

Peer Review File

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Reviewer A

Excellent overview of the challenges that end of life and hospice patient face in obtaining opioids, in light of the ongoing opioid epidemic. I also appreciate the inclusion of inequities among low- and middle-income countries globally as well as among minority groups. *The only small change I would make would be adding more specific suggestions and/or recommendations to overcome these challenges and placing these within the body of the commentary, as opposed to a brief mention in the conclusion.*

Reply: In response to the editor's thoughtful feedback, we have incorporated more specific suggestions and recommendations to overcoming the challenges of opioid access. We have included these in the main body of the commentary, as follows (**change in the text: pages 8-10, lines 176-200**).

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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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 World Health Organization.”

Reviewer B

This editorial commentary reasonably covers the latest situation and issues about adequate opioid treatment on cancer pain. This would contribute to trigger disentangling the current difficult situation of opioids for cancer pain management.

Reply: Thank you.

Change in the text: None.

Reviewer C

Critical topic

Reply: Thank you.

Change in the text: None.

Reviewer D

The authors do an excellent job of chronicling the history and subsequent practice and policy changes that have led to current barriers to access of much needed opioid medication among patients with cancer. Importantly, there is a discussion of how these barriers disproportionately affect minorities and people in developing countries. *My only suggestion is that the authors could discuss how lawsuits against pharmaceutical companies (which the authors allude to in the manuscript) could impact or have impacted supply of opioids. Given the recent Supreme Court decision on the bankruptcy plan for Purdue Pharma, such a discussion would be timely and relevant to this paper.*

Reply: We thank Reviewer D for this helpful suggestion. We have added greater detail on the ways in which lawsuits against pharmaceutical manufacturers and distributors have impacted opioid supply (pages 4-5, lines 81-97), as follows:

Change in the text:

“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).”

After hearing oral arguments in December 2023, a Supreme Court decision remains pending on the case for the proposed bankruptcy settlement of Purdue Pharma, with a decision expected in the summer of 2024 (pending at the time of writing). However, a consideration of the potential impact of such a settlement has been added to the manuscript (page 5, lines 98-103), as follows:

“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, Kinoa Pharma, which would continue manufacturing Oxycontin and other opioids, with profits utilized for settlement payments, opioid crisis abatement, and overdose rescue medications.”