Gaps in the Use of Long-Acting Opioids Within Intervals of Consecutive Days Among Cancer Outpatients Using Electronic Pill Caps

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Abstract

Objective. This study describes individual cancer patients' nonuse of extended-release or long-acting (ER/LA) opioids, including periods of gap between opioid doses taken. **Design.** Secondary analysis of a three-month observational study of prescribed ER/LA opioids monitored using electronic pill caps. **Setting.** Two outpatient oncology clinics of a large health system in the Mid-Atlantic region. **Participants.** Inclusion was based on self-identified African Americans and whites, at least 18 years old, diagnosed with solid tumors or multiple myeloma. For the current analysis, the additional inclusion criterion was prescription of an oral ER/LA opioid for cancer pain to be taken around the clock. **Methods.** The electronic monitoring period for each study participant was partitioned into intervals of *days between days* with one or more openings (using medication event monitoring systems) representing rates of ER/LA opioid nonuse over consecutive days and over time. **Results.** Of the sample (N = 109), two-thirds of the cancer patients had some nonuse of prescribed ER/LA opioids, with one in four having nonuse during 31.5–87.5% of their electronic-monitoring periods. Nonuse over periods of five or more, six or more, and seven or more consecutive days occurred for 37.6%, 34.9%, and 30.3% of the participants, respectively. **Conclusions.** About one in three ambulatory cancer patients in this study had substantial gaps between days of ER/LA opioid use, potentially resulting in risk of overdose depending upon the prescribed ER/LA opioid type, dose, and length of the time the opioid was stopped and resumed at the previous dose. This phenomenon has received little to no attention in the opioid safety discourse.

Key Words: Long-Acting Opioids; Opioid Adherence; Opioid Tolerance; Cancer Pain; Opioid Self-Management; Opioid Risks

Introduction

Patients with cancer are exempt from most state legislation and policy initiatives on prescribing opioids [1], and major oncology and professional societies overwhelmingly support this exclusion for patients with cancer pain [2–4]. Simultaneously, patients with cancer are more likely to receive opioid therapy for managing moderate to severe cancer or cancer treatment–related pain, and the therapy may continue for months after initial cancer diagnosis [5, 6]. Moreover, with newer treatments and more survivors, many patients continue opioids for years after remission. These clinical and policy realities require a more critical understanding of opioid use among patients with cancer, especially the highly potent extended-release and long-acting (ER/LA) opioids.

The US Food and Drug Administration (FDA) initiated a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids in 2012 with the goal of reducing serious adverse outcomes while maintaining patient access to these opioids to relieve moderate to severe pain [7]. ER/LA opioids should be taken “exactly as prescribed” to avoid potential harms and are not intended for as-needed use [7]. Nevertheless, about 51–79% of cancer outpatients report intentional nonadherence to their prescribed analgesics due to opioid concerns, opioid stigma, or unmanaged or undermanaged side effects, as well as socioeconomic concerns [8–12].

Few published studies have drawn attention to the issue of ER/LA opioid use patterns among cancer outpatients [11, 13, 14], and even fewer have described patterns of opioid use over time among patients with cancer who are prescribed around-the-clock opioids [15, 16]. A recent multimethod study (N = 17) of LA opioid adherence over time among cancer outpatients using an electronic medication monitoring system found that most cancer patients set their own opioid adherence goals and regimens [15]. These findings are consistent with an earlier study (N = 191), also using an electronic medication monitoring system, which identified unique patterns of heterogeneity in analgesic adherence among cancer outpatients over a 12-week period [16].

Most studies of opioid adherence among cancer outpatients have found that underuse, rather than overuse, of opioids is the main clinical issue in this group of patients [10–15, 17]. While the issue of overuse of prescribed opioids has traditionally been a policy and practice concern [18–20], the issue of variable patterns of opioid use, including underuse of prescribed around-the-clock ER/LA opioids may also pose important safety concerns.

Variable use of ER/LA opioids has been found to increase the risk of opioid-induced respiratory depression (OIRD) and both fatal and nonfatal overdose [21]. Long-acting formulations are associated with increased time of exposure and, at baseline, have been found to increase risk of unintentional overdose compared with equal

morphine milligram equivalents of short-acting preparations [22]. Because of this correlation and as a response to the opioid epidemic, the FDA instituted the aforementioned risk evaluation and mitigation strategy (REMS) for long-acting opioids in 2012 [7].

Due to the risks associated with ER/LA opioids, the FDA and CDC suggest that it may be prudent to delay initiation of long-acting opioids until a patient establishes opioid tolerance [7, 20, 23]. Tolerance is a physiological process that occurs when opioid analgesics are administered and is defined as the requirement for escalating doses of opioids to maintain a desired analgesic effect due to desensitization and downregulation of opioid receptors [24, 25]. Once initiated, ER/LA formulations are intended to be taken regularly, and as such, all FDA labeling is consistent with around-the-clock dosing as prescribed.

One measure of tolerance is the morphine milligram equivalent (MME; or morphine equivalent daily dose [MEDD]) prescribed over the prior seven-day period. The FDA defines patients exposed to a minimum of 60 MME per day for the last seven days as opioid tolerant [26]. Patients who do not have established opioid tolerance have been found to be at 37% increased risk of opioid poisoning in the week following initiation of a high-dose (≥ 90 MME) long-acting opioid [23].

Despite the aforementioned concerns associated with underuse, poor adherence, and gaps in therapy, several studies have reported significant deviations in adherence to prescribed ER/LA opioids among cancer outpatients. A sizeable majority (51–79%) of cancer outpatients report using intentional nonadherence to prescribed analgesics due to opioid concerns, opioid stigma, or unmanaged or undermanaged side effects [8–12]. Across these studies, the percentage of “dose adherence” (i.e., % of prescribed ER/LA opioid dose taken) by cancer outpatients (SD) ranged from 60% (28.5%) [14] to 94% (range = 34–100%) [15]. Even in studies that report a high percentage of LA opioid dose adherence, there is wide variability and significant deviation rates. For example, in one study, while self-reported adherence to LA opioids (SD) was 85.4% (21.0%), 28% of cancer patients reported an opioid frequency that did not match their prescribed daily frequency [13].

Our previous study found a similarly low level of adherence to LA opioids, especially among African Americans (63% vs 78%, $P < 0.001$) [11]. These rates are closely comparable to another study conducted with an independent sample of African Americans with cancer pain [14]. No studies to our knowledge have characterized patterns of nonuse, especially gaps between doses, among patients who are prescribed around-the-clock LA opioids for cancer pain.

The purpose of this study was to describe individual cancer patients’ nonuse of prescribed around-the-clock

LA opioids, including a period of gap between consecutive opioid doses taken.

Methods

This study was a secondary analysis of a three-month prospective observational study conducted at two outpatient oncology clinics of a large NCI-designated cancer center in the Mid-Atlantic region [11, 16]. Inclusion in the study was based on self-identified African Americans and whites, at least 18 years of age, diagnosed with solid tumors or multiple myeloma, with cancer-related pain. Patients were excluded if they were prescribed ATC analgesics using a transdermal system due to limitations of medication event monitoring system (MEMS) vials. Pain and pain-related function in the parent study were assessed using the widely validated Brief Pain Inventory [27]. The study was approved by the Institutional Review Board of the University of Pennsylvania, and all patients provided informed consent. For the current analysis, the additional inclusion criterion was prescription of an oral ER/LA opioid for cancer pain to be taken around the clock.

MEMS Use

Individual patients' opioid use was electronically monitored in real time using an MEMS (MWV Switzerland Ltd.)—MEMS is an electronic medication bottle cap with a built-in microprocessor, which records the occurrence and time of MEMS cap opening in real time. The procedures were described in detail in the parent study [11, 16]. In brief, patients were instructed in the correct use of the MEMS bottle, to only use the bottle to take the prescribed monitored analgesics, to notify the study staff of any changes in the prescription, and to document this information in a study log, which was triangulated against patients' electronic medical records. Any medication holidays (e.g., days hospitalized) were removed from the denominator. Any instances of bottle opening other than when taking the index analgesic were adjusted in the denominator using PowerView software. These events included openings only to count pills or refill the medication. Added events occurred if a patient took out pills (e.g., for a three-day trip).

Nonuse Between Days of Use

The electronic monitoring period for each study participant was partitioned into intervals of days between days with one or more MEMS openings, representing periods of ER/LA opioid *nonuse*. These periods started at the beginning of either the first day of study participation or at the beginning of a day just after a day with a MEMS opening. The length of each period is the number of subsequent days of ER/LA opioid nonuse. For example, a length of 0 means the MEMS was opened on the beginning day of the period, and so the period is one day long.

A length of one means the MEMS was not opened on the beginning day of the period, but was opened on the next day, so the period is two days long. Ranges and frequencies of percentages of days of nonuse within periods of length one or more, two or more, . . . and seven or more days were reported to describe rates of ER/LA opioid nonuse over consecutive days. Numbers of consecutive days of ER/LA opioid nonuse were plotted for selected patients to provide visualization of their individual ER/LA opioid nonuse over time.

Ranges and frequencies were also reported for the percentage of days characterized by exceeding prescription, that is, days of taking more than the prescribed dose out of the total days of adherence monitoring.

Results

In the parent study [16], ER/LA opioids were prescribed for 109 (57.1%) of the 191 participants. For this subgroup, ER/LA opioid-taking was monitored for 33–112 days, with most (106 or 97.2%) having been monitored for ≥ 85 days.

Table 1 presents the sociodemographic and illness-related characteristics of the study population. The mean age (SD) was 54 (11.7) years, the majority were married and had private health insurance, about 71% were whites and had advanced cancer. Table 2 contains frequencies and percentages for the ranges of the percentage of LA opioid nonuse over intervals of one to seven consecutive days. A total of 66.1% of the participants had some nonuse during electronic monitoring, with 24.8% of the participants having nonuse during 31.5–87.5% of their electronic monitoring periods. Nonuse over periods of five or more, six or more, and seven or more consecutive days occurred for 37.6%, 34.9%, and 30.3% of the participants, respectively.

Figure 1 contains plots over time of numbers of subsequent days of ER/LA opioid nonuse for four selected participants, exemplifying the nonuse patterns. For example, participant A was followed for 92 days, with periods of nonuse of one and three days for 4.3% days of nonuse. Participant B was followed for 91 days, with periods of nonuse of one and three days for 12.1% days of nonuse. Participant C was followed for 92 days, with periods of nonuse of one to six days for 51.1% days of nonuse. Participant D was followed for 90 days, with periods of nonuse of one to 19 days for 68.9% days of nonuse.

Of the 109 participants, 21 (19.3%) participants took no more than the prescribed opioid doses during study participation. The percentage of days of exceeding the prescribed doses within study participation was 1.0–5.0% of days for 56 (51.4%) of the participants, 5.4–9.9% of days for 19 (17.4%) participants, and 10.3–35.9% of days for the remaining 13 (11.9%) participants.

Table 1. Sociodemographic, illness, and pain-related characteristics of the study participants (N = 109)

Variable	Range	Freq (%)	Mean (SD)
Age	23–74		54.2 (11.7)
Education	Elementary	2 (1.8)	
	High school	29 (26.6)	
	College/trade school	57 (52.3)	
	More than college	21 (19.3)	
Income	<\$10,000	4 (3.7)	
	\$10,000–\$20,000	12 (11.0)	
	\$20,000–\$30,000	9 (8.3)	
	\$30,000–\$50,000	23 (21.1)	
	\$50,000–\$70,000	25 (22.9)	
	\$70,000–\$90,000	15 (13.8)	
	>\$90,000	21 (19.3)	
Primary insurance	Private	66 (60.6)	
	Medicare	4 (3.7)	
	Medicaid	24 (22.0)	
	Multiple	3 (2.8)	
	VA/other	12 (11.0)	
Marital status	Married	64 (58.7)	
	Separated	8 (7.3)	
	Divorced	17 (15.6)	
	Widowed	5 (4.6)	
	Never married	15 (13.8)	
Race	Black/African American	32 (29.4)	
	White	77 (70.6)	
Cancer stage	I	9 (8.2)	
	II	13 (11.9)	
	III	16 (14.7)	
	IV	36 (33.0)	
	Unknown or unsure	35 (32.1)	
Time since cancer diagnosis, mo	2–120		37.4 (35.8)
Prescribed ER/LA opioid	Oxycodone extended-release	89 (81.7)	
	Morphine controlled-release	11 (10.1)	
	Methadone	9 (8.3)	
Worst pain (last week)	(0 = no pain to 10 = worst pain imaginable)		6.8 (2.3)
Average pain (last week)	(0 = no pain to 10 = worst pain imaginable)		4.7 (1.9)
Least pain (last week)	(0 = no pain to 10 = worst pain imaginable)		3.4 (1.9)
Pain-related functional interference score	(0 = no interference to 70 = complete interference)		35.2 (15.9)

ER = extended-release; LA = long-acting; VA = Veterans Administration.

Discussion

Recent studies have identified inconsistent patterns of opioid use in outpatients with cancer [28–30]. While studies have identified considerable inconsistencies and patients using their own parameters for reducing the use of prescribed opioids [11, 13–16], no studies have characterized gaps in consecutive days between opioid doses taken. We employed a novel existing data set to assess opioid use patterns using longitudinal electronic medication monitoring and found a high rate of ER/LA opioid nonuse for consecutive days between doses. In fact, about one in three patients had gaps of seven or more days between doses. This is an important finding, as the FDA warns against the use of long-acting opioids for *as-needed* pain relief [31] and gaps of this duration may

expose patients to important safety risks, such as reduced or loss of opioid tolerance.

In fact, when a gap in therapy is present or a patient underdoses their opioid medication for a period of time, the risk of loss of tolerance is always present, as are the corresponding risks of re-initiation. The duration of the gap necessary to potentiate a loss of tolerance depends upon the pharmacokinetic features of the specific medication or formulation. It is important to note that LA/ER opioids can be those that have been formulated as such in a tablet or capsule, a topical patch, or transdermal system (matrix or reservoir system formulations), but they can also be those that have inherently long half-lives [7]. For example, methadone is widely distributed throughout the body and is released from tissues into the blood for up to three weeks following the final dose [32].

Table 2. Percentage of days of nonuse within intervals of consecutive days for participants on long-acting opioids (N = 109)

Length of Intervals of Consecutive Days of Nonuse*	Ranges for the Percentage of Days of Nonuse During Electronic Monitoring within Intervals of Given Length†	No. (%)
1 or more	0.0	37 (33.9)
	1.0–4.3	18 (16.5)
	4.4–29.7	27 (24.8)
	31.5–87.5	27 (24.8)
2 or more	0.0	46 (42.2)
	2.1–15.2	27 (24.8)
	16.3–87.5	36 (33.0)
3 or more	0.0	53 (48.6)
	3.1–22.8	29 (26.6)
	23.9–85.2	27 (24.8)
4 or more	0.0	63 (57.8)
	4.1–17.2	19 (17.4)
	17.6–85.2	27 (24.8)
5 or more	0.0	68 (62.4)
	4.5–80.7	41 (37.6)
6 or more	0.0	71 (65.1)
	5.7–80.7	38 (34.9)
7 or more	0.0	76 (69.7)
	7.6–73.9	33 (30.3)

*Number of days of opioid nonuse starting from one day of use to the next day of use.

†Percentage of days within all periods of nonuse of given length out of the total number of days of adherence monitoring.

Figure 1. Plots of numbers of subsequent days of long-acting opioid nonuse for selected patients.

Extended-release oxycodone and sustained-action morphine are both pharmaceutically manipulated to release at slower rates and do not have inherently long half-lives based on their pharmacology. Further, there are multiple different sustained-action formulations of morphine on the market, which vary in their specific half-lives and recommended dosing parameters. Regardless of the particular dosage form or pharmaceutical variation, tolerance to either medication is dictated by both medication- and patient-specific variables such as disease progression, concomitant medications, and pharmacogenomics [21, 32, 33]. Disease progression resulting in organ impairment, particularly liver and kidney damage, and can have a significant impact on medication metabolism.

The findings of this study have several key implications for clinical practice and programs including a need for appropriate prescription, patient counseling on safety of opioid use, and need to take ER/LA opioids exactly as prescribed. The CDC recommends the *start low and go slow* approach to when prescribing opioids [34]. Extended-release/long-acting opioids should not be initiated in patients without established opioid tolerance (i.e., who have been exposed to a minimum of 60 MME per day of opioids for seven consecutive days) to minimize opioid poisoning. For converting from one opioid to another, it is crucial to note that MME is intended as a comparator of analgesia rather than a comparator of CNS-depressant effect or respiratory risk. Extreme caution should be exercised in comparing opioid medications using MME, particularly when atypical opioids such as methadone, tramadol, buprenorphine, and tapentadol are in question, all of which have extended-release formulations or inherently have a long half-life and/or high volume of distribution such as methadone and levorphanol [32]. For patient counseling, clinical interventions should focus on addressing patients' specific concerns around opioid adherence (e.g., opioid side effects and/or stigma) and working with patients toward the shared goals of pain relief, improving function. Sometimes it may become important to appropriately taper ER/LA opioids while optimizing nonopioid pain treatments or use of short-acting opioids as needed [35] if the risks outweigh the benefits [20, 35].

While our study was limited to one cancer center and dates before the release of the CDC opioid guidelines for chronic pain [20], our findings of underuse and inconsistent use of prescribed ER/LA opioids have high convergence with other more recent reports on ambulatory cancer patients [14, 15, 36]. Our study adds to this body of literature by further documenting a high rate of ER/LA opioid nonuse for consecutive days between doses. Beyond opioid safety concerns, intervals of opioid nonuse may contribute to patients living with significant pain, which can impair function and cause suffering [36]. Although the majority of the patients in this analysis demonstrated either underuse or a small percentage of

days of exceeding the prescribed dose, a small subsample (11.9%) also exhibited a notable opioid overuse pattern (i.e., exceeding prescribed dose), potentially due to unrelieved pain or aberrant drug-related behaviors. Recent reviews suggest that patients with cancer have comparable risks for opioid misuse as the general public [37], and this phenomenon continues to warrant further research and intervention development.

There is an urgent need for individually tailored interventions to address patients' specific concerns around opioid adherence and use. Also, patients with cancer should be included in the opioid stewardship programs that many US health systems are adopting [38]. However, it is critically important that the goal of these programs should go beyond opioid surveillance and reduction and should have an appropriate focus on reducing opioid stigma and addressing specific patient concerns in optimizing pain care for those oncology patients who continue to need opioids to maintain function and quality of life.

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