The Influence of Allowable Refill Gaps on Detecting Long-Term Opioid Therapy: An Analysis of Population-Based Administrative Dispensing Data Among Patients with Knee Arthritis Awaiting Total Knee Arthroplasty

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ABSTRACT

BACKGROUND: It is challenging to detect long-term opioid therapy (LTOT) using administrative data, as refill gaps can disrupt opioid utilization episodes. Previous studies have used various methods to define LTOT and allowable refill gaps with little supporting evidence.

OBJECTIVE: To describe the effect of allowable refill gaps on detecting LTOT among a cohort of patients with arthritis awaiting total knee arthroplasty (TKA) using 3 different methods.

METHODS: A retrospective analysis of multicenter population-based data between January 1, 2012, and December 31, 2016, identified patients prescribed opioids before TKA in Alberta, Canada. We described 3 methods to detect LTOT based on a (1) fixed number of days between prescriptions; (2) fraction of the preceding prescription length; and (3) combination method that selected whichever refill gap was greatest. We then compared the number of patients classified as long-term opioid users by varying the number of days between prescriptions from 1-90 days (fixed method) or 0.04-3.2 times the duration (fraction method) for each method and refill gap.

RESULTS: Of the 14,252 patients included in our cohort, 4,393 patients (31%) had an opioid prescription within 180 days before TKA. Detection of LTOT varied from 4.4% to 14.6% (fixed method), 4.2% to 13.2% (fraction method), and 4.5% to 15.1% (mixed method) as refill gaps varied from minimum to maximum. As refill gaps increased, the dose and duration of opioids in the utilization episode decreased for all 3 methods.

CONCLUSIONS: The allowable refill gap between opioid prescriptions can influence the estimated rate of LTOT when using administrative pharmaceutical dispensing data. Definitional parameters should be carefully considered when using administrative data to define consistent opioid use.

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What this study adds

- The allowable refill gap can substantially change the estimated rate of long-term opioid use and influence clinical outcomes.
- Fixed, fraction, and mixed methods provide similar estimates of consistent opioid use at comparable refill gap thresholds.

Over the past 2 decades, the number of opioids prescribed for chronic noncancer pain conditions, such as arthritis, has dramatically increased.¹⁻⁵ These prescribing patterns are thought to be responsible for the increased prevalence of patients prescribed long-term opioid therapy (LTOT); that is, “daily or near-daily use of opioids for at least 90 days, often indefinitely.”⁶⁻⁸ LTOT among patients with symptomatic arthritis has gained substantial clinical and research interest as both Canadian and American opioid prescribing guidelines now suggest a much more limited, if any, role of opioids for these patients.⁹⁻¹¹ These recommendations are based on the accumulating evidence that suggests opioids provide no improvement in pain or function when compared to acetaminophen or ibuprofen but have increased rates of adverse events.^{12,13}

LTOT before surgery has also been associated with increased rates of postoperative complications and worse patient outcomes after elective surgery.¹⁴⁻¹⁶ For instance, a recent meta-analysis reported that patients with hip or knee arthritis prescribed opioids before surgery had worse patient-reported outcomes after elective total joint arthroplasty.¹⁷ However, the prevalence of LTOT in North America for this patient population is still unclear, as rates are not only dependent on regional prescribing practices but are also affected by methodological parameters used to detect LTOT.¹⁸⁻²²

Pharmaceutical administrative databases containing medication-dispensing records from community pharmacies are routinely used to analyze opioid prescriptions in Canada and the United States, as data are readily available for large numbers of patients and are relatively inexpensive to access.^{1,21,23-25} However, it can be challenging to identify

What is already known about this subject

- Continuous medication users often have small gaps between prescription dispensings, referred to as refill gaps.
- Multiple methods have been described to calculate allowable refill gaps to define consistent medication use with pharmaceutical administrative dispensing data.

consistent opioid utilization episodes that meet the threshold for LTOT, since any gaps between contiguous prescriptions disrupt the classification episode.²⁶⁻²⁸ These gaps are a result of inconsistent prescription refill patterns, where there may be a short period between the previous prescriptions calculated end date and the dispensing date of the subsequent prescription.²⁷ A grace period, referred to as an allowable refill gap, is often used to analyze these pharmaceutical-dispensing records, since patients appear to consistently use the prescribed medication despite small gaps between prescriptions.^{21,27,28}

In other clinical areas, there has been significant interest to describe methods that account for allowable refill gaps, and the different influence that these methods can have on estimating consistent medication use.^{27,28} Current LTOT research uses arbitrary allowable refill gaps thresholds, with little understanding of how different methods and refill gaps might influence the estimated rates of LTOT or patient outcomes.^{20,23,29,30}

The primary objective of this study was to describe the influence of allowable refill gaps on estimating LTOT among a cohort of patients with knee arthritis awaiting total knee arthroplasty (TKA). Our secondary objectives were to determine the influence of allowable refill gaps on patient-reported daily opioid dose, mean opioid episode duration, and patient outcomes after TKA.

Methods

Study Design

A retrospective review of individual-level data identified patients who underwent primary, elective unilateral TKA between January 1, 2013, and December 31, 2015, in Alberta, Canada. This patient cohort was selected because it was thought to represent a stable population of patients with chronic noncancer pain secondary to end-stage knee arthritis, as confirmed by their requirement for TKA. Canada's socialized health care system does not restrict access to TKA, but patients wait on average 6 months for surgery.³¹ Patients who underwent a subsequent contralateral TKA were included only once for whichever procedure occurred first. Patients who underwent simultaneous bilateral TKA or revision TKA within 1 year of the index procedure were excluded from the analysis. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in this observational study.³² The study protocol was approved by the research ethics board at the University of Alberta, Edmonton, Alberta (Pro00076296).

Data Sources

Surgical data were obtained from the Alberta Bone and Joint Health Institute. This database contains patient demographic information, procedure details, and clinical outcomes after TKA. Opioid-dispensing data were obtained from the Pharmaceutical Information Network (PIN), a provincial

pharmaceutical repository that maintains individual-level pharmacotherapy records and dispensing information from all community pharmacies in Alberta, based on the province's universal health insurance program. Because Canada has universal health care coverage, these databases represent population-based dispensing practices within each Canadian province.

A record was created in PIN each time a medication was dispensed from a community pharmacy in Alberta and contained the drug information number, anatomic therapeutic code, date dispensed, dose, and duration (days supplied). Each PIN entry was linked to a patient's Unique Lifetime Identifier (ULI), a unique number assigned to all persons who receive health services in Alberta. Each patient's PIN profile was queried for the 180 days before the index surgery to determine their opioid-dispensing history. The end date for each dispensing was then calculated by adding the duration to the dispensing date for each PIN entry. All datasets were deterministically linked using patient ULIs that were previously scrambled with an algorithm that deidentified each ULI but still preserved the ability to link across datasets.

We determined the allowable refill gap between opioid prescriptions by 3 different methods (Figure 1). First, we determined the allowable refill gap between prescriptions using a fixed days method.^{27,33} This method sets a maximum number of days allowed between the end of one prescription and the start date of the next recorded prescription, which is independent of the length of prescriptions being analyzed. We varied the number of days from 1 to a maximum of 90 days. The upper limit of 90 days was chosen as this guarantees that each patient would have a least 1 day of opioid prescription if classified an opioid user (OU) in the 180-day window. The 180-day opioid-free period had been previously used in studies investigating LTOT and is the established threshold for opioid discontinuation.²³

Second, we applied a fraction method to determine the allowable refill gap between prescriptions.²⁷ This method used the length of the preceding prescription duration to determine the following allowable refill gap. We varied the fraction incrementally from 0.04-3.2. Previous work investigating cardiovascular medication adherence aligned 90-day prescriptions with a fraction of 1, since this was the maximum amount of days that health insurance would compensate pharmacies.²⁷ In our study, we aligned the fraction and fixed methods based on Canadian opioid guidelines that suggest opioid prescriptions be limited to less than 28 days.⁹ Therefore, a fraction gap of 1 was aligned to a fixed refill gap of 28 days.

In addition, a third method (mixed method) was developed that combined the fixed and fraction methods and defaulted to the largest refill gap calculated (Figure 1).

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FIGURE 1 Overview of Opioid Classification Episodes Using Different Methods and Refill Gaps

^aCalculated using the preceding prescription length of 30 days and a fraction of 0.25 ($30 \text{ days} \times 0.25 = 7.5 \text{ days}$).

^bCalculated using the preceding prescription length of 30 days and a fraction of 0.5 ($30 \text{ days} \times 0.5 = 15 \text{ days}$).

^cCalculated using the preceding prescription length of 60 days and a fraction of 0.5 ($60 \text{ days} \times 0.5 = 30 \text{ days}$).

^dTotal opioid episode duration calculated based on mixed methods.

Primary Outcome: Long-Term Opioid Use

Long-term OUs were defined as patients who had 90 days or more of continuous opioid dispensings within 180 days before TKA; this group was our primary outcome of interest. These parameters were consistent with the definition of LTOT. Intermittent OUs had recorded opioid dispensings within the 180 days before TKA but did not meet the threshold parameters for a long-term OUs. Opioid-naïve patients did not have a recorded opioid dispensing within 180 days before TKA and were not included in the refill methods analysis. The allowable refill gap was dependent on the specific method (fraction, fixed, or mixed).

Secondary Outcomes

Opioid Utilization Episode Duration. The duration of a patient's opioid utilization episode was determined by the difference between the first opioid-dispensing date and the end date of the last continuous opioid prescription. The continuous opioid utilization episode terminated if the gap between the end date of the preceding prescription and the start date of the next opioid prescription exceeded the allowable refill gap or a surgical date was encountered (Figure 1). Therefore, the total days in the opioid utilization episode contained both the number of active days a patient held an opioid prescription and the allowable refill gap (days) between prescriptions (Figure 1). If patients had multiple prescriptions, then the dispensation date and days supplied were used to adjust the end date of the

prescriptions for each subsequent dispensation. If 2 or more overlapping prescriptions with the same dispensing date and days supplied were encountered, the prescriptions beyond the first would not extend the length of the episode but would count toward the total dosage morphine equivalent dose (MED) received. If a short prescription was received within a longer prescription (where the new prescription's supply days did not extend past the predicted end of the previous prescription), then the total dosage (MED) was added to the treatment course, but the end date of the prescription course was not adjusted. In this instance, the fraction method would also continue to use the fraction of the previous, longer prescription. If a prescription was expected to end beyond the currently estimated end date, then a new end date was estimated using the dispensation date and total days supplied of the prescription, and the fraction days were also adjusted to match the fraction of this prescription.

Daily Morphine Equivalent Dose. Patients' individual opioid dispensings were converted to a daily MED by multiplying the daily dose (mg) by the corresponding MED.³⁴ Morphine conversion factors were based on established conversion opioid factors.⁹ The daily dose of opioid was calculated by dividing the total MED for the opioid utilization episode by the corresponding duration of the episode as calculated by the fixed, fraction, or mixed method.

TABLE 1 Characteristics of the Study Cohort and Opioid Prescriptions

Variable	
Patients (n)	14,252
Mean age (SD)	66.8 (9.3)
Female, n (%)	8,608 (60.4)
Total opioid prescriptions (n)	17,617
Individual opioid prescription duration, median days (IQR)	24 (21.0)
Type of opioid prescriptions, n (%)	
Codeine	6,755 (38.3)
Tramadol	4,203 (23.9)
Oxycodone	2,836 (16.1)
Hydromorphone	1,708 (9.7)
Morphine	1,196 (6.8)
Fentanyl	319 (1.8)
Other ^a	600 (3.5)

^aOther: tapentadol, meperidine, butorphanol, opium, and buprenorphine.
IQR = interquartile range; SD = standard deviation.

WOMAC Score 12 Months After TKA. We compared OU (long-term and intermittent) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores 12 months after TKA to those of opioid-naïve patients (reference group) to determine whether the allowable refill gap influences the results of patient outcomes after surgery. The WOMAC is a validated, disease-specific patient-reported outcome instrument commonly used to measure patients' joint pain and function after TKA.^{35,36} Scores ranging from 0-100 are generated for each patient from a Likert scale, with higher scores indicative of better outcome.³⁵ Scores stabilize between 6 and 12 months after TKA, and a difference of 10 points on the WOMAC score represents a detectable clinical difference between groups.³⁷ Our previous work reported that WOMAC scores after TKA are influenced by opioid use before surgery.¹⁷

Statistical Analysis

Medians and interquartile ranges (IQRs) were reported for nonparametric variables, while means and 95% confidence intervals (CIs) were reported for variables that were normally distributed. Groups were compared using student's t-test for normally distributed variables and the Mann-Whitney test for nonparametric comparisons. Linear regression was performed using the patient's opioid classification as the independent variable and 12-month WOMAC score as the dependent variable. Coefficients were interpreted compared to the defined reference group (opioid-naïve patients). Significance was set at <0.01. Data preparation and statistics were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Study Cohort

This cohort consisted of 14,252 patients with a mean age of 66.8±9.3 years; 60.4% were female (Table 1). Of these patients, 4,393 patients (31%) had an opioid prescription in the 180-day period before surgery, with a median number of opioid prescriptions per patient of 3 (IQR=5). Of the 17,617 individual opioid prescriptions analyzed, the median length for prescriptions was 25 days (IQR=20). Codeine (38.3%), tramadol (23.9%), and oxycodone (16.1%) were the most commonly prescribed opioids (Table 1).

Long-Term Opioid Use

As the allowable refill gap increased, the proportion of patients classified as an intermittent OU increased, while the number classified as long-term OUs decreased for all 3 methods (Table 2). The number of patients classified as a long-term OUs ranged from 4.4%-14.6% (fixed method), 4.2%-13.2% (fraction method), and 4.5%-15.1% (mixed method), while the number of patients classified as intermittent OUs varied from 26.4%-16.2% (fixed method), 26.6%-17.6% (fraction method), and 26.4%-15.8% (mixed method; Table 2). This represented a 232% (fixed method), 214% (fraction method), and 236% (mixed method) increase in the number of patients classified as long-term OUs. OU refill gap thresholds were varied from a minimum to maximum (Table 2). Opioid-naïve patients remained stable at 69% for all methods across all refill gap thresholds. Between-method variation (fixed, fraction, and mixed) changed no more than 1.9% for intermittent OUs and long-term OUs at all fraction or fixed-day refill gap thresholds.

Active Opioid Days in 180 Days Before TKA

The fixed method minimized the maximum number of days that intermittent OUs held an active opioid prescription in the 180 days before surgery compared with the fraction method (Appendix A, available in online article). At a fraction of 0.5, the intermittent OU cohort had a patient with an active opioid prescription for 178 days (fraction method) compared with 166 days using the fixed-days method. Again, at a fraction of 1, the intermittent OU group had a patient who held an active opioid prescription for 162 days compared with 147 days using the fixed methodology. In contrast, the fraction method maximized the minimum number of days that long-term OUs held active opioid prescription in the 180 days before surgery. Long-term OUs had a minimum of 71 days at a fraction of 0.5 compared with 67 days at a refill gap of 14 days. At a fraction of 1, the long-term OU group had a minimum of 40 days compared with 32 days using the fixed-days method (Appendix A).

As the refill gap increased, the percentage of days long-term OUs held opioid prescriptions in the 180 days before surgery decreased. Long-term OUs held an opioid prescription for 90.2% of the 180-day window for all 3 methods

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TABLE 2 Comparison of the Prevalence of Opioid Use with Fraction, Fixed, and Mixed Methods

Fraction	Fixed	Intermittent Opioid User ^a			Long-Term Opioid User ^b		
		Mixed ^c	Fraction ^d	Fixed	Mixed ^c	Fraction ^d	Fixed
		% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
0.04	1	26.4 (3,758)	26.6 (3,792)	26.4 (3,763)	4.5 (635)	4.2 (601)	4.4 (630)
0.25	7	23.8 (3,396)	24.1 (3,438)	24.0 (3,423)	7.0 (997)	6.7 (955)	6.8 (970)
0.5	14	22.5 (3,210)	22.9 (3,263)	23.0 (3,278)	8.3 (1,183)	7.9 (1,130)	7.8 (1,115)
0.75	21	21.4 (3,044)	22.0 (3,136)	21.9 (3,121)	9.5 (1,349)	8.8 (1,257)	8.9 (1,272)
1	28	20.5 (2,927)	21.3 (3,035)	21.0 (2,998)	10.3 (1,466)	9.5 (1,358)	9.8 (1,395)
1.5	42	19.1 (2,715)	20.2 (2,872)	19.6 (2,794)	11.8 (1,678)	10.7 (1,521)	11.2 (1,599)
2	56	18.0 (2,558)	19.2 (2,740)	18.5 (2,636)	12.9 (1,835)	11.6 (1,653)	12.3 (1,757)
2.5	70	17.0 (2,427)	18.6 (2,647)	17.5 (2,492)	13.8 (1,966)	12.3 (1,746)	13.3 (1,901)
3	84	16.1 (2,297)	17.9 (2,551)	16.6 (2,365)	14.7 (2,096)	12.9 (1,842)	14.2 (2,028)
3.2	90	15.8 (2,248)	17.6 (2,514)	16.2 (2,314)	15.1 (2,145)	13.2 (1,879)	14.6 (2,079)

^aIntermittent OU defined as opioid prescriptions in 180 days before index TKA but does not meet criteria for a long-term OU.

^bLong-term OU defined as 90 days of consistent opioid use in 180 days before index TKA.

^cMixed method selects whichever refill gap is greater (fixed or fraction).

^dFraction gap based on percentage length of previous opioid prescription.

OU=opioid user; TKA=total knee arthroplasty.

at the minimum allowable refill gap. At the maximum allowable refill gap, long-term OUs held an opioid prescription for 66% (fixed method), 70.2% (fraction method), and 65% (mixed method) of the entire 180-day window before TKA surgery. The difference between the percentage of days that long-term OUs and intermittent OUs held opioid prescriptions in the 180-day period before surgery decreased as the allowable refill gap increased (Appendix A).

Morphine Equivalent Dose

As the allowable refill gap increased, there was a decrease in median MED for long-term OU classification episodes (Appendix B, available in online article). Median MED decreased 62.3%, from 77.1 mg MED to 29.3 mg MED (fixed method); decreased 53.5%, from 74.2 mg MED to 34.5 mg MED (fraction method); and decreased 62.0%, from 75.1 mg MED to 28.2 mg MED (mixed method) as the allowable refill gap varied from minimum to maximum (Appendix B). No intermittent OU had a calculated MED classification episode; none of these patients met the parameters to be included as a long-term OUs.

Effect of Opioid Classification on WOMAC Scores 12 Months After TKA

The difference in WOMAC scores 12 months after TKA increased from -13.41 to -8.30 (40%) for long-term OUs when the allowable refill gap increased from 1-90 days compared with opioid-naïve patients ($P<0.001$; Table 3). The difference in scores between long-term OUs and opioid-naïve patients crossed the threshold that is considered clinically significant after TKA as the allowable refill gap moved from 1-1.5 (fraction method) or 28-42 days (fixed method). Intermittent

OU 12-month WOMAC scores increased from -4.80 to -3.58 points (17%) for long-term OUs when the allowable refill gap increased from 1-90 days compared with opioid-naïve patients ($P<0.001$; Table 3). Similar trends were observed for the fraction and fixed methods (Table 3).

Discussion

Despite the growing number of reports outlining rates of opioid use in North America, there is no consensus on how best to define consistent opioid use with administrative pharmaceutical dispensing data.^{23,29,38,39} This has created uncertainty and confusion regarding the actual rates of opioid use in North America among various patient populations, including those with arthritis.^{14,15,22,40} Reported rates of LTOT among patients with hip or knee arthritis awaiting surgery have varied from 5%-40% and are likely not only due to variation in regional opioid prescribing practices but also the parameters used to define opioid exposure. Consistent with these reports, 31% of patients were dispensed opioids within 180 days of TKA in our study, but the rate of LTOT was dependent on the allowable refill gap. The allowable refill gap also influenced the groups' calculated daily opioid dose, opioid utilization episode mean duration, and whether the difference in outcome scores between long-term OU and opioid-naïve patients after TKA was considered clinically significant.

Developing standardized methods to detect consistent opioid use with pharmaceutical dispensing data that align with parameters of LTOT is of great interest, as this threshold is associated with increased rates of adverse events and underlying physiological changes.^{41,42} Long-term exogenous opioid exposure has been reported to change the endogenous opioid

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TABLE 3 Impact of Opioid Classification on 12-Month WOMAC Scores Using Different Refill Gaps

Fraction ^c	Fixed ^c	Opioid Exposed ^a				Opioid User ^b			
		n	Estimate	SE	P Value	n	Estimate	SE	P Value
0.04	1	3,758	-4.80	0.87	<0.0001	635	-13.41	2.19	<0.0001
0.25	7	3,396	-4.17	0.90	<0.0001	997	-12.52	1.68	<0.0001
0.5	14	3,210	-3.94	0.91	<0.0001	1,183	-11.85	1.54	<0.0001
0.75	21	3,044	-3.72	0.93	<0.0001	1,349	-11.48	1.45	<0.0001
1	28	2,927	-3.90	0.94	<0.0001	1,466	-10.23	1.38	<0.0001
1.5	42	2,715	-3.76	0.97	0.0001	1,678	-9.52	1.28	<0.0001
2	56	2,558	-3.66	1.00	0.0002	1,835	-9.07	1.22	<0.0001
2.5	70	2,427	-3.54	1.02	0.0005	1,966	-8.84	1.18	<0.0001
3	84	2,297	-3.62	1.04	0.0005	2,096	-8.36	1.14	<0.0001
3.2	90	2,248	-3.58	1.05	0.0006	2,145	-8.30	1.13	<0.0001
Fraction^d									
0.04		3,792	-4.90	0.86	<0.0001	601	-12.95	2.24	<0.0001
0.25		3,438	-4.30	0.89	<0.0001	955	-12.33	1.72	<0.0001
0.5		3,263	-3.97	0.91	<0.0001	1,130	-12.09	1.57	<0.0001
0.75		3,136	-3.56	0.92	0.0001	1,257	-12.65	1.50	<0.0001
1		3,035	-3.65	0.93	<0.0001	1,358	-11.51	1.43	<0.0001
1.5		2,872	-3.76	0.95	<0.0001	1,521	-10.25	1.35	<0.0001
2		2,740	-3.34	0.97	0.0006	1,653	-10.40	1.28	<0.0001
2.5		2,647	-3.33	0.98	0.0007	1,746	-10.03	1.25	<0.0001
3		2,551	-3.46	0.99	0.0005	1,842	-9.43	1.22	<0.0001
3.2		2,514	-3.57	1.00	0.0004	1,879	-9.06	1.20	<0.0001
	Fixed								
	1	3,763	-4.80	0.87	<0.0001	630	-13.41	2.19	<0.0001
	7	3,423	-4.13	0.89	<0.0001	970	-12.99	1.71	<0.0001
	14	3,278	-4.17	0.91	<0.0001	1,115	-11.46	1.58	<0.0001
	21	3,121	-3.83	0.92	<0.0001	1,272	-11.48	1.47	<0.0001
	28	2,998	-3.94	0.94	<0.0001	1,395	-10.40	1.41	<0.0001
	42	2,794	-3.99	0.96	<0.0001	1,599	-9.31	1.31	<0.0001
	56	2,636	-4.10	0.98	<0.0001	1,757	-8.58	1.25	<0.0001
	70	2,492	-3.90	1.00	0.0001	1,901	-8.50	1.20	<0.0001
	84	2,365	-4.05	1.03	<0.0001	2,028	-7.99	1.17	<0.0001
	90	2,314	-4.00	1.03	0.0001	2,079	-7.96	1.15	<0.0001

Note: Reference group is opioid-naïve patients.

^aOpioid exposed defined as opioid prescriptions in 180 days before index TKA but does not meet criteria for an OU.

^bOpioid user defined as 90 days of consistent opioid use in 180 days before index TKA.

^cMixed method selects whichever refill gap is greater (fixed or fraction).

^dFraction gap based on percentage length of previous opioid prescription.

OU = opioid user; SE = standard error; TKA = total knee arthroplasty; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

system in regions of the brain that regulate both patient's emotions and perception of chronic pain.⁴¹ It is thought that change to the endogenous opioid system provides a framework to understand why certain high-risk patients with chronic pain, such as those with a history of arthritis and depression, self-select for LTOT.⁴³ These patients with a negative affect state are much more likely to transition from short-term to long-term opioid therapy at a higher dose compared with patients who do not have a history of depression or related conditions.⁴⁴ More work is needed to clarify this complex relationship to further understand these high-risk patients, which may help reduce the number of inappropriate opioid prescriptions, in keeping

with current opioid North American prescribing guidelines.⁴¹ The current study will inform future work, since it is based on established parameters for LTOT and adaptable to any pharmaceutical database that contains dispensing dates and prescription durations.^{20,21,24,45}

Our approach will enable investigators to determine rates of LTOT using consistent definitions, which will facilitate comparisons of opioid use among different patient populations. Unifying methods that define LTOT have the potential to clarify regional prescribing patterns, the effectiveness of opioid prescribing programs, and variances among different patient populations. For example, Hadlandsmayth et al. (2018) reported

FIGURE 2 Impact of a 1-Day Refill Gap on Opioid Utilization Episode Duration Using Fixed (1 Day) or Fraction Method (0.5)

that 20% of patients were long-term OUs before receiving a TKA in the United States using an allowable refill gap of 14 days with a fixed-day method.²⁰ In comparison, only 8% of patients were long-term OUs among our Canadian cohort using the same refill gap method. This is the first report we are aware of that compares rates of LTOT in this patient population between Canada and the United States using a similar case definition and suggests that, despite similar opioid prescribing guidelines, Canada may have lower rates of LTOT among this patient population.^{9,10} However, these results should be interpreted with caution, as the fixed method was adapted to opioid prescriptions without considering how opioid-specific prescribing practices might affect the classification of long-term OUs.

In other clinical areas, the fixed method of determining refill gaps has been criticized as a static approach that does not consider the length of patient-specific prescriptions.²⁷ These limitations in the fixed method were also noted when applied to opioid prescriptions in our cohort. Particularly, when applied to short-term opioid prescriptions, some patients were classified as long-term OUs despite having more days without than with an active opioid prescription (Appendix A). In cardiovascular persistence medication studies, the fraction method appears to provide a better estimate of consistent medication use, as each allowable refill gap is relative to the preceding prescription.²⁷ However, when applied to opioid prescriptions, we found that despite circumventing the fixed-method limitations, missing a single day can disrupt the opioid classification episode at a threshold of < 1 when daily dispensing of opioids is encountered (Figure 2).

This limitation in the fraction approach can misclassify long-term high-dose patients who are often dispensed daily opioids to reduce the risk for opioid misuse and overdose.⁹ In our results, a patient who was prescribed opioids for 178 days of a possible 180 days was classified as an intermittent OU at fractions < 1 (Appendix A). To circumvent the limitations of both approaches for opioid prescriptions, we developed a mixed method that calculated both fixed and fraction methods and defaulted to whichever refill gap was greatest (Figure 1). This method overcame the fraction methodological limitations and maximized the difference between intermittent and

long-term OU mean episode duration and daily opioid dose (Appendix A).

A strength of our study was the ability to describe the influence of allowable refill gaps on the detection of LTOT using different methods and relate these changes to a validated patient-reported outcome measure, where scores have previously been shown to be influenced by opioid use.^{17,36} We also identified a subgroup of patients (intermittent OUs) who had distinctive characteristics and outcomes from both long-term OUs and opioid-naïve patients; these patients were previously excluded in other analyses.^{30,45} Analysis of these 2 distinct groups of OUs highlighted the importance of the 90-day threshold for LTOT. Patients who had consistent opioid dispensing for at least 90 days utilized opioids more frequently and at higher daily doses compared with intermittent OUs. These findings are consistent with reports that suggest that if patients use opioids for longer than 90 days, they tend to use opioids indefinitely.^{21,46,47}

Limitations

This study has some limitations to consider. One limitation was the assumption that opioid dispensing is a surrogate for patient consumption. Multiple methods have been used to determine opioid consumption, including urine or blood tests, patient-reported use, or refill data.⁴⁸ While blood serum levels or urine tests are expensive and logistically complex if a large number of patients are required, patient-reported opioid use typically underreports actual opioid use rates.^{49,50} In a study of patients awaiting TKA, patients underreported opioid use by as much as 46% compared with an opioid monitoring database.⁵⁰

While our study was restricted to patients from Alberta, our provincial-wide database is likely representative of a general population of patients with symptomatic arthritis waiting for TKA, since Canada provides universal health care to all residents and our findings were not restricted to 1 center or surgeon.⁴⁵ Additional research in other settings and disease states would help clarify the generalizability of our study results to determine if these effects are consistent in other prescribing environments or patient populations.

Finally, we were not able to establish an allowable refill gap that best predicts LTOT. Nevertheless, we believe that our

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detailed analysis and described methodology provide valuable information regarding the effect of various allowable refill gaps and different methods that can be used to define LTOT to allow more consistent definition of opioid use and ensure that comparisons across groups are based on clear definitions.

Conclusions

A significant number of patients with symptomatic knee arthritis were dispensed opioids before TKA, but the allowable refill gap influenced the estimated rate of LTOT. The allowable refill gap also influenced long-term OUs' calculated daily opioid dose, mean opioid utilization episode, and whether clinically significant differences were achieved after TKA when compared with opioid-naïve patients. These findings underscore the importance of carefully considering the methods and allowable refill gaps before designing or interpreting study results that examine consistent opioid use. Future work that relates these algorithms to clinical metrics, such as physician-diagnosed LTOT or LTOT complications, would help clarify the sensitivity and specificity of various refill gap thresholds.

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DISCLOSURES

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APPENDIX A Duration of Opioid Utilization (Days) Before Index Procedure Based on Different Refill Gaps

Mixed ^a		Intermittent Opioid User ^b							Long-Term Opioid User ^c							P Value ^e
Fraction ^d	Fixed ^a	n	Mean	Min	Max	95L	95U	Utilization ^e %	n	Mean	Min	Max	95L	95U	Utilization ^e %	
0.04	1	3,758	50.3	1.0	178.0	48.8	51.9	28.0	635	162.5	95.0	180.0	160.7	164.2	90.3	<0.001
0.25	7	3,396	39.5	1.0	164.0	38.3	40.8	22.0	997	158.6	83.0	180.0	157.1	160.0	88.1	<0.001
0.5	14	3,210	34.9	1.0	162.0	33.7	36.0	19.4	1,183	152.6	67.0	180.0	151.0	154.1	84.8	<0.001
0.75	21	3,044	31.0	1.0	155.0	29.9	32.0	17.2	1,349	146.8	40.0	180.0	145.2	148.5	81.6	<0.001
1	28	2,927	28.5	1.0	147.0	27.5	29.4	15.8	1,466	142.5	32.0	180.0	140.8	144.3	79.2	<0.001
1.5	42	2,715	24.8	1.0	133.0	24.0	25.7	13.8	1,678	134.1	21.0	180.0	132.2	136.0	74.5	<0.001
2	56	2,558	22.5	1.0	119.0	21.7	23.3	12.5	1,835	128.0	13.0	180.0	126.0	129.9	71.1	<0.001
2.5	70	2,427	20.9	1.0	104.0	20.2	21.7	11.6	1,966	122.9	6.0	180.0	120.8	124.9	68.3	<0.001
3	84	2,297	19.7	1.0	93.0	19.0	20.5	11.0	2,096	117.9	1.0	180.0	115.7	120.0	65.5	<0.001
3.2	90	2,248	19.3	1.0	90.0	18.6	20.0	10.7	2,145	116.1	1.0	180.0	113.9	118.2	64.5	<0.001
Fraction ^d																
0.04		3,792	51.4	1.0	180.0	50.5	50.5	28.5	601	162.3	95.0	180.0	160.5	164.1	90.2	<0.001
0.25		3,438	40.7	1.0	178.0	39.4	42.1	22.6	955	159.4	83.0	180.0	158.0	160.9	88.6	<0.001
0.5		3,263	36.1	1.0	178.0	34.9	37.2	20.0	1,130	154.6	71.0	180.0	153.1	156.1	85.9	<0.001
0.75		3,136	32.9	1.0	178.0	31.9	34.0	18.3	1,257	150.4	50.0	180.0	148.9	152.0	83.6	<0.001
1		3,035	30.6	1.0	162.0	29.6	31.6	17.0	1,358	146.9	50.0	180.0	145.3	148.5	81.6	<0.001
1.5		2,872	27.3	1.0	154.0	26.4	28.2	15.2	1,521	140.7	40.0	180.0	139.0	142.4	78.2	<0.001
2		2,740	24.9	1.0	154.0	24.0	25.7	13.8	1,653	135.6	13.0	180.0	133.8	137.5	75.4	<0.001
2.5		2,647	23.5	1.0	154.0	22.7	24.3	13.0	1,746	131.9	6.0	180.0	130.0	133.8	73.3	<0.001
3		2,551	22.2	1.0	131.0	21.5	23.0	12.3	1,842	127.9	1.0	180.0	126.0	129.9	71.1	<0.001
3.2		2,514	21.8	1.0	131.0	21.0	22.5	12.1	1,879	126.5	1.0	180.0	124.5	128.4	70.3	<0.001
	Fixed															
	1	3,763	50.5	1.0	178.0	48.9	52.1	28.1	630	162.4	95.0	180.0	160.7	164.2	90.2	<0.001
	7	3,423	40.3	1.0	166.0	39.0	41.6	22.4	970	159.3	87.0	180.0	157.9	160.7	88.5	<0.001
	14	3,278	36.6	1.0	166.0	35.4	37.8	20.3	1,115	154.6	67.0	180.0	153.1	156.2	85.9	<0.001
	21	3,121	33.0	1.0	158.0	31.9	34.1	18.4	1,272	148.8	40.0	180.0	147.1	150.4	82.7	<0.001
	28	2,998	30.4	1.0	147.0	29.3	31.4	16.9	1,395	144.3	32.0	180.0	142.6	146.0	80.2	<0.001
	42	2,794	26.7	1.0	135.0	25.8	27.7	14.8	1,599	136.2	21.0	180.0	134.2	138.1	75.6	<0.001
	56	2,636	24.2	1.0	124.0	23.3	25.1	13.4	1,757	130.1	13.0	180.0	128.1	132.1	72.3	<0.001
	70	2,492	22.1	1.0	110.0	21.3	22.9	12.3	1,901	124.8	9.0	180.0	122.7	126.8	69.3	<0.001
	84	2,365	20.8	1.0	96.0	20.0	22.1	11.5	2,028	119.9	7.0	180.0	117.8	122.1	66.6	<0.001
	90	2,314	20.1	1.0	90.0	19.4	20.9	11.2	2,079	118.2	6.0	180.0	116.1	120.3	65.7	<0.001

^aMixed method selects whichever refill gap is greater (fixed or fraction).

^bIntermittent OU defined as opioid prescriptions in 180 days before index TKA but does not meet criteria for a long-term OU.

^cLong-term OU defined as 90 days of consistent opioid use in 180 days before index TKA.

^dFraction gap based on percentage length of previous opioid prescription.

^eP value calculated with 2-sample Students t-test comparing median dose between 2 groups.

95L=95% confidence lower limit; 95U=95% confidence upper limit; IQR=interquartile range; Min=minimum; Max=maximum.

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APPENDIX B Calculated Daily Morphine Equivalence Dose (mg/day) for the Classification Episode Based on Different Refill Gaps

Mixed ^a		Long-Term Opioid User ^b							
Fraction ^c	Fixed	n	Mean	Median	IQR	Min	Max	95L	95U
0.04	1	635	151.9	75.1	125.6	4.5	3,200.0	133.0	170.8
0.25	7	997	122.5	64.0	96.9	4.4	2,827.6	110.4	134.6
0.5	14	1,183	106.7	58.5	82.1	2.5	2,620.1	96.7	116.7
0.75	21	1,349	97.2	52.4	70.9	2.5	2,620.1	88.4	106.0
1	28	1,466	91.2	47.0	66.5	2.5	2,620.1	83.0	99.3
1.5	42	1,678	81.8	40.6	60.1	2.8	2,458.1	74.8	88.9
2	56	1,835	76.3	36.1	53.6	2.1	2,458.1	69.7	82.9
2.5	70	1,966	71.6	32.1	50.1	1.9	2,458.1	65.5	77.8
3	84	2,096	67.5	29.3	47.3	1.7	2,458.1	61.7	73.3
3.2	90	2,145	66.2	28.3	46.8	1.5	2,458.1	60.5	71.9
Fraction ^c									
0.04		601	147.5	74.2	126.5	4.5	3,200.0	129.2	165.9
0.25		955	124.5	64.7	99.4	4.4	2,827.6	111.9	137.1
0.5		1,130	109.5	59.2	86.2	2.5	2,620.1	99.0	119.9
0.75		1,257	101.6	54.8	77.1	2.5	2,620.1	92.2	111.0
1		1,358	95.5	50.1	72.9	2.5	2,620.1	86.8	104.2
1.5		1,521	88.1	44.0	65.9	2.8	2,620.1	80.2	96.0
2		1,653	83.1	40.8	60.7	2.1	2,458.1	75.9	90.4
2.5		1,746	79.5	38.1	56.3	1.9	2,458.1	72.6	86.4
3		1,842	75.6	35.2	53.2	1.7	2,458.1	69.1	82.2
3.2		1,879	74.5	34.5	52.1	1.7	2,458.1	68.0	80.9
Fixed									
	1	630	153.3	77.1	125.5	4.5	3,200.0	134.1	172.4
	7	970	125.7	65.5	98.5	4.4	2,827.6	113.2	138.2
	14	1,115	112.6	60.3	87.8	4.4	2,620.1	101.9	123.2
	21	1,272	102.3	55.4	75.0	3.9	2,620.1	93.0	111.7
	28	1,395	95.3	50.5	68.4	3.9	2,620.1	86.8	103.9
	42	1,599	85.1	42.1	62.2	3.1	2,458.1	77.7	92.5
	56	1,757	78.9	37.5	55.9	2.9	2,458.1	72.1	85.7
	70	1,901	73.9	33.5	52.0	2.5	2,458.1	67.6	80.2
	84	2,028	69.9	30.5	49.3	2.3	2,458.1	63.9	75.9
	90	2,079	68.2	29.3	47.8	1.5	2,458.1	62.4	74.1

^aMixed method selects whichever refill gap is greater (fixed or fraction).

^bLong-term OU defined as 90 days of consistent opioid use in 180 days before index TKA.

^cFraction gap based on percentage length of previous opioid prescription.

95L = 95% confidence lower limit; 95U = 95% confidence upper limit; IQR = interquartile range; Min = minimum; Max = maximum.