

EDITORIAL

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# Extended-release, long-acting opioid self-management patterns may pose safety risks in ambulatory persons with cancer pain

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Persons with cancer are exempt from the recently updated 2022 Centers for Disease Control and Prevention opioid guidelines for pain as well as most state legislation and policy initiatives on prescription opioids [1]. They are also more likely to receive opioid therapy for longer periods of time to manage moderate to severe cancer or cancer treatment-related pain [2]. While the issue of overuse of prescribed opioids by patients has traditionally been a policy and practice concern, studies have found that underuse, rather than overuse, is the main clinical issue in persons with cancer [3]. Variable patterns of opioid use, including underuse of prescribed around-the-clock opioids, may pose important safety concerns. Unfortunately, this issue has received little due attention in cancer pain literature.

The US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy for extended release and long-acting (ER/LA) opioids cautions that these opioids are not intended for as-needed use and should be taken “exactly as prescribed” to avoid potential harms [4]. LA/ER opioids are formulations such as a topical patch, transdermal system, matrix formulation, tablet, or capsule but can also be those with naturally long half-lives such as methadone. The FDA labeling for ER/LA opioids is consistent with around-the-clock dosing as prescribed.

Inconsistent use of ER/LA opioids increases the risk of opioid-induced respiratory depression as well as that of fatal and nonfatal overdose. Specially, long-acting opioid formulations can increase the risk of unintentional overdose when compared with equal morphine milligram equivalents (MME) of short-acting formulations [5].

The FDA also recommends delaying initiation of long-acting opioids until patients develop opioid tolerance, defined as the need for higher doses of opioids to maintain desired analgesic effect (due to desensitization and downregulation of opioid receptors). The FDA defines patients exposed to a minimum of 60 MME for the previous seven consecutive days as opioid tolerant [4].

Despite cautions and concerns linked with inconsistent use and gaps in opioid therapy, several studies have reported significant deviations in adherence to prescribed ER/LA opioids among cancer outpatients due to opioid concerns, opioid stigma, and unmanaged or under-managed side effects, as well as socioeconomic concerns [6, 7]. The role of side effects and SES in adherence patterns particularly affects persons of racial and ethnic minority backgrounds who are at a greater risk for clinician bias in pain treatment [8].

Even among research studies reporting a high percentage of long-acting opioid dose adherence, wide variability and significant deviation rates exist. In one study, although self-reported adherence to long-acting opioids was 85% (*SD*, 21%), more than 1 in 4 patients cancer patients reported an opioid frequency that did not match their prescribed daily frequency [7].

While only one study has characterized patterns of nonuse in terms of gaps between doses, among patients

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who are prescribed long-acting opioids for cancer pain [9], the findings are instructive. We found that about 1 in 3 cancer outpatients had gaps of 7 or more consecutive days between doses taken of prescribed ER/LA opioids [9]. This is notable as gaps of this duration may expose patients to important safety risks, including reduced opioid tolerance.

In fact, when a gap in opioid use occurs over a period of time, the risk of reduction or loss of tolerance is predictably present. By extension, there are corresponding risks associated with reinitiation of the treatment at the previous dose by the patient. The level of the risk depends upon pharmacokinetic properties, interindividual variables such as disease progression, organ impairment, specifically liver and kidney damage, and co-use of other prescribed medications [10].

It is good news that the CDC has corrected its previous course, and persons with cancer (including those who have completed active cancer treatments) are now excluded from the CDC opioids guidelines. However, there is a need for individually tailored counseling on safety of opioid use for outpatients with cancer who are prescribed ER/LA opioids or those receiving long-term opioid therapy. Counseling should address patients' specific concerns around opioid adherence (e.g., opioid stigma, affordability, and SES factors).

From a research perspective, studies of longitudinal opioid use patterns among cancer outpatients remain limited. Only a few published studies have drawn attention to the important issue of ER/LA opioid use patterns among cancer outpatients, and even fewer have described patterns of opioid use over time among those who are prescribed around-the-clock opioids. There remains a need for more critical understanding and monitoring of opioid use patterns among patients with cancer, especially those prescribed highly potent ER/LA opioids. There is also an urgent need for developing individually tailored interventions that address patients' specific concerns around opioid adherence and use, as well as real time or ongoing monitoring of patients' opioid use patterns that can alert clinicians and trigger appropriate clinical interventions to promote patient safety.

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