opioids, including hydromorphone, morphine, and fentanyl (12). A major contributor to this supply problem is that the DEA has continued to reduce its annual quota for the manufacturing of opioids for the last several years in order to combat the opioid epidemic (13).

In response to legal settlements that required many of them to pay billions of dollars, many pharmacies have changed their stocking, dispensing, and monitoring practices. Some pharmacies placed specific limits on the dose and duration of opioid prescriptions that can be filled and required prior authorizations for these medications (14). Pharmacy benefit managers were utilized to implement and enforce such efforts and physicians were required to seek exemptions if they wished to bypass these requirements for specific patients (14). Most recently, in the 2021 and 2022 National Opioid Settlements, the nation's largest pharmacy chains (Walgreens, CVS, and Walmart), pharmaceutical distributors (McKesson, Cardinal Health, and AmerisourceBergen), and pharmaceutical manufacturers (Johnson & Johnson, Allergan, and Teva) agreed to pay over \$44 billion combined for their role in the opioid epidemic and implement changes in how they handle and dispense opioids, including setting rigid, undisclosed caps on the amount of opioids that may be distributed, beyond which opioid supply may be abruptly cut off (15). In addition,

opioid manufacturers have either been banned (Johnson & Johnson) or significantly restricted (Teva, Allergan) in marketing and selling opioids. Early reports indicate that these restrictions have resulted in pharmacies struggling to secure opioid supply, physicians spending hours on the phone with pharmacies to bypass restrictions, and patients being unable to fill medically necessary opioid prescriptions, such as for cancer pain (15). Further disruptions to opioid supply and manufacturing may be expected pending a Supreme Court decision (expected within weeks from the time of writing) on the bankruptcy settlement of Purdue Pharma, the maker of OxyContin. However, the effects of such a bankruptcy on opioid supply remain uncertain, as the settlement would involve transferring the company's assets to a new non-profit company, Knoa Pharma, which would continue manufacturing OxyContin and other opioids, with profits utilized for settlement payments, opioid crisis abatement, and overdose rescue medications.

Recent years have seen a surge in the costs of opioid production and distribution, primarily due to the imposition of excise taxes and fees, leading to significant changes in affordability and access. The supply and affordability of opioids, like all production goods, are heavily dependent on the costs of production and distribution, which in turn affect the purchase price. Five states—Delaware, Maine, Minnesota, New York, and Rhode Island—have thus far passed legislation in 2019–2020 imposing such taxes and fees on opioid manufacturing and distribution (16). Three of these states (Maine, New York, Rhode Island) have tax or fee exemptions for opioids used to treat opioid use disorder (e.g., buprenorphine, methadone); none have exemptions for people with cancer or near end of life. Most states have allocated these funds to support measures to combat the opioid epidemic and treat opioid use disorder. However, actual revenues from these taxes and fees are reported to be far lower than expected (e.g., \$30 million in New York, compared to an anticipated \$100 million), because opioid manufacturers and wholesalers have reportedly reduced or ceased their opioid sales altogether (17). This reduction or cessation of production is greatest with lower-cost generic opioids because of their narrower profit margins compared to their brand-name counterparts. The net effect of all of these changes may be to drive up opioid prices directly and diminish the availability of lower-cost generic alternatives. This surge in opioid prices and reduction of generic alternatives could worsen existing disparities in opioid access, disproportionately affecting marginalized communities and individuals who may already struggle to

afford essential pain medications.

Legislation at the federal level may be creating additional difficulties in access to opioids, which may compound those created by state legislation. A national opioid tax was introduced in Congress in 2021 as Senate Bill 1723 which, if passed, would establish a federal excise tax on prescription opioids, with revenues distributed through block-grants to support opioid use disorder treatment (16). Unlike state laws, this federal tax would allow exemptions to apply, not only to opioids used to treat opioid use disorder, but also to those prescribed to people with cancer pain, enrolled in hospice, or with other conditions for which opioids are deemed necessary by the prescriber. However, the process to obtain such exemptions would be cumbersome, with patients receiving either a tax rebate or a discount at the point of purchase (16), potentially placing further limitations on opioid access for these populations.

The multiple barriers to opioid access are concerning for all people with cancer and other conditions for which opioids are medically necessary, but it is particularly so for vulnerable subgroups already at increased risk of pain undertreatment. These include racial and ethnic minoritized individuals and those experiencing socioeconomic deprivation. For example, pharmacies located in predominantly non-White neighborhoods were found to be less likely than those in primarily White neighborhoods to stock a range of essential opioid medications (18). In addition, several US studies and systematic reviews (19) have found that non-White individuals were less likely than White individuals to receive adequate analgesia in the emergency department and in oncology settings. Other studies have found that patients from lower income neighborhoods who present to emergency departments are less likely to receive opioids for equivalent levels of pain compared to those from more affluent areas (20). Although the overdose epidemic has occurred predominantly among non-Hispanic White populations, Black individuals are significantly more likely than White individuals to be required to undergo urine drug screening and to have their opioids discontinued in response to abnormal results (9,21). Furthermore, even in the last 3 months of life, Black and Hispanic patients with cancer were less likely to receive any opioid and more likely to have a lower opioid dose and to undergo urine drug screening compared to White older adults with cancer (9). Such disparities are particularly important to address in the context of cancer, which affects a population that is racially, ethnically, and socioeconomically diverse and geographically dispersed in regions with varying

levels of medical and social support.

The stark racial and ethnic disparities in opioid access underscore the global challenge faced by individuals with cancer, particularly when comparing those from high-income countries to those from low- and middle-income countries, where the greatest disparities in opioid access for people with cancer are observed (22). Low- and middle-income countries comprise most of the global burden of cancer, accounting for 70% of all cancer-related deaths (23). People with cancer residing in these countries are at particularly high risk of cancer-related pain due to the limited treatments, late stage at diagnosis, and high mortality associated with cancer in these countries. However, over 90% of all available opioids are consumed in a small number of high-income countries (Australia, Canada, New Zealand, US, and several European countries), representing 10–15% of the global population. By contrast, roughly 50% of the world's poorest people reside in countries receiving only 1% of all opioids (23). Most countries in Africa, for example, do not have basic opioids (e.g., morphine immediate release) in stock and those that do have a limited supply that is often restricted to major urban centers with multiple regulatory, supply chain, financial, policy, and cultural/perceptual barriers to their availability (24). Regulatory barriers in these settings include the requirement for special authorization for outpatient, inpatient, or hospice prescriptions, special licensing for prescribing physicians, duplicate or particular prescription forms (some countries requiring physicians to purchase these forms), dispensing at hospital-based rather than local pharmacies, and limits on dose and duration (ranging from 2 days in Ghana to 2 weeks in Egypt, Kenya, and Malawi) (23).

The following recommendations may help to improve opioid access for people with cancer and other serious illnesses:

- ❖ Encouraging dialogue among physicians, health systems, and local pharmacies about the prescription opioid needs of their patients to facilitate a more reliable supply. Such dialogue may help pharmacies to order sufficient types and quantities of opioids with reduced risk of overstocking. Independent pharmacies may respond to incentives, such as receiving opioid prescriptions with all other prescriptions for a patient, including those with profit margins higher than opioids.
- ❖ Advocacy and lobbying at state and federal levels to increase the DEA's opioid manufacturing quotas and support policy and legislative initiatives. The latter

may include easing opioid taxes/fees and ensuring that point-of-purchase exemptions exist for people with cancer and other serious illnesses.

- ❖ The development, implementation, and evaluation of clinical guidelines related to opioid prescribing that balance the needs for pain management in people with cancer with the risks of opioid excess. Although the CDC published revised clinical guidelines for prescribing opioids in November 2022 (25), the effects of this revised guideline's implementation on opioid access and sociodemographic disparities for people with cancer require further evaluation and potentially further revisions of the guideline.
- ❖ Educational outreach that incorporates principles of equity should be undertaken for clinicians, pharmacists and community health partners on cancer pain management and the benefits and risks of opioid therapy.
- ❖ Country-specific efforts, particularly in low-resource settings, should be locally championed to address the unique barriers to opioid access in each region. Such efforts may be aided by global partners, collaborators, philanthropists, and organizations such as the WHO.

Conclusions

There are few medications with as much effectiveness as opioids in the treatment of cancer pain and with as many barriers and complexities in ensuring appropriate access to them. The vast overmarketing of opioids for benign conditions over the last three decades have contributed to millions of deaths globally and untold suffering due to addiction. However, the legislation and regulation that are intended to contain the opioid epidemic have had the unintended effect of limiting access to them among individuals with the greatest need, such as those with cancer or at end of life. There are also sociodemographic and geographic disparities in access to opioids for people in high-income countries, such as the US, and the lack of any access to them for most people in the world, who largely reside in low resource settings. No single or simple solution can rectify this complex problem. Rather, multiple clinical, educational, and policy initiatives are needed to address the individual-, system-, and societal-level factors affecting access to opioid analgesia for people with cancer. Such initiatives are most urgent in low resource settings where the burden of cancer is greatest and access to opioids most limited. Across diverse settings, a fine balance is required

to address the twin goals of reducing inappropriate opioid prescribing and improving equitable and safe access to medically necessary opioids, such as for the treatment of moderate-to-severe cancer pain.

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