Perioperative opioid demand and risk factors for long-term opioid use among anterior cruciate ligament reconstruction and repair patients in Alberta

by

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Abstract

Chapter 2 (Study 1):

Background: Opioid use beyond typical postoperative pain timelines remains an adverse surgical outcome. Anterior cruciate ligament reconstruction and repair (ACLRR) are common surgeries whose perioperative opioid demands have not been characterized in a Canadian setting.

Methods: In this retrospective cohort study, we identified ACLRRs performed between 2009–2017 in Alberta among patients aged 10–65. Using linked community pharmacy dispensation data, we evaluated time trends in the percentage of patients with preoperative opioid exposure and in initial postoperative opioid dispensation characteristics for opioid-naïve patients. We described typical month-to-month opioid demand for one year following ACLRR, wherein we distinguished patients exhibiting >90 days of opioid supply (LTOT).

Results: Across 15,675 ACLRRs, preoperative opioid exposure increased from 2009 (6.6%) to 2016-17 (9.9%). Opioid-naïve patients more frequently received postoperative opioids in 2016–17 (89.2%) than in 2009 (66.7%). By 2016–17, initiating dispensations among opioid-naïve patients became more likely to contain tramadol (49.6%), involve ≥50 morphine milligram equivalent daily dosages (43.6%), and be indicated for use over 5–7 days (57.8%). 304 patients (1.9%) exhibited LTOT during their first postoperative year. LTOT rate was stratified by patient preoperative opioid exposure, ACLRR surgical type, and patient age, but did not significantly change over the study period.

Conclusion: Perioperative opioid dispensations in ACLRR increased in frequency and dosage from 2009–2017 in Alberta, especially among patients without preoperative opioid exposure,

alongside no significant change to overall postoperative LTOT rate. ACLRR-specific clinical guidance may be necessary for future widespread adoption of opioid-sparing and multimodal postoperative analgesia.

Chapter 3 (Study 2):

Background: Postoperative long-term opioid therapy (LTOT) provides minimal patient benefit while conferring substantial potential for harm. Among anterior cruciate ligament (ACL) reconstruction and repair (ACLRR) patients, the roles of preoperative non-opioid drug exposure and initial postoperative opioid dispensation characteristics on LTOT have not been elucidated.

Hypothesis/Purpose: To identify preoperative, intraoperative and postoperative patient-level characteristics associated with changes in LTOT likelihood among patients undergoing ACLRR, while following recommendations to robustly define LTOT and to broadly include initiating opioid dispensation characteristics.

Study Design: Cohort study.

Methods: Physician billing codes were used to index ACLRRs performed between 2009–2017 in Alberta, Canada. Patient demographics, comorbidity history, preoperative opioid exposure and preoperative non-opioid drug exposure were determined for all ACLRR following linkage. Initial postoperative opioid dispensations were identified and categorized by dosage and duration for all preoperatively opioid-naïve patients. Associations between patient-level characteristics and postoperative LTOT were described via multivariable logistic regression models using three LTOT outcome constructs of varying stringency. Models were generated for the whole ACLRR cohort, as well as for the subset of patients undergoing ACLRR who were both opioid-naïve and who received opioids within their first 30 postoperative days.

Results: 15,675 ACLRRs were included for analysis. Complete-cohort LTOT prevalence ranged from 304 (1.9%; Primary LTOT) patients to 1,701 (10.9%; Prior studies' LTOT) patients. Preoperative opioid dispensation showed the strongest association with all LTOT outcome constructs. Other patient-level risk factors associated with increased LTOT included patient age >29, preoperative exposure to antidepressants, antipsychotics, and benzodiazepines; histories of substance use disorder and uncomplicated diabetes; and ACL repair <14 days from injury versus ACL reconstruction. Among patients without preoperative opioid exposure, initiating opioid dispensations of ≥50 morphine milligram equivalent daily dosage and of 15+ day duration were associated with increased LTOT. Patterns of association differed based on LTOT outcome choice.

Conclusion: Numerous patient-level associations with increased LTOT are present among patients undergoing ACLRR, although preoperative opioid exposure remains a chiefly important predictor. Substantial differences in patterns of association between LTOT outcome constructs indicate a need for use of robust LTOT outcome measures in future research.

Preface

The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board – Health Panel, Project Name "Epidemiology of knee injury and anterior cruciate ligament reconstruction in Alberta", Pro00090820, June 21, 2019.

The data analyses in Chapters 2 and 3 are my original work, with assistance provided by Y. R. Paudel. D. Gross, M. Sommerfeldt, and D. Voaklander were supervisory authors who contributed to manuscript edits in Chapters 1–4. Y. R. Paudel, M. Sommerfeldt and D. Voaklander were involved additionally in study concept formation and data acquisition.

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Chapter 1: Background and Rationale

Significant changes to opioid usage patterns in Canada, 1995-present

Canada prescribes prescription opioid analgesics at one of the highest quantities per capita in the world [1]. It shares this distinction with its largest neighbor—the United States—and with high-income European nations including Germany and the United Kingdom[1]. Canada's status as a top opioid prescriber has persisted despite more than a 36% reduction in opioid prescribing rates between 2009 and 2019[1], as this in no way offset the massive increase in North American opioid prescribing from the mid-1990s to early 2010s[2,3]. That period in pain medicine saw multiple instrumental changes to guidelines in pain management and to accessibility of specific drug formulations, both of which influenced prescription opioid use in Canada.

Beginning in 1995, a landmark quality improvement guideline from the American Pain Society emphasized the need to more regularly assess and document patient pain in acute and cancer settings, suggested that unresolved pain constituted a "red flag" for clinicians, and promoted the importance of patient satisfaction in pain control[4]. This perspective has been interpreted as elevating pain to a "fifth vital sign"[5–7]. Concurring, practice guidelines for chronic non-cancer pain (CNCP), published in 1997 and supported by the American Society of Anesthesiologists, recommend that unidimensional patient pain scales be the "primary source of pain assessment"[8] and provide examples of multiple pain intensity scales for patients to use. Both documents reference opioids as a potentially beneficial analgesic, with the former showing no preference for analgesic type, and the latter suggesting that opioids be considered when a patient's analgesic need is unmanaged using other modalities[4,8]. These documents synergized with the 1996 approval and subsequent aggressive North American marketing of controlled-

release oxycodone "OxyContin" – an opioid with analgesic potency greater than that of morphine, which was promoted heavily to clinicians for use in acute pain and CNCP settings[9]. This provided a springboard for prescribers to expand the use of opioids for a wider range of patient pain needs, including those where other non-opioid analgesic modalities might have previously been employed[2].

Canada quickly adapted to this perspective change. In 1998, the Canadian Pain Society approved a consensus statement, eventually published in 2002, regarding opioid use and CNCP[10]. This statement also affirmed the utility of long-term opioid therapy for CNCP unmanaged using other analgesic modalities, while somewhat cavalierly rejecting the notion of substantial harms related to opioid misuse, iatrogenic opioid addiction, or side effects like respiratory depression in a CNCP setting[10]. Bolstered by an updated American guideline on acute and cancer pain with core tenets on opioid use remaining relatively unchanged[11], the 2000s saw Canada experience an approximate tripling in opioid dispensation rates[12]. In the latter half of the decade, almost half of all Canada's high-dose opioid prescriptions (>200 mg morphine equivalent per day) were dispensed as oxycodone, with the highest rates of high-dose opioid dispensation in Ontario and Alberta[13].

By 2010, approximately a fifth of the Canadian adult population reported having consumed opioid analgesics in the preceding year[14]. This upwards trend had been flagged as a significant problem, specifically as deaths from prescription opioid overdose now outnumbered those from the consumption of heroin and cocaine[15]. Diversion of strong prescription opioids was proposed as a likely mechanism for these changes, and this was confirmed in street-level studies of drug accessibility in British Columbia between 2006 and 2010[16]. A mounting call to action supported decreasing access to the prescription opioids most commonly involved in opioid

poisoning and overdose death, namely long-acting oxycodone, in the Canadian pharmaceutical market. This took place in a two-fold manner.

Firstly, in early 2012, OxyContin was reformulated as OxyNeo, a tamper-resistant variant of long-acting oxycodone which was more difficult to crush and gelled when added to liquid[17]. This aimed to minimize the useability of OxyNeo for non-medical consumption, and in turn, its likelihood of being diverted. Secondly, all provinces in Canada other than Alberta removed OxyNeo-branded long-acting oxycodone from their standard provincial drug coverage programs, while grandfathering in OxyContin users and allowing special exceptions for palliative and cancer patients[17]. When OxyNeo was discontinued in late 2012, its generic, non-tamper-resistant counterpart was covered only in Quebec, British Columbia—where coverage was later discontinued in 2015—and Nova Scotia[17].

These changes did reduce the consumption of controlled-release oxycodone across Canada, as its dispensing declined by nearly half between 2012 and 2016[17]. However, it simultaneously resulted in the partial substitution of oxycodone for alternative long-acting prescription opioids, specifically hydromorphone[18], which had fewer prescribing restrictions. Furthermore, the reduction of affordable prescription oxycodone for patients who previously used high-dose opioids, coupled with less available diverted oxycodone via the introduction of prescription monitoring programs[19], may have contributed to street demand for cheaper synthetic opioids[20]. Post-2016, individuals in Canada who die from opioid overdose are much more likely to have consumed illicitly produced fentanyl as opposed to unadulterated prescription opioids[21]. Numerous intervention targets have been proposed as countermeasures to this increase in opioid-associated morbidity and mortality – from preventing incident opioid use disorder to providing supports for individuals at a high risk of opioid-related harm[22]. The conclusion that remains

clear, however, is that a single or one-size-fits-all approach is inadequate if substantial reductions in opioid harms are desired[23–25].

As of 2022, an updated clinical practice guideline for pain-associated opioid prescribing has been released for the United States to supersede CNCP guidelines from 2016 [26]; no such guideline has been published in Canada since 2017[27]. The 2022 guideline provides recommendations for opioid prescribing in acute through chronic pain timelines and acknowledges that earlier guidelines were misinterpreted in scope and intent[26], resulting in overly strict opioid therapy initiation and maintenance prescribing. While the guideline reiterates the utility of opioid-sparing and multimodal therapies for most subacute and chronic pain conditions, it concedes neither are always readily available[28]. Furthermore, for acute pain etiologies where opioid-sparing treatment regimens are unlikely to provide adequate analgesia, it recommends that prescribers provide individualized or procedure-specific opioid analgesia—as short as needed; typically less than 7 days—with follow-up at least biweekly to assess patient needs. Despite being included within the clinical practice guideline, these individualized postoperative opioid use guidelines—primarily targeting surgeons and anesthesiologists—often rely on consensus[28] and have been scrutinized as an avenue which remains in need of stronger evidence-based guidance[29–31].

Perioperative opioid use – current trends and best practice guidelines

Patients who undergo surgery are routinely prescribed post-operative opioids in Canada[32–34], and according to a study from Ontario, constitute approximately a sixth of all opioid therapy initiations in opioid-naïve individuals[35]. These are not necessarily worrying statistics – opioids remain an effective form of analgesia for patients to blunt severe acute post-operative

pain[31], and treatment discontinuation is typically expected from the patient at or prior to the post-acute surgical period[36]. In a best-case scenario, the patient is provided a course of opioids in direct accordance with their dosage and duration needs, while considering their surgical indication and comorbidities, by a discerning prescriber. However, prescribing trends do not reflect this paragon: a systematic review by Bicket et al. found that at minimum, two-thirds of surgical patients were oversupplied with opioids, and that prescriptions typically contained two or more times the opioid tablet quantity warranted by patients' eventual consumption levels[37]. Unused opioid prescriptions such as these may furthermore be at risk for diversion to family and friends[38,39].

Whereas many postoperative opioid prescriptions result in adequate pain management and unused pharmaceuticals, a small but clinically important group of surgery patients develop persistent postoperative pain (PPOP) and may continue to use opioids as their primary analgesic modality. The mechanisms by which this chronic pain develops are not fully elucidated but are currently believed to differ from the nociceptive mechanisms underlying acute pain[40–43]. Most typically, this long-term therapy is defined as "≥90 days of cumulative or continuous use or supply within 1 year"[44], which in a surgical context is typically indexed to date of surgery[45]. Further mentions in this chapter of "long-term" opioid therapy (LTOT), unless otherwise specified, reference this definition.

Unfortunately, while opioid analgesia is effective in acute pain, there are several factors that diminish its effectiveness and safety in CNCP. Primarily, and importantly for the PPOP patient, LTOT averages only a clinically nonrelevant analgesic benefit—less than 1cm on a 10cm visual analog scale—and a lack of meaningful change to functional outcomes when compared to placebo or non-steroidal anti-inflammatory drugs (NSAIDs)[46]. Good-quality

evidence also points to dose-dependent effects of long-term opioid therapy on nausea and vomiting[46] as well as overdose risk[47], which is further magnified in patients with psychiatric comorbidities[48] or overlapping benzodiazepine prescriptions[49].

Furthermore, analgesic tolerance—requiring increases in daily dose for an equianalgesic effect—is common in LTOT[50]. A subset of LTOT patients develops this tolerance, while developing relatively less tolerance to opioid-induced centrally mediated respiratory depression; even when dutifully monitored, this can promote the development of ataxic breathing and central sleep apnea, as well as worsen obstructive sleep apnea (OSA) symptoms[51]. One study estimated that more than 40% of CNCP patients on LTOT had symptomatic OSA[52]. Since OSA is an independent risk factor for numerous manifestations of cardiovascular disease[53], its exacerbation in LTOT patients remains a legitimate health concern.

Lastly, LTOT can be contraindicated in opioid-induced hyperalgesia (OIH), a phenomenon whereby opioid administration paradoxically worsens pain sensitivity. While the mechanisms of OIH are still under investigation, it is typically managed via opioid dose tapering, opioid rotation, or adjuvant pharmacotherapy[54]. Surgical populations may be at a greater risk of postoperative OIH due to the use of high-dose intraoperative opioid analgesia, although reducing the use of remifentanil during surgical general anesthesia appears to circumvent some of this increased risk[55].

Altogether, LTOT for patients with PPOP risks ineffective analgesia, nausea and vomiting, sleep and cardiac dysfunction, paradoxical hyperalgesia, and overdose. Prescribers are tasked with balancing these benefits and harms of postoperative opioid analgesia – providing

adequate acute analgesia while minimizing the risk of LTOT, especially in previously opioid-naïve patients.

ACL repair and reconstruction – its unique patient demographic and relationship to analgesic demand

Ontario data suggests that approximately 3% of all opioid-naïve patients undergoing elective surgery will transition to LTOT[56], with around a tenth of these patients continuing to use opioids persistently for more than one year[57]. However, among major elective surgeries, and even within orthopedic surgery, anterior cruciate ligament (ACL) reconstruction and ACL repair (ACLRR) present a relatively unique patient cohort which may not be representative of a more general surgical population. Specifically, patients undergoing ACLRR are differentiated by the typical demographics of ACL injury and indications for surgical versus nonsurgical intervention, which can influence their analgesic demand and risk of LTOT.

The ACL is one of four major ligaments located within the knee joint[58], but accounts possibly for half of all knee injuries[59]. While tallies for yearly ACL injuries are not routinely collected information in North America, estimates suggest that at least 120,000 and up to 200,000 occur per year in the United States[60,61], and that individuals carry a yearly risk for ACL injury of around 1 in 3000[62]. These injuries are typically not seen until adolescence and have sex-specific age distributions: their incidence peaks in males between twenty and twenty-nine years of age[63], whereas in females, two incidence peaks—one in later adolescence, and another from 40 to 49 years of age—can exist[64,65]. ACL injury typically takes place in a sports or physical activity setting during sudden decelerations or direct knee contact[66], with higher levels of athletic competition further increasing rate of injury[67]. Compared to older populations with degenerative joint disease who may be comorbid and limited in exercise capacity but indicated

for surgery[68], patients with ACL injuries are more physically active and younger, and so are less likely to have comorbid chronic disease or chronic pain[69–72].

Indications for surgical intervention of ACL injuries widen this gap. The American Academy of Orthopaedic Surgeons recommends, with limited evidence, rehabilitation without surgical intervention as better indicated for less active patients and patients with less joint laxity[73]; other studies have identified patients who opt for conservative ACL treatment as less competitive[74] and less likely to desire returning to high-force pivoting sports[75]. Conversely, surgical ACL interventions are recommended in active 18–35-year-old patients[73], in patients with damage to other knee ligaments or knee menisci [58], and in patients with recurrent knee instability[76]. Notably, acute pain from ACL trauma does not always require surgery for its resolution[77,78] and so opting for ACLRR is not a reliable indicator of inadequately managed pain. In summary, individuals who eventually opt to undergo ACLRR will typically be younger and more athletic than their opt-out counterparts, and while they may have more complex injuries, they do not necessarily have severe presurgical pain requiring opioid analgesia.

Course of perioperative pain control in ACLRR

Studies specifically assessing preoperative opioid use prevalence in ACLRR vary– from 9% when restricted to opioid use approximately two weeks prior to surgery[79], to 35% at or less than three months prior to surgery[80]. While athletic populations, including those with acute ACL injury, may use analgesic medications to continue their sport involvement while injured and in pain[81,82], these behaviors appear sport-specific so are not necessarily representative of the entire ACLRR population, and instead may explain some variation in these findings.

Many intraoperative analgesic modalities exist for patient pain control in the immediate postoperative period after ACLRR. As identified by Davey and colleagues, this includes the use of nerve blocks, nerve block adjuncts, intra-articular injections, oral medication, intravenous medication, transexamic acid, compressive stockings, and cryotherapy[83]. Apart from use of transexamic acid, where findings tentatively support an analgesic benefit up to 4 weeks, the analgesia resulting from these intraoperative treatments lasts no more than a few days, which is inadequate to manage longer-duration postoperative pain, and certain procedures—namely femoral and sciatic nerve block—can impede functional recovery timelines[84]. ACLRR patients who desire analgesia beyond this immediate postoperative period typically require prescribed pharmacotherapy at discharge.

As of 2023, guidelines specific to ACLRR do not provide recommended ranges of postoperative opioid analgesic dispensation, and no PROSPECT (PROcedure SPECific postoperative pain managemenT) Working Group guideline exists[85]. In their place, typical ranges of dose and durations for postoperative opioid use may be inferred from studies which directly assess patient opioid analgesic demand following ACLRR. These studies, in the North American setting, can broadly be categorized into acute (first episode of postoperative opioid use) and long-term (up to 1 year) timelines.

Current evidence of opioid analgesic demand in the acute postoperative period of ACLRR

The vast majority of studies which describe opioid use in ACLRR do so within the constraints of acute pain timelines and are typically case series from single institutions or physicians. Opioid consumption in this type of study often utilizes patient-reported counts of pill consumption[86–91] or rate of initial prescription refill[90,92] to demonstrate patient opioid demand.

Opioid consumption patterns are not uniform across these studies[89]. In general, studies do not show an appreciable effect of prescription pill quantity[89,90] or dosage[91] on short-term pill consumption patterns. Selected studies, where authors recommend quantitative prescription ranges, are detailed here.

Scully and colleagues assessed short-term ACL reconstruction opioid demand via the association of refill rates of initial opioid prescriptions with initial prescription duration, finding a median prescription length of 5 days in ACL reconstruction, and prescription lengths of 15 days resulting in the lowest likelihood of refill[92]. They concluded that an initial prescription duration between 6 and 15 days effectively balanced the likelihood of refill with likelihood of opioid over-prescription. Thompson and colleagues, in their study of short-term ACL reconstruction postoperative opioid use at a single institution, instead utilized pill count and morphine milligram equivalent (MME) dosages to track patients' consumption patterns and suggested a prescription maximum of twenty 5mg hydrocodone pills[86], representing 100 total MME[27]. They, advocating more strongly for prescription moderation, recommend that follow-up examinations with a physician take place for the 30% of patients prescribed such a dose whom the authors assume are likely to require a refill. This parallels a limit proposed by Lovecchio and colleagues in their single-institution study, of 20 5mg pills of oxycodone[87], representing 150 total MME[27].

Current evidence of opioid analgesic demand and risk factors for LTOT in the long-term postoperative period of ACLRR

Studies which document opioid demand in ACLRR during the late postoperative period are fewer in number and can be detailed individually. Anthony and colleagues identified ACL reconstruction patients from a large United States health system database between 2007 and

2014 and quantified their postoperative opioid use as the presence of opioid prescription fills for each of patients' first twelve postoperative months[80]. They found that approximately 75% of patients filled opioid prescriptions in the first postoperative month, which decreased sharply to 10%, 7% and 4.7% in postoperative months 2, 3 and 12 respectively. They identified young (<25 years) patients, patients with preoperative opioid use, and patients undergoing additional meniscal repair or meniscectomy as having increased risk of prescription filling at and beyond 3 months[80]. A study by Rao and colleagues was also conducted using a large United States health system database and identified further risk factors for opioid prescription filling beyond three months: female sex, BMI ≥ 25, chronic pulmonary disease, American Society of Anesthesiologists classification ≥3, ACL repair with chondroplasty, hypertension, activity during injury (motor vehicle or other non-work, non-sports injury), and substance abuse[93]. They, in contrast, found that patients' likelihoods of opioid fills beyond three months increased with age and attributed this to differing base rates of opioid utilization between adolescents and under-30 adults, as well as parental protectiveness of adolescents from opioid use. A third study by Forlenza and colleagues, consisting of ACL reconstruction patients from a single United States medical institution, quantified a risky opioid consumption profile by showing that dispensing of >513 MME from the period fifteen days prior to fifteen days following patients' ACL reconstruction increased the risk of patient opioid use more than three-fold at 6 and 12 postoperative months[79]. Lastly, and most recently, Anderson and colleagues described postsurgical ACL reconstruction opioid use patterns and LTOT risk factors in a large cohort of active-duty United States military personnel[94]. In their cohort, approximately one-fifth of ACL reconstruction patients used opioids preoperatively, and more than a quarter of patients transitioned to LTOT, as defined by opioid dispensation taking place more than 90 days

following surgery. They identified preoperative opioid use, substance misuse, and age <30 or >50 as risk factors for LTOT and show a dose-dependent relationship between perioperative opioid dosage (± 30 days of surgery) and LTOT risk. They note, however, that their study assesses a cohort of patients with physically and mentally stressful occupational demands, which potentially lowers its generalizability among more general ACLRR populations.

These groups of studies each incompletely characterize opioid demand in ACLRR. Notably, the combined contribution of initial prescription dosage and duration to future LTOT has not been assessed in the long-term postsurgical period—as it has been for patients undergoing general surgery[95] and other orthopedic surgeries[33,96]—nor do summary metrics of opioid consumption in the late postsurgical period even exist, beyond the proportion of individuals who were dispensed prescriptions each postoperative month. Cruder outcome definitions of LTOT such as those which rely on month-to-month dichotomized opioid use/non-use or prescription count may also not reflect nuances in opioid dispensing habits. This issue in granularity can be remedied by using LTOT definitions which incorporate day-to-day individual prescription use, alongside measures of prescription dosage or duration, such as MME per day or days' supply. Multiple pharmacoepidemiologic reviews have acknowledged this limitation of imprecise opioid dispensation data, and recommend, where possible, the use of more robust LTOT outcome measures[44,45].

Moreover, the studies which currently describe ACLRR postoperative opioid use in North America generate their conclusions from data obtained in the United States. Two of the three multicentre late period risk factor studies utilize administrative health data from health organizations with private or mixed payer healthcare[93,97]. In the United States, patients with private health care insurance coverage have better access to orthopedic surgery procedures[98,99]

and are more likely to opt for surgical rather than conservative ACL treatment[100]; furthermore, patient access to health care coverage is stratified by socioeconomic status and race[101,102]. Thus, these administrative health databases may be representative only of a subset of residents from geographic locations served by healthcare systems. While systemic barriers to health care access also exist in Canada[103–105], by and large, necessary surgical procedures in Canada are publicly funded[106] via provincial health insurance programs, so Canadian provincial administrative health databases more faithfully represent the population of their constituent geographical areas.

Thesis aims and practical applications

Firstly, this thesis aims to a) describe opioid analgesic use during the perioperative period of ACLRR more thoroughly than is currently available in North American literature. Secondly, this thesis aims to identify risk factors for LTOT following ACLRR using a robust LTOT definition and a broader catalogue of putative LTOT risk factors than have currently been assessed in ACLRR. The data generated from this thesis will be compared to prior research to conclude whether previously observed trends and risk factors generalize to a Canadian publicly funded healthcare setting.

This thesis is exploratory in nature, so analysis will not be driven by *a priori* hypotheses regarding perioperative opioid use patterns or LTOT risk factors, although when possible, risk factors for LTOT previously elucidated in ACL surgery will be included for candidate variable selection to allow for comparison. The definition of LTOT utilized in this thesis chapter—and intended for use throughout the thesis—is more stringent than the definition of LTOT used in prior ACLRR literature. It seems likely that more patients will satisfy an LTOT definition of ≥1 prescription refill in the late postoperative period versus satisfying a >90 days' supply definition

of LTOT; therefore, it is expected that LTOT percentage reported in this thesis will be lower than those reported in studies by Rao[93] or Anthony[97]. Sensitivity analyses using multiple definitions of LTOT will be necessary to compare LTOT proportion more directly between these studies with differing LTOT outcome measures, and to assess whether LTOT risk factors remain stable.

The data generated from this thesis will be split into two main sections: one for descriptive analysis of perioperative opioid use in ACL reconstruction, and another for LTOT risk factor model building. The descriptive analysis chapter, especially temporal trends, may be utilized by Canadian clinicians involved with perioperative pain control—including family physicians, orthopedic surgeons, and anesthesiologists—to assess their prescribing habits among different clinically important sub-populations or over time. These data may also be useful to provincial or national regulatory bodies, such as the Canadian Institute for Health Information (CIHI) or Canadian Centre on Substance Use and Addiction (CCSA), as evidence to be used in reports or recommendations for practice.

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Chapter 2: Perioperative opioid utilization in anterior cruciate ligament reconstruction and repair – a retrospective cohort analysis in Alberta from 2009–2017

This chapter has been formatted for publication in a peer-reviewed journal.

Introduction

Opioid analgesics are frequently prescribed for postoperative pain control[1], and possibly represent a sixth of all opioid initiations in the Canadian healthcare system[2]. Postsurgical pain management guidelines have generally eschewed opioids as a standalone analgesic modality, in favor of opioid use as one component of a broader multimodal analgesic protocol[3–5]. Still, an estimated 3% of opioid-naïve surgery patients in Canada transition to long-term opioid therapy (LTOT)[6] – continued opioid use at and beyond three months postoperatively. The risk-benefit profile of LTOT shifts towards opioid-associated harms, including gastrointestinal distress, respiratory depression, sleep apnea exacerbation, opioid-induced hyperalgesia, and overdose[7–10]. LTOT furthermore confers, on average, minimal analgesic benefit compared to placebo or to non-steroidal anti-inflammatory drugs (NSAIDs)[7]. It is therefore prudent to view the postoperative transition to LTOT as an adverse outcome, especially in preoperatively opioid-naïve patient populations, where practitioner-modifiable initial prescription characteristics—opioid dosage, duration, and type—show strong associations with eventual LTOT[11,12].

Anterior cruciate ligament reconstruction and repair surgeries (ACLRR) are becoming more common in Canada[13,14]. Yearly rate estimates of ACL reconstruction in 2015 and 2019, of 48.5 and 51.2 respectively per 100,000 population, correspond to more than 20,000 ACLRRs being performed each year as of 2023[15]. Patients with ACL injuries who opt for ACLRR are typically young, with age-specific surgery incidence peaking prior to thirty[16], and less comorbid than patients undergoing orthopedic surgery for degenerative joint disease[17,18]. Canadian population-level data documenting perioperative opioid utilization in ACLRR is not readily available, as compared to Canadian provincial-level data for other orthopedic procedures[19,20] or American integrated health system-level data for ACLRR[21–23]. Given the demographic and

comorbidity dissimilarity between patients undergoing ACLRR versus other orthopedic surgeries[16–18], alongside variable orthopedic knee surgery outcomes[24,25] between Canada and the United States, previously derived perioperative opioid use metrics may not necessarily overlap with ACLRR in a Canadian setting.

Pattern and trend identification in ACLRR perioperative opioid use is a form of healthcare outcome monitoring which is complementary to the goals of Canadian pain management and opioid use quality improvement initiatives[26–28]. We conducted a retrospective cohort analysis of patients undergoing ACLRR in a Canadian province to describe their perioperative opioid utilization. This permits comparisons both with pain management guidelines and with other research.

Methods

This study was approved by the University of Alberta's Health Research Ethics Board – Health Panel (Pro00090820). Direct participant identifiers were anonymized prior to receipt of the data. As this study utilized retrospective routinely collected administrative health data, informed consent was not obtained. We followed RECORD reporting guidelines (Appendix A, Table 6).

Study data sources

The study data consisted of five data sources: clinical data from inpatient (Discharge Abstract Database; DAD) services; clinical data from ambulatory care (National Ambulatory Care Reporting System; NACRS) services; pharmaceutical dispensation data from community pharmacy (Pharmaceutical Information Network; PIN) services; Alberta Health Care Insurance

Plan (AHCIP) billing data (Practitioner Claims), and yearly AHCIP registration data (Provincial Registry). Complete data were available from January 1, 2008 to March 31, 2019. Each patient had a consistently anonymized Unique Lifetime Identifier (ULI) which allowed for deterministic data linkage.

Study design and cohort enumeration

This is a retrospective cohort study using individual-level routinely collected health and demographic data. Billing codes used to indicate ACLRR (Appendix A, Table 7) were flagged in the Practitioner Claims database and a cleaning algorithm was performed prior to indexing (Appendix A, Table 8). Patients undergoing multiple ACLRR were indexed for each ACLRR. ACLRRs were subsequently excluded from analysis due to 1) incomplete AHCIP coverage; 2) surgery date; 3) cancer diagnosis; 4) subsequent ACLRR during follow-up; and 5) patient age. This process excluded patients who died during the two-year follow up or otherwise lapsed their AHCIP coverage as well as non-residents.

Exposure and outcome ascertainment timelines

The preoperative period was defined as the 365-day period ending one day prior to the date of admission for the episode of care which overlapped the indexed ACLRR date. The postoperative period was defined as the 365-day period beginning on the date of admission for patients undergoing ACLRR in ambulatory care, and on the discharge date of the episode of care which overlapped the indexed ACLRR date for patients undergoing inpatient ACLRR. Month-to-month postoperative periods were operationalized as twelve consecutive 30-day periods beginning on postoperative day 1 and ending on postoperative day 360.

Preoperative comorbidities, surgical technique, demographic characteristics

Patient preoperative comorbidity burden was identified using Quan's Charlson Comorbidity Index[29] with original weights[30] (Appendix A, Table 7). Comorbidities were considered present if any comorbidity-associated code in NACRS or DAD databases was observed during a patient's preoperative period. ACLRR surgical procedure was categorized using Practitioner Claims database billing codes (Appendix A, Table 7). This study identified primary and revision ACL reconstruction (ACLR), ACLR with concomitant meniscectomy or meniscal repair, as well as ACL repair occurring <14 days from acute injury (Appendix A, Table 7).

Patient age and sex were identified using the Provincial Registry database. Patient age was set to the patient's reported age at the end of the fiscal year where the indexed ACLRR occurred, then categorized (10–19 to 50–65 years).

Pharmaceutical exposures

The PIN dataset contained every instance that prescription drugs were dispensed to ACLRR patients in Alberta community pharmacies. Each dataset row corresponded to a single drug dispensation, and housed information on dispensation date, Canadian Drug Product Database Drug Identification Number (DIN), drug Anatomical Therapeutic Chemical (ATC) code, unit of dispensation, quantity, and estimated days' supply. This study assumed that drug dispensations were consumed beginning on their dispensation date and in accordance with estimated days' supply.

Dispensations with ATC codes N02A**x** and R05DA**x** were identified as opioids and their DINs were matched to records from Canada's Drug Product Database. Drug formulation and route of administration were used to include or exclude the dispensation from analysis (Appendix A, Table 7). Opioid dispensations were converted into morphine milligram equivalent (MME) dosages using the Centers for Disease Control and Prevention (CDC) 2020 conversion factors[31]. Patients' opioid supply was identified as present or absent and quantified in MME each day during the preoperative and postoperative periods. This study used a modified version of a previously developed opioid use calculation toolkit[32].

Patients were defined as opioid-naïve—having no recent preoperative opioid exposure—if during the last 90 days of the preoperative period, they had no opioid supply. For opioid-naïve patients who were dispensed any opioids during their first 30 postoperative days, their first postoperative dispensation was categorized by daily MME and duration, using categories adapted from prior research on LTOT risk[33,34], and by opioid type. In addition, patients were identified if they received dispensations of non-steroidal anti-inflammatory drugs (NSAIDs) during their first 30 postoperative days (Appendix A, Table 7).

LTOT outcome ascertainment

Patients were considered to exhibit LTOT if during the entire postoperative period, they had >90 days of opioid supply.

For each of the twelve consecutive postoperative 30-day periods (months), patients were considered to have monthly opioid exposure if they had opioid supply at any point during the respective postoperative period.

Statistical analysis

Patient characteristics were operationalized to dichotomous or categorical variables and reported using count and proportion. Fisher's exact test and chi-square tests were used for univariate comparisons of proportion. Cochran-Armitage tests and logistic regression with orthogonal contrasts were respectively used for univariate and multivariate-adjusted tests of trend in proportion over time (2009–2017). Significance was set at $p < 0.05$.

Data processing for this study was performed using SAS/STAT 9.4 for Windows.

Results:

Cohort characteristics

15,675 ACLRRs were included for analysis from an initial 32,099 enumerated ACLRRs. (Figure 1).

Cohort demographic, comorbidity, and surgical characteristics are presented in Table 1. Individuals aged 10-29 made up majority of the cohort at 7,917 (50.5%) patients, and 6,447 patients (43.2%) were female. Apart from the combined 2016-17 surgical period, surgery count increased year-over-year from 1,730 (11.0% of the cohort) in 2009 to 2,061 (13.2% of the cohort) in 2015. After accounting for all diagnoses during the 1-year preoperative period, only 402 patients (2.6%) exhibited a weighted Charlson comorbidity score of >1, of which only 42 exhibited a score of ≥2. Primary ACLR with meniscectomy, the surgery type indicated in over half (8,229, 52.5%) of the cohort, was more than twice as prevalent as any other procedure. Revision surgery patients made up under 8% (1,155) of the ACLRR cohort. Only 1.3% (202) of

patients underwent ACL repair within 14 days of acute injury, and in fewer than 4% (584) of surgeries had ACLRR taken place in the two preceding years.

Patients undergoing ACLRR had preoperative opioid exposure in 1,293 (8.3%) surgeries (Table 2). This percentage trended upwards from 6.8% of patients in 2009 to 9.9% of patients in 2016-17 ($p < 0.001$ for univariate and multivariate-adjusted trends).

Figure 1: Flow diagram from initial enumerated ACLRR cohort to study-eligible cohort

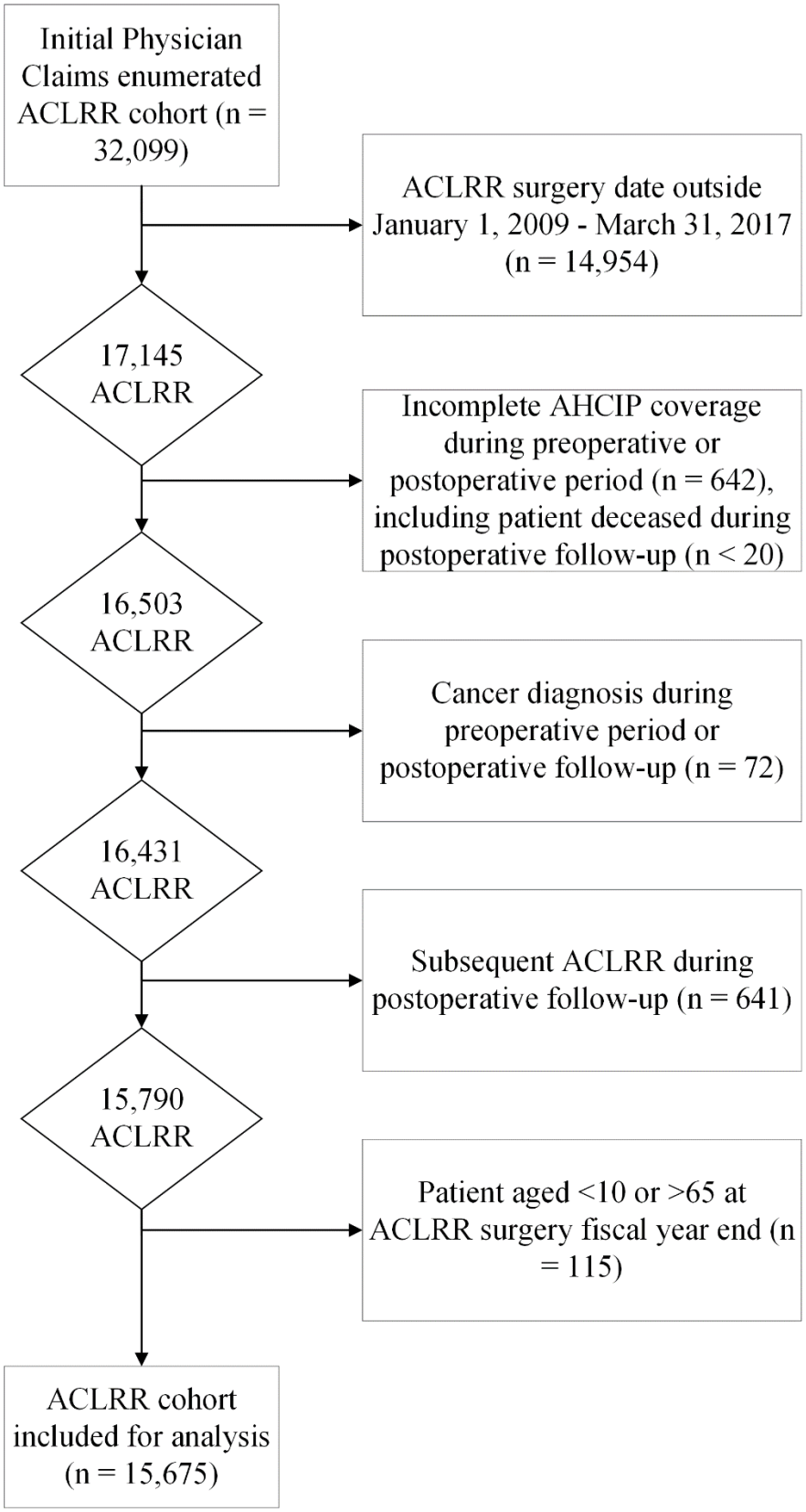


Table 1: Baseline characteristics of patients undergoing ACLRR (n = 15,675) ACLRR

Characteristic	No. of surgeries (%)
Demographic	
Female sex	6,774 (43.2)
Age category	
10-29	7,917 (50.5)
30-39	4,077 (26.0)
40-49	2,678 (17.1)
50-65	1,003 (6.4)
Surgery period	
2009	1,730 (11.0)
2010	1,731 (11.0)
2011	1,738 (11.1)
2012	1,828 (11.7)
2013	1,840 (11.7)
2014	2,005 (12.8)
2015	2,061 (13.2)
2016-2017	2,742 (17.5)
Comorbidities	
1-year longitudinal Charlson comorbidity index, weighted	
0	15,273 (97.4)
1	360 (2.3)
≥2	42 (0.3)
Surgical	
Recent ACLRR (two-year lookback)	584 (3.7)
Surgical procedure	
ACL reconstruction with bone-patellar tendon graft	2,733 (17.4)
ACL reconstruction with meniscectomy	8,229 (52.5)
ACL reconstruction with meniscal repair	3,356 (21.4)
Early ACL repair, within 14 days	202 (1.3)
Revision ACL reconstruction	341 (2.2)
Revision ACL reconstruction with meniscectomy	597 (3.8)
Revision ACL reconstruction with meniscal repair	217 (1.4)

Table 2: Proportion of preoperative opioid use in ACLRR, by year, 2009–2017

Subgroup	No. of surgeries (%)	Univariate trend (2009-2017) test *p*-value	Multivariate-adjusted* trend (2009-2017) test *p*-value
Overall preoperative opioid use	1,293 (8.3)		
Surgery period		$p < 0.001$	$p < 0.001$
2009	118 (6.8)		
2010	115 (6.6)		
2011	133 (7.7)		
2012	150 (8.2)		
2013	170 (9.2)		
2014	165 (8.2)		
2015	172 (8.4)		
2016-17	270 (9.9)		
*Test for linear trend in multivariate logistic regression controlling for age and sex			

Postoperative opioid initiation in opioid-naïve patient subgroup

Approximately 4 in 5 opioid-naïve ACLRR patients were initiated onto opioid medications in their first 30 postoperative days (Table 3). This percentage trended upwards over time between 66.7% at cohort inception in 2009 to 89.2% by 2016-2017 ($p < 0.001$ in univariate and multivariate-adjusted trend tests).

Table 3: Proportion of postoperative opioid prescription filling within 30 days of healthcare discharge following ACLRR among opioid-naïve patients, 2009-2017

Subgroup	No. of surgeries (%)	Univariate trend (2009-2017) test *p*-value	Multivariate-adjusted* trend (2009-2017) test *p*-value
Overall opioid-naïve subgroup (n = 14,382)	11,491 (79.9)		
Surgery period		$p < 0.001$	$p < 0.001$
2009	1,075 (66.7)		
2010	1,135 (70.2)		
2011	1,221 (76.1)		
2012	1,337 (79.7)		
2013	1,354 (81.1)		
2014	1,521 (82.7)		
2015	1,645 (87.1)		
2016-17	2,203 (89.2)		
*Test for linear trend in multivariate logistic regression controlling for age, sex, and surgical procedure			

Opioid analgesic choice in first prescription

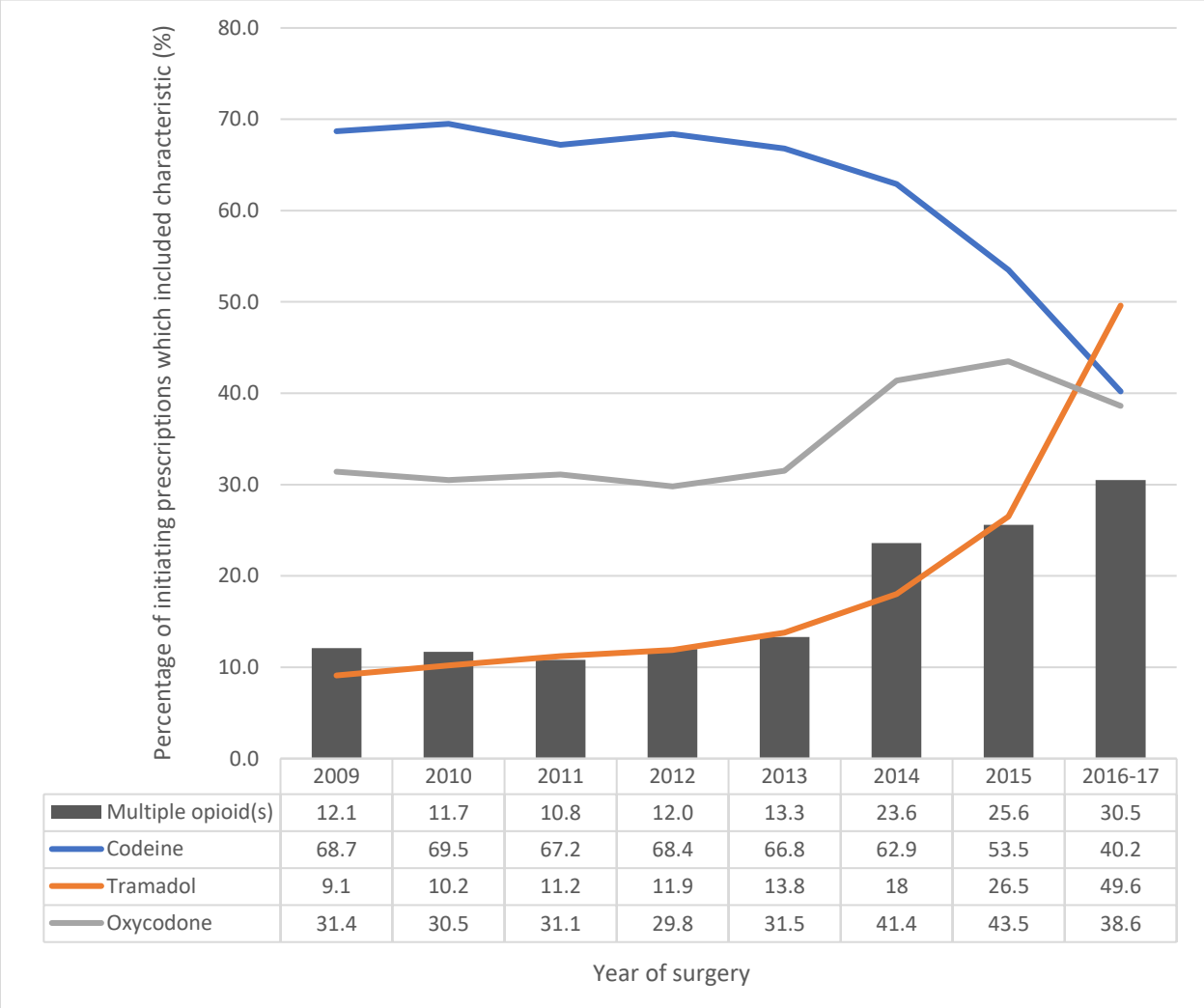
Among opioid-naïve ACLRR patients who were dispensed an opioid analgesic-containing prescription within 30 days following healthcare discharge, 97% received an initial prescription containing codeine, tramadol, or oxycodone (Figure 2). Codeine remained the most commonly dispensed initiating opioid analgesic from 2009 (67.8%) to 2015 (53.5%), though by 2016-17 was the second most common opioid choice and was present in proportionally fewer (40.2%) initiating prescriptions. Similarly, oxycodone remained the second most commonly dispensed initiating opioid analgesic from 2009 (31.4%) through 2015 (43.5%) but trended upwards in initiating dispensation proportion throughout the study period. Tramadol-containing initiating dispensations rose substantially in dispensation proportion across the study period from

2009 (9.1%) to 2016-17 (49.6%), by which time they were the most commonly dispensed initiating opioid.

Initial dispensations where patients received more than one opioid-containing prescription on the same day increased from 2009 (12.1%) to 2016-17 (30.5%) of initial dispensations in 2009 to 30.5% in 2016-17.

All trends in first prescription opioid choice persisted in both univariate and multivariate-adjusted analyses (all $p < 0.001$).

Figure 2: Proportion of initiating dispensations to opioid-naïve ACLRR patients containing codeine, tramadol, oxycodone, and multiple opioid formulations (bar), by year, 2009-Mar 2017.



	2009	2010	2011	2012	2013	2014	2015	2016-17
Multiple opioid(s)	12.1	11.7	10.8	12.0	13.3	23.6	25.6	30.5
Codeine	68.7	69.5	67.2	68.4	66.8	62.9	53.5	40.2
Tramadol	9.1	10.2	11.2	11.9	13.8	18	26.5	49.6
Oxycodone	31.4	30.5	31.1	29.8	31.5	41.4	43.5	38.6

Legend: X-axis (top row) indicates year of surgery; Y-axis indicates percentage of initiating dispensations which contained specified opioid(s).

Trends in daily dosage (MME) of initiating opioid dispensation in opioid-naïve ACLRR patients

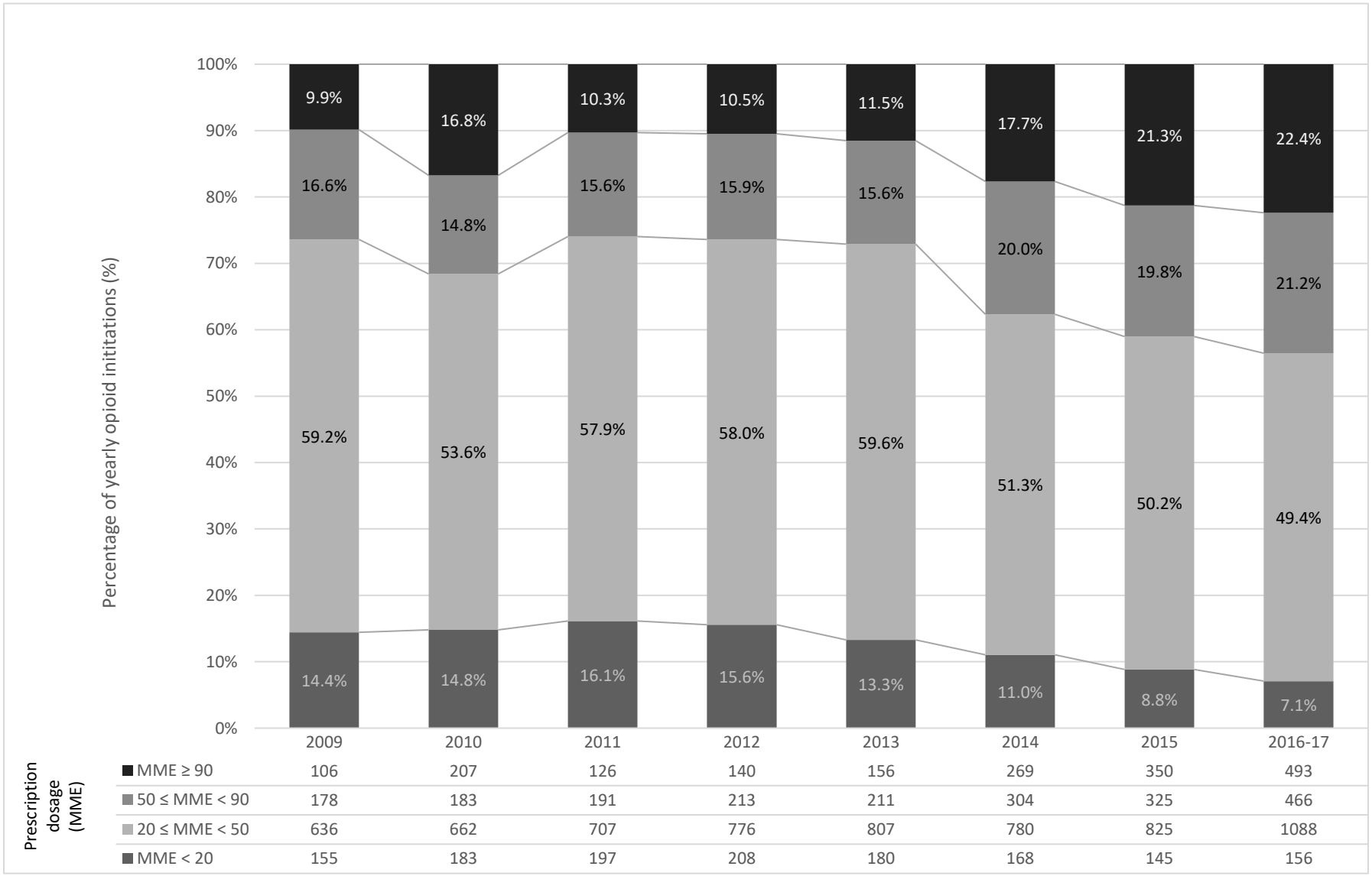
Patients undergoing ACLRR without preoperative opioid exposure were most likely to receive an initial dispensation daily dosage of $20 \leq \text{MME} < 50$ (Figure 3), although proportionally fewer patients received such dosages in 2016-17 (49.4%) versus 2009 (59.2%)

(trend $p < 0.001$). The same patients were least likely to receive an initiating dispensation of <20 MME/day and their likelihood of receiving such a dosage decreased from 2009 (14.4%) to 2016-17 (7.1%) (trend $p < 0.001$). Patients became more likely to receive an initiating dispensation daily dosage of 50 ≤ MME < 90 or ≥90 MME 0.001), respectively from 16.6% and 9.9% in 2009 to 21.2% and 22.4% in 2016-17 (both trend $p < 0.001$). These time trends persisted in multivariate logistic regression after controlling for sex, age and surgery type (all trend $p <$ 0.001). Overall mean initiating dispensation daily dosage (Appendix A, Table 9) increased from 44.3 MME in 2009 to 57.3 MME in 2016-17 (univariate and multivariate-adjusted trends $p <$ 0.001).

Trends in duration (days' supply) of initiating opioid dispensation in opioid-naïve ACLRR patients

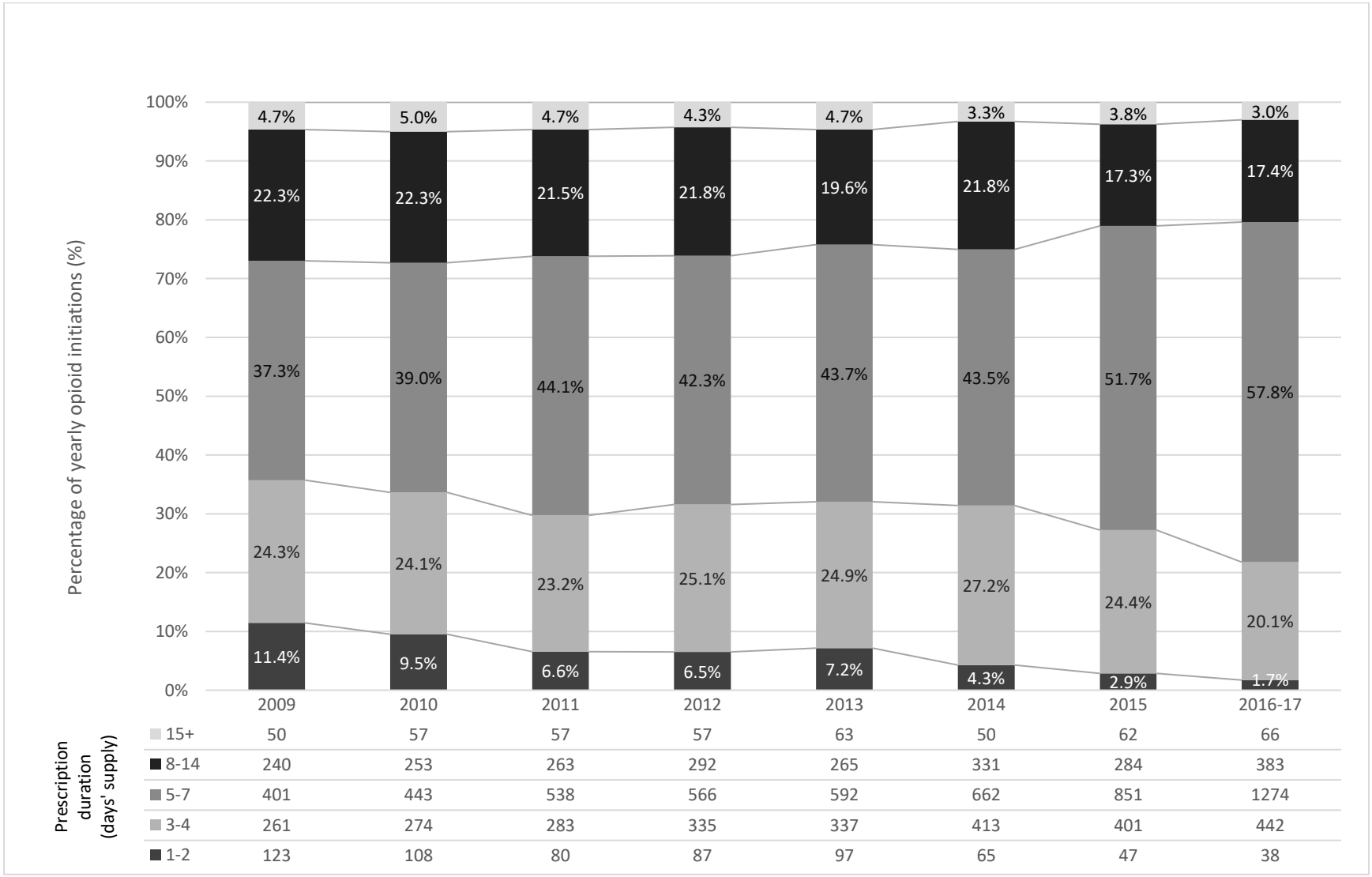
In 2009, 37.3% of opioid-naïve patients received initiating dispensations of duration 5-7 days (Figure 4) which by 2016-2017 accounted for 59.2% of all initiations (trend $p < 0.001$). This upwards trend coincided with decreases from 2009-2017 in the dispensed proportion of all other dispensation duration categories (each univariate $p < 0.001$) besides dispensations 3-4 days in length ($p < 0.14$). All statistically significant trends persisted in multivariate logistic regression after accounting for sex, age and surgery type (trend $p < 0.01$). Few initiating prescriptions of 15 or more days in duration were prescribed across the study period (4.0%). Overall mean initiating dispensation duration increased from 6.23 days in 2009 to 6.29 days in 2016-17 (Appendix A, Table 9); while this represented a statistically significant trend in univariate analysis ($p < 0.04$), no such trend was present after accounting for distributional changes in age, sex and ACLRR procedure type ($p < 0.09$).

Figure 3: First postoperative dispensation daily dosage distribution among opioid-naive ACLRR patients who were dispensed an opioid within 30 days of healthcare discharge, 2009-March 2017



Prescription dosage (MME)	2009	2010	2011	2012	2013	2014	2015	2016-17
MME ≥ 90	106	207	126	140	156	269	350	493
50 ≤ MME < 90	178	183	191	213	211	304	325	466
20 ≤ MME < 50	636	662	707	776	807	780	825	1088
MME < 20	155	183	197	208	180	168	145	156

Figure 4: First postsurgical opioid dispensation duration distribution among opioid-naïve ACLRR patients who were dispensed an opioid within 30 days of surgery, 2009-March 2017



Opioid use patterns in the first twelve months following ACLRR

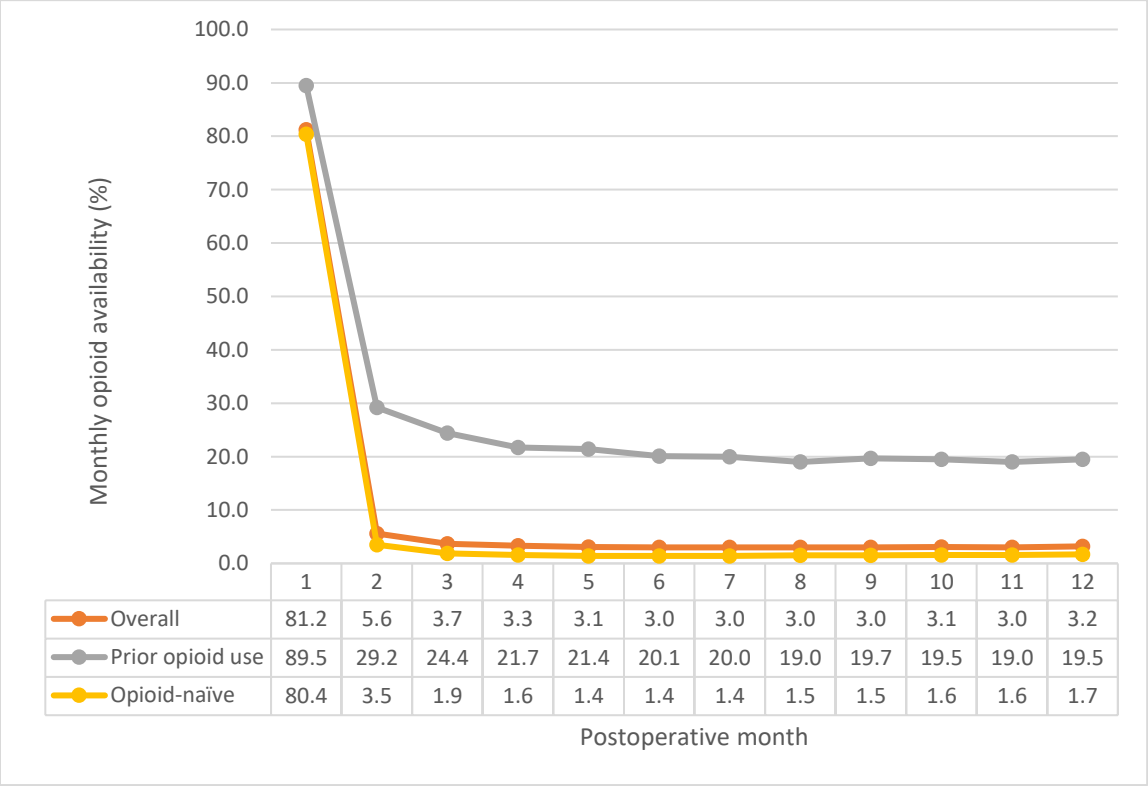
Overall opioid use percentage declined over the course of the first twelve postoperative 30-day (month) periods following ACLRR, from 81.2% in postoperative month one to 3.2% in postoperative month twelve (Figure 5).

Among previously opioid-naïve ACLRR patients, substantive month-to-month decreases in opioid use percentage took place between postoperative months one (80.4%) and two (3.5%) (Figure 5). Absolute month-to-month percentage differences in opioid use did not exceed 0.1% beyond postoperative month four. Among these patients, month-to-month transitions between opioid use and non-use beyond postoperative month four occurred such that between 30-40% of patients who used opioids in a given postoperative month had also used opioids in the prior postoperative month (absolute percentage 0.5–0.6%), whereas the remaining 60-70% of patients who used opioids (absolute percentage 0.9–1.1%) had not used opioids during the prior postoperative month (Figure 6).

Among patients with preoperative opioid use, substantive month-to-month decreases in opioid use percentage took place between postoperative months one (89.5%) and two (29.2%), with smaller subsequent decreases up to postoperative month six (20.1%) (Figure 5). Beyond postoperative month six, absolute month-to-month percentage differences in opioid use were larger compared to the opioid-naïve subcohort but did not exceed 0.5%. Among these patients, month-to-month transitions between opioid use and non-use beyond postoperative month six occurred such that between 78–86% (absolute percentage 15.3–16.4%) of patients who used opioids in a given postoperative month had also used opioids in the prior postoperative month,

whereas the remaining 14–22% of patients who used opioids (absolute percentage 2.6–4.4%) had not used opioids during the prior postoperative month (Figure 6).

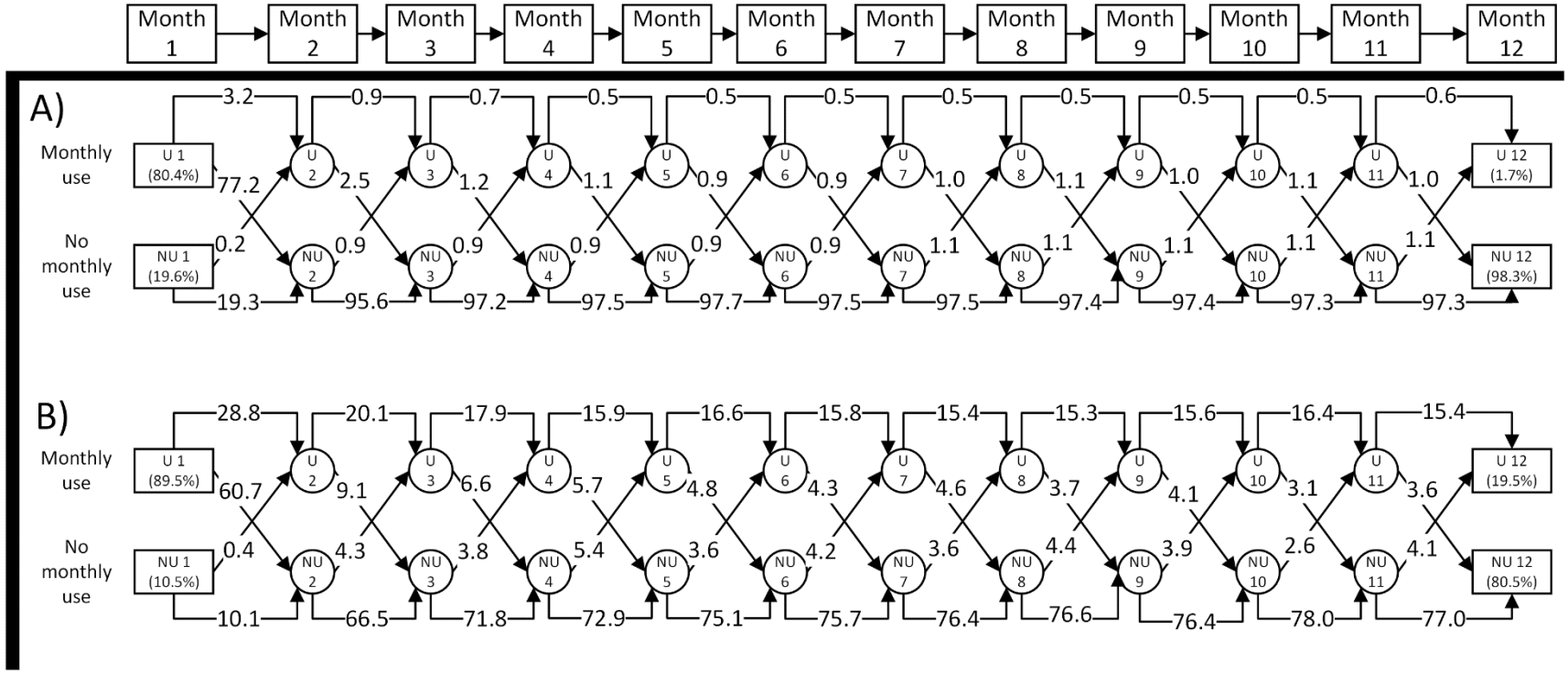
Figure 5: Monthly opioid analgesic availability percentage in the first twelve 30-day postoperative periods following ACLRR



	1	2	3	4	5	6	7	8	9	10	11	12
Overall	81.2	5.6	3.7	3.3	3.1	3.0	3.0	3.0	3.0	3.1	3.0	3.2
Prior opioid use	89.5	29.2	24.4	21.7	21.4	20.1	20.0	19.0	19.7	19.5	19.0	19.5
Opioid-naïve	80.4	3.5	1.9	1.6	1.4	1.4	1.4	1.5	1.5	1.6	1.6	1.7

Legend: X-axis represents each of twelve 30-day (month) periods beginning at indexed ACLRR surgery date for each patient. Y-axis represents the percentage of patients with opioid supply. Values are presented for overall cohort, sub-cohort of patients with preoperative opioid exposure, and sub-cohort of patients with no prior opioid exposure.

Figure 6: Transition probability diagram for month-to-month opioid analgesic use in the first twelve 30-day postoperative periods following ACLRR

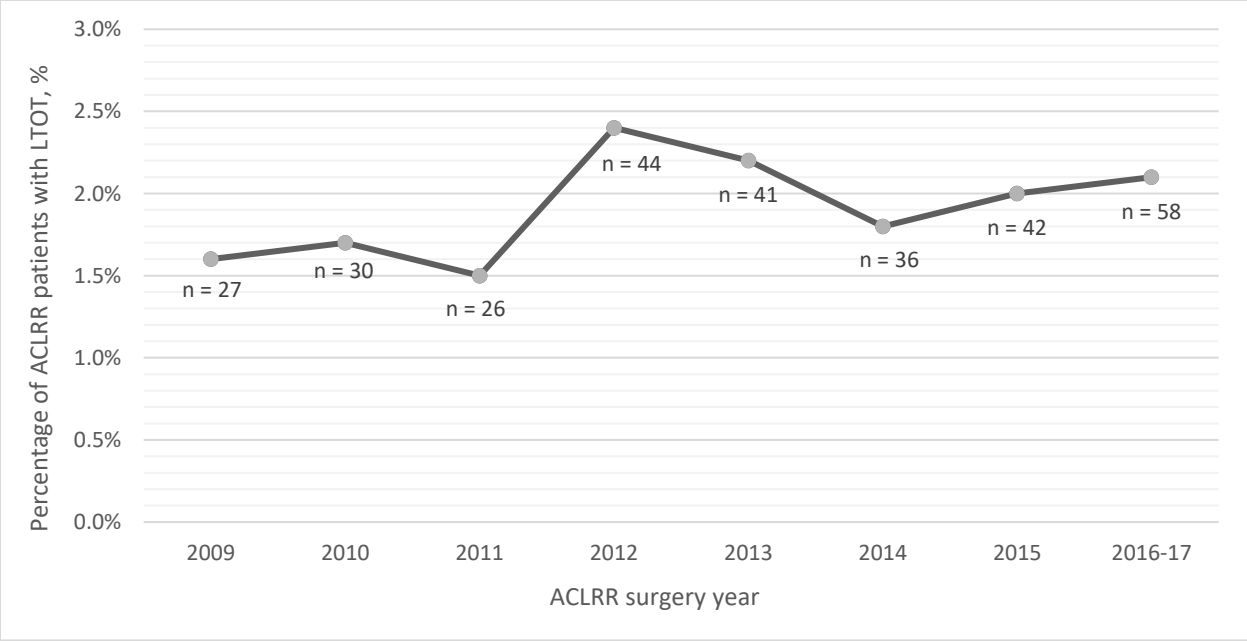


Legend: A) Transition probabilities among preoperative opioid-naïve patient cohort (n = 14,382); B) Transition probabilities among preoperative opioid user cohort (n = 1293). Arrows represent four possible month-to-month transitions between use (U) and non-use (NU): use to use, use to non-use, non-use to use, or non-use to non-use. Arrow numbers represent percent of cohort with each of four possible transitions, which sum to 100% for each transition period.

LTOT proportion following ACLRR

Across the entire ACLRR cohort, 1.9% (304) of patients met the definition for LTOT in the 365 days following surgery. No statistically significant linear trend in LTOT rate was present across the cohort period in univariate ($p < 0.41$) or multivariate-adjusted ($p < 0.24$) trend tests (Figure 7). Subgroup-specific LTOT rates (Table 4) were stratified markedly by prior opioid use status, with only 0.4% (59) of opioid-naïve patients transitioning to LTOT compared to 19.0% (245) of patients with any preoperative opioid use ($p < 0.001$). LTOT was not sex-specific ($p < 0.27$) but increased with age (univariate trend $p < 0.001$). LTOT rate also stratified by surgery type, including meniscal involvement ($p < 0.001$), revision versus primary surgery ($p < 0.05$), and ACL repair at <14 days from acute injury ($p < 0.001$).

Figure 7: Percentage of ACLRR patients meeting LTOT definition in the 365 days following ACLRR, by surgery year, 2009 - Mar 2017.



Data labels below graph indicate period LTOT counts.

Table 4: Proportion of patients meeting the definition for LTOT in the year following ACLRR, by prior opioid use, demographic, and surgical characteristics

Characteristic	No. of LTOT in first year (% within category)	Test statistic *p*-value
Preoperative opioid use		$p < 0.001$*
Pre-operative opioid use (any days' supply, 90 days prior to day of index surgery)	245 (19.0)	
Naïve	59 (0.4)	
Sex		$p < 0.27$*
Male	141 (2.1)	
Female	163 (1.9)	
Age category		$p < 0.001$‡
10-29	46 (0.6)	
30-39	87 (2.1)	
40-49	113 (4.2)	
50-65	58 (5.8)	
Meniscal involvement		$p < 0.001$*
No meniscal involvement	86 (2.6)	
Meniscectomy	177 (2.0)	
Meniscal repair	41 (1.2)	
Revision surgery		
Primary	271 (1.9)	$p < 0.05$*
Revision	33 (2.9)	
ACL repair at <14 days from acute injury		
ACL reconstruction	>294 (>1.9)	$p < 0.001$*
Acute ACL repair	<20 (<6.6)	
*Indicates chi-square test statistic (test of equality); ‡indicates Cochran-Armitage test statistic (test for trend)		

Non-opioid analgesic drug dispensation trends in ACLRR

Patients undergoing ACLRR were dispensed NSAIDs within their first 30 postoperative days following 6,300 (40.2%) surgeries (Table 5). This proportion ranged from 8.1% among opioid-naïve users with no opioid use in postoperative month 1 to 48.2% among opioid-naïve

patients with opioid use in postoperative month 1 ($p < 0.001$), and declined from 2009 (38.7%) to 2016-17 (36.2%; univariate trend $p < 0.001$).

Table 5: Postoperative NSAID prescription patterns following ACLRR, by perioperative opioid use and surgery year, 2009-2017

Characteristic	Number of ACLRR patients prescribed NSAID within 30 days following healthcare discharge (%)	Test statistic *p*-value
Overall cohort	6,300 (40.2)	
Perioperative opioid use		
Opioid-naïve, no opioid use within first 30 postoperative days	227 (8.1)	p < 0.001*
Opioid-naïve, opioid use within first 30 postoperative days	5578 (48.2)	
Prior opioid use, no opioid use within first 30 postoperative days	26 (19.1)	
Prior opioid use, opioid use within first 30 postoperative days	469 (40.6)	
Surgery year		
2009	670 (38.7)	p < 0.001‡
2010	715 (41.3)	
2011	747 (43.0)	
2012	807 (44.2)	
2013	806 (43.8)	
2014	767 (38.3)	
2015	795 (38.6)	
2016-17	993 (36.2)	
*Indicates chi-square test statistic (test of equality); ‡Indicates Cochran-Armitage test statistic (test for trend)		

Discussion:

Compared to 2009, Albertan patients undergoing ACLRR in 2016-17 more frequently entered surgery with recent preoperative opioid exposure, and patients without exposure became

more likely to fill an opioid prescription during their first postoperative month. Also by 2016-17, more than two fifths of preoperatively opioid-naïve patients undergoing ACLRR received an initial postoperative dispensation daily dosage exceeding 50 MME. Despite no increase in overall cohort LTOT rate (1.94%), these findings are unexpected, given current evidence which supports opioid dosage reductions.

Preoperative opioid prescribing

We identified preoperative opioid exposure in 8.3% of patients undergoing ACLRR. This use percentage is lower than those reported by Rao et al[23] (25.5%) as well as Anthony et al[21] (35%). The present study preoperative opioid use definition closely matches that of Anthony et al., and given the similar time periods captured within these studies, this may be a true difference in preoperative opioid demand. USA-Canada differences between rates of opioid prescriptions filled in advance of surgery might account for some of this difference. In a large American health claim database, Howard et al observed that 13.7% of patients who were preoperatively opioid-naïve received an initial prescription in advance of surgery[35]. Our preoperative data shows an excess of approximately 100 opioid dispensations in the most immediate presurgical month (Appendix A, Table 10) compared to the second and third most immediate preoperative months, equating to potential early prescriptions, as per Howard, for fewer than 1% of the overall ACLRR cohort.

Postoperative opioid initiation

Approximately four in five opioid-naïve patients undergoing ACLRR received an opioid dispensation within 30 days of healthcare discharge. Anthony et al reported similar opioid initiation (approximately 75%) in their ACLR cohort[21]. The absolute percentage increase of

24.4% from 2009-2017 we observed for this initiation metric contrasts study data from 2013–2017 in Ontario[20], which found no such large increase for patients undergoing procedures with anticipated postoperative pain in line with estimates for ACLRR[36–38], nor for other joint-associated orthopedic procedures. Our data, more substantially aligns with British Columbia total knee arthroscopy (TKA) data from 2003-2016, where postoperative opioid initiation increased by an average of 0.8% year-to-year, and 94% of patients received opioids s within 30 days postoperatively[19]. Our overall opioid dispensation proportion is also similar to patients' 7-day post-discharge opioid dispensation proportion following knee meniscectomy in Ontario from 2013–2016[1].

Initiating dispensation characteristics among opioid-naïve patients undergoing ACLRR changed appreciably during the study period. Tramadol replaced codeine as the most commonly dispensed postoperative opioid by 2016-17, in an upwards trend exceeding those seen following TKA in British Columbia[19], moderate anticipated pain surgical procedures in Ontario[20], and overall per capita tramadol prescribing in Alberta[39]. Unlike codeine or oxycodone, tramadol was not classified as a *Schedule I* controlled substance in Canada until 2022[40], so it is plausible that recommendations to more carefully prescribe traditional opioids prompted substitution of codeine with tramadol, as hypothesized in British Columbia's TKA data[19]. While more frequent NSAID co-dispensation might have been expected in response to the same recommendations, our data instead shows NSAID co-dispensation following fewer than half of ACLRRs and a downwards trend from 2009-2017.

We observed an increase in proportion of initiating dispensations which included more than one opioid prescription over the study period. This is consistent with prescribing data following TKA in British Columbia[19] and presents the possibility of more frequent therapeutic

duplication. Unfortunately, since we could not capture dispensation indication or prescriber intent, we cannot conclusively identify specific opioid co-administrations as inappropriate or high risk.

We found that ultrashort (1-2 day) and long (7-14, 15+ day) duration dispensations were utilized less frequently by the end of the study period. This aligns with postoperative pain management guideline recommendations to utilize prescriptions not exceeding 7 days in length[38,41], is consistent with patient-reported postoperative opioid use in ACLRR[37,42,43], and likely reduces refill need accompanying ultrashort duration dispensations. Average dispensation daily dosage, on the contrary, increased over the study period to >50 MME, alongside the proportion of patients without preoperative opioid exposure initiated on dispensations at the second highest ($50 \leq MME < 90$) and highest (≥ 90 MME) daily dosage categories. While no single opioid dosage threshold exists straddling which all adverse events begin or cease to take place, rates of LTOT, opioid misuse, overdose and death are all positively associated with opioid prescription dosage[2,44]. Furthermore, postoperative opioid reduction interventions in ACLRR do not appear to negatively affect patient postoperative pain[45] or refill frequency[46]. Together, there is minimal justification for these upwards trends among patients undergoing ACLRR without preoperative opioid exposure. Future procedure-specific guidance which encourages prescribers to adopt opioid-minimizing or opioid-sparing regimens already observed to be efficacious in ACLRR[45–47]—comparable to those already created by PROSPECT for TKA and for rotator cuff repair[48]—are needed if an evidence-based change in ACLRR postoperative opioid prescribing is desired.

Opioid use in the first postoperative year

We observed LTOT among 1.94% of patients undergoing ACLRR. That LTOT rates stratified by preoperative opioid use status, mirrors prior ACLRR[21–23] and non-ACLRR data[49]. Notably, we observed an opioid use proportion at and beyond six months which was nearly double that of Anthony et al[21]. Our study accounts for day-to-day opioid supply, and includes dispensations which overlapped multiple postoperative months, instead of absence/presence of monthly prescription filling. While this provides a more granular representation of monthly postoperative opioid utilization, it remains unclear whether definition alone accounts for observed differences in month-to-month use. Comparatively, our observed rate of LTOT among patients undergoing ACLRR without preoperative opioid exposure (0.4%) does mirror patient data from Orfield et al's American statewide claims database study (<0.5%)[50], which used a cumulative opioid supply-based LTOT definition. They note that ACLR resulted in the lowest LTOT rate across 50 common orthopedic procedures; showcasing this, all other listed knee procedures in their study resulted in LTOT rates of at least fivefold those in ACLR. This gives credence to surgery classification methods which reflect potential postoperative drug utilization—for example, by expected postsurgical pain level, as in Nunn et al[19] and Jivraj et al[20]—as opposed to "orthopedic surgery" as a catch-all.

We found, among patients undergoing ACLRR with opioid supply beyond postoperative month six, those with preoperative opioid use were more likely to have continued a use episode which began in a prior postoperative month, whereas opioid-naive patients were more likely to have begun and subsequently ended a use episode in the same month. This is an intuitive, but relatively novel, method of describing opioid re-initiation and discontinuation processes, and has not yet been substantially utilized in surgery pharmacoepidemiology. This finding should provide some assurance to prescribers that providing late-period postoperative opioid

prescriptions to preoperatively opioid-naïve individuals does not alone necessitate further continuous or long-term use.

Study strengths and limitations

Our study benefited from access to an entire cohort of publicly conducted ACLRRs in a Canadian province over nearly a decade, alongside complete community pharmacy dispensation records and comprehensive cohort characterization by demographic and comorbidity risk factors. The granular dispensation data allowed for identification of initial prescription characteristics among opioid-naïve patients, enabled LTOT ascertainment based on cumulative day-to-day instead of month-to-month supply, and accounted for carryover use – improvements from American ACLRR cohort studies where data access was more limited[21,23].

Our study is not without limitations. Its recommendations mostly apply to patients without preoperative opioid exposure, who represented over ninety percent of the study population but the minority of LTOT patients. In comparison, opioid prescribing for postoperative pain among patients already consuming opioids warrants patient-specific assessment and consultation with pain management specialists prior to the development of a postoperative analgesia regimen and it is imprudent to suggest such patients follow recommendations targeted at patients without preoperative opioid exposure.

This study utilized retrospective data not expressly collected for research and is therefore susceptible to certain biases common to pharmacoepidemiology. Community pharmacy dispensation records do not capture unfilled prescriptions, pharmacotherapy obtained during hospital care episodes, non-prescription pharmacotherapy, or prescription pharmacotherapy obtained via diversion. Furthermore, to derive patients' daily opioid availability, this study

assumed that patients consumed dispensations beginning on their dispensation date and in line with expected days' supply. Consequently, we underestimated consumption among patients who sought opioids other than those available to them via community pharmacies, and overestimated consumption among patients who discontinued opioid pharmacotherapy prior to exhausting their dispensation[51].

Conclusion

Perioperative opioid use is lower in ACLRR than in many other orthopedic surgery procedures and is moderately comparable between Canadian and American surgical populations, especially among opioid-naïve patients. While no overall upwards trend in postoperative LTOT took place in Alberta from 2009-2017, initiating opioid dosage escalations over the same time period depart from evidence-based recommendations that favor multimodal pain management. Creating procedure-specific guidance for clinicians is recommended.

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Appendix A

Table 6: The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	A) ii b) ii	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1) ii 1.2) ii 1.3) ii
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	26-27		

Objectives	3	State specific objectives, including any prespecified hypotheses	27		
Methods					
Study Design	4	Present key elements of study design early in the paper	27-31		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	27-31		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give	A) 28, Fig. 1	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to	6.1) Appendix A, Table 7 6.2) 29, Appendix A, Table 7 6.3) N/A

		matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	28-31, Appendix A, Table 7	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Appendix A, Table 7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	30-31		
Bias	9	Describe any efforts to address potential sources of bias	28, 29, 31, Appendix A, Table 8		
Study size	10	Explain how the study size was arrived at	Figure 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	31		
Statistical methods	12	(a) Describe all statistical methods, including those	a) 31 b) 31 c) 28, Figure 1		

		used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	d) 28, Figure 1		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1) 27 12.2) Appendix A, Table 8
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data	27, 28

				linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	27, 28, Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 1		
Outcome data	15	*Cohort study* - Report numbers of outcome events	Tables 2-5, Figures 2-7		

		or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	A) Tables 2-5, Figures 2-7 B) Table 1, Figure 3, Figure 4, Table 4 C) N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
Discussion					
Key results	18	Summarise key results with reference to study objectives	47-52		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	52-53	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	52-53
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	53		
Generalisability	21	Discuss the generalisability (external validity) of the study results	52		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	N/A

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Table 7: Administrative health data codes used to ascertain surgery exposures, risk factor exposures, outcomes

Exposure/outcome category	Code structure
ACLRR codes	
National Ambulatory Care Reporting System (NACRS) / Hospital Inpatient Data	*Canadian Classification for Health Interventions (CCI) codes:* 1.VL.80x, 1.VN.80x
Practitioner claims data	*Billing codes:* 93.45A, 93.45B, 93.45C, 93.45D, 93.45E, 93.45F, 93.45J
Charlson comorbidity index risk factor sub-codes (ICD-10-CA codes)* **	
Myocardial infarction (weight 1)	I21.x, I22.x, I25.2
Congestive heart failure (weight 1)	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease (weight 1)	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease (weight 1)	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia (weight 2)	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease (weight 1)	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Connective tissue / rheumatic disease (weight 1)	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease (weight 1)	K25.x-K28.x
Mild liver disease (weight 1)	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without complications (weight 1)	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0,E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with complications (weight 2)	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Paraplegia and Hemiplegia (weight 1)	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9

Renal disease (weight 2)	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Cancer (weight 2)	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Moderate or severe liver disease (weight 3)	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic carcinoma (weight 6)	C77.x-C80.x
HIV/AIDS (weight 6)	B20.x-B22.x, B24.x
Opioid analgesic codes	
Initial identification of opioid	*Anatomical Therapeutic Chemical codes:* N02Ax, R05DAx
Opioid exclusion categories	*Anatomic Therapeutic Chemical* code-based exclusion*:* i) Drugs containing only dextromethorphan (R05DA09) or combination (R05DA20) ii) Opioid-naloxone combinations (A06AH04) *via Drug Identification Number* matched with Government of Canada *Drug Product Database:* i) Liquid, nasal, rectal, parenteral formulation
Other drug product codes	
Non-steroidal anti-inflammatory drug use	M01Ax

* codes obtained from Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining Comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov; 43(11): 1130-9

** weights obtained from Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8. PMID: 3558716.

Table 8: Cleaning algorithm for Practitioner Claims database

Algorithm steps	i. Same-date ACLRR claims by multiple practitioners on a single patient were interpreted as a single ACLRR surgery. ii. Discrepancies in ACLRR billing code between practitioners were resolved by retaining the practitioner claim from the designated primary surgeon. iii. Discrepancies in surgery date during a single episode of care were resolved by retaining the earliest claim date. iv. Instances of billing code *93.45B*, representing early cruciate ligament repair, required the same-day NACRS or DAD-linked episode of care to document an ACLRR via CCI code.

Table 9: Average initiating opioid prescription dosage and duration among previously opioid-naïve ACLRR patients, year by year, 2009-2017

	Group	Daily dosage (MME)	Duration (days)
Year	Overall opioid-naïve subgroup (n = 11,491), mean [SD]	49.2 [31.7]	6.30 [4.18]
	Surgery period, mean [SD]		
	2009	44.3 [31.1]	6.23 [4.13]
	2010	43.0 [27.4]	6.49 [5.27]
	2011	43.7 [28.3]	6.48 [4.41]
	2012	44.0 [27.6]	6.28 [4.25]
	2013	45.5 [29.6]	6.28 [4.33]
	2014	51.9 [32.9]	6.18 [3.65]
	2015	55.1 [33.4]	6.25 [3.98]
	2016-17	57.3 [34.7]	6.29 [3.80]
Surgery period univariate trend	2009-2017	$p < 0.001$	$p < 0.04$
Surgery period multivariate-adjusted trend*	2009-2017	$p < 0.001$	$p < 0.09$
*test for linear trend in multivariate linear regression controlling for age, sex, and surgical procedure			

Table 10: Preoperative dispensations by period, and excess dispensations in the proximal preoperative period.

Period	Preoperative month(s) (days, in reference to start of ACLRR-linked episode of care)	Opioid dispensation count (n)	Mean monthly dispensations (n)	Excess dispensation (n)
Distal preoperative period	Months 2 to 3 (-31 to -90)	1,620	810	Baseline
Proximal preoperative period	Month 1 (-1 to -30)	908	908	98

Chapter 3: Patient-level risk factors for long-term opioid pharmacotherapy among patients undergoing anterior cruciate ligament reconstruction and repair: a retrospective cohort study

The contents of this chapter are formatted for submission to a peer-reviewed journal.

Introduction:

Effective treatment of postoperative pain involves maximizing analgesic efficacy while minimizing undesirable treatment effects. Prior consensus during the immediate postoperative period—opioid pharmacotherapy as the primary source of pain control—has largely been replaced with recommendations for the use of multimodal analgesia[1], in response to a burgeoning field of research which suggests that it can equal or better pain outcomes versus opioid monotherapy and provide high patient satisfaction[2–5]. This focused research has been conducted, in part, as a response to increases in prescription opioid-associated morbidity and mortality in the United States and Canada from the mid-1990s to early 2010s[6,7]. Despite a push for change, patients of both countries still receive larger opioid prescriptions than in other countries with comparably advanced health systems for the same procedures without clear benefits to acute postsurgical pain levels[8]. Furthermore, surgical patients who transition to long-term opioid therapy (LTOT), commonly defined as ≥90 days of opioid consumption within a yearlong period[9,10], exhibit a significantly increased risk of opioid-associated harms[11]. Identifying surgical patients who are at a higher risk of LTOT allows targeted risk communication to the patient and provides prescribers opportunities to intervene during the perioperative period.

Risk factors for LTOT following anterior cruciate ligament surgery (ACLRR) have previously been elucidated using data collected from large integrated health systems in the United States[12–14]. The purpose of this study is to identify associations between patient-level risk factors and LTOT in ACLRR using a broad catalogue of putative risk factors, and to include, as a potential risk factor, initial opioid dispensation characteristics, which predict LTOT in a general opioid-naïve population[15]. This study furthermore seeks to follow recent

recommendations within opioid pharmacoepidemiology, to utilize robust measures of LTOT during analysis[9,10].

Methods:

This study was approved by the University of Alberta Health Research Ethics Board – Health Panel (Pro00090820). Direct participant identifiers were anonymized prior to receipt of the data. This study solely used anonymized, routinely collected individual-level administrative health data, and participant consent was not required. This study follows RECORD reporting guidelines (Appendix B, Table 16).

Study data sources

The study utilized five data sources: clinical data from inpatient (Discharge Abstract Database; DAD) services; clinical data from ambulatory care (National Ambulatory Care Reporting System; NACRS) services; pharmaceutical dispensation data from community pharmacy (Pharmaceutical Information Network; PIN) services; Alberta Health Care Insurance Plan (AHCIP) billing data (Practitioner Claims), and yearly AHCIP registration data (Provincial Registry). Complete data were available from January 1, 2008 to March 31, 2019. Each patient had a consistently anonymized Unique Lifetime Identifier (ULI) which allowed for deterministic data linkage.

Study design and cohort enumeration

This is a retrospective cohort study using routinely collected administrative health and demographic data. Billing codes indicating ACLRR (Appendix B, Table 17) were flagged in the Practitioner Claims database and a cleaning algorithm was performed prior to indexing

(Appendix B, Table 18). Patients undergoing multiple ACLRR were indexed for each ACLRR. ACLRRs were subsequently excluded from analysis if: 1) surgery took place before January 1, 2009 or after March 31, 2017; 2) the patient was not insured under AHCIP from the fiscal year prior to their surgery to the fiscal year two years after their surgery; 3) the patient underwent another ACLRR within two years following index surgery; 4) the patient had a cancer-associated diagnostic code in the year prior to or within two years following ACLRR; or 5) the patient was under ten years of age or older than 65 years of age at the end of the fiscal year in which the ACLRR took place. This process excluded patients who died during the two-year follow up or otherwise lapsed their AHCIP coverage as well as non-residents.

Exposure and outcome ascertainment timelines

The preoperative period was defined as the 365-day period ending one day prior to the date of admission for the episode of care which overlapped the indexed ACLRR date. The postoperative period was defined as the 365-day period beginning on the date of admission for patients undergoing ACLRR in ambulatory care, and on the discharge date of the episode of care which overlapped the indexed ACLRR date for patients undergoing inpatient ACLRR. Month-to-month postoperative periods were operationalized as twelve consecutive 30-day periods beginning on postoperative day 1 and ending on postoperative day 360.

Preoperative comorbidities, intraoperative exposures, demographic characteristics

Preoperative comorbidities identified for this study were the 17 subcategories of Quan's Charlson Comorbidity Index[16] with original weights[17], mental health and substance use associated diagnoses, and an algorithm for chronic pain[18] (Appendix B, Table 17). Comorbidities were identified from prior literature[10,12–14] on LTOT in general surgery and in ACLRR.

Comorbidities were considered present if any comorbidity-associated code in NACRS or DAD databases was observed during the preoperative period.

Categorization of ACLRR surgical procedure took place using surgery-specific billing codes from the Practitioner Claims database. This study identified primary ACL reconstruction (ACLR), revision ACLR, ACLR with concomitant meniscectomy or meniscal repair, as well as ACL repair occurring <14 days from acute injury (Appendix B, Table 17).

Patient age and sex were identified using the Provincial Registry database. Patient age was set to the patient's reported age at the end of the fiscal year where the indexed ACLRR occurred, then categorized (10–19 to 50–65).

Pharmaceutical exposures

The PIN dataset contained every instance that prescription drugs were dispensed to ACLRR patients in Alberta community pharmacies. Each row of the dataset corresponded to a single drug dispensation, and housed information on dispensation date, Canadian *Drug Product Database* Drug Identification Number (DIN), drug Anatomical Therapeutic Chemical (ATC) code, unit of dispensation, quantity, and estimated days' supply. This study assumed that drug dispensations were consumed beginning on their dispensation date and in accordance with estimated days' supply.

Dispensations with ATC codes N02A**x** and R05DA**x** were identified as opioids and their DINs were matched to records from Canada's *Drug Product Database*. Information regarding drug formulation and route of administration was used to include or exclude the dispensation from analysis (Appendix B, Table 17). Opioid dispensations were converted into morphine milligram equivalent (MME) dosages using the Centers for Disease Control and Prevention

(CDC) 2020 conversion factors[19]. Patients' opioid supply was identified as present or absent and quantified in MME each day during the preoperative and postoperative periods. This study used a modified version of a previously developed opioid use calculation toolkit[20].

Patients were defined as opioid-naïve—having no recent preoperative opioid exposure—if during the last 90 days of the preoperative period, they had no opioid supply. For opioid-naïve patients who were dispensed any opioids during their first 30 postoperative days, their first postoperative dispensation was categorized by daily MME and duration, using categories adapted from prior research on LTOT risk[15,21].

Patients were identified if they received dispensations of antidepressants, antipsychotics, benzodiazepines, or non-steroidal anti-inflammatory drugs (NSAIDs) (Appendix B, Table 17) during the preoperative period. Dispensations at any point during the preoperative period constituted preoperative drug exposure for these non-opioid drug classes. Patients were also identified if they received dispensations of NSAIDs during their first 30 postoperative days.

LTOT outcome ascertainment

Patients exhibited LTOT under this study's primary LTOT definition if during the entire postoperative period, they had >90 days of opioid supply. This LTOT definition (Primary) matches the most used calendar time cut-off to define LTOT[10]. Two preplanned sensitivity analyses in LTOT definition were carried out. First, indicating repeated refill of opioid dispensations beyond typical postsurgical pain timelines (Intermediate definition), patients exhibited LTOT if they had any opioid supply during at least three of postoperative months 4-12, which is herein referred to as the late postoperative period. Second, and closely matching

definitions of LTOT from previous studies in ACLRR[12,13], patients exhibited LTOT (Prior Studies' definition) if they had any opioid supply between postoperative days 91-365.

Statistical analysis

Patient characteristics were operationalized to dichotomous or categorical variables and reported using count and proportion. Characteristics exhibiting a count of <20 were excluded from analysis[22]. Fisher's exact test was used for univariate comparison of LTOT prevalence between opioid-naïve and non-naïve patients. Prior to model building, variables were assessed for multicollinearity (variance inflation factor >5).

We used multivariable logistic regression to describe the associations of patient-level characteristics for each of the three LTOT outcomes. Augmented backwards elimination (ABE) with standardized change-in-estimate was employed for model candidate variable selection[23]. This process allows a model to retain variables which show a statistically significant association with LTOT, retain confounder variables to allow better approximation of model coefficients, and exclude variables which exhibit neither associative nor confounding properties. ABE models altogether retain variables which might otherwise be removed during purely significance-based variable selection processes but provide more model parsimony than models without candidate variable selection[23]. In addition, this study used Firth correction to reduce sparse data bias from low anticipated LTOT outcome prevalence and ACLRR patient comorbidity. Associations were reported using adjusted odds ratios (aORs) with 95% confidence intervals. Trend tests were performed *post* hoc using orthogonal contrasts. Significance was set at $p < 0.05$.

An initial model using the complete ACLRR cohort was generated first for the primary definition LTOT outcome, then the candidate variables selected from the initial model were

respectively used to fit models for the intermediate and prior studies' definition LTOT outcomes. This process was repeated to generate another three models among the subset of patients undergoing ACLRR who were both preoperatively opioid-naïve and who received an opioid dispensation within their first 30 postoperative days.

Data processing for this study was performed using SAS/STAT 9.4 for Windows.

Results

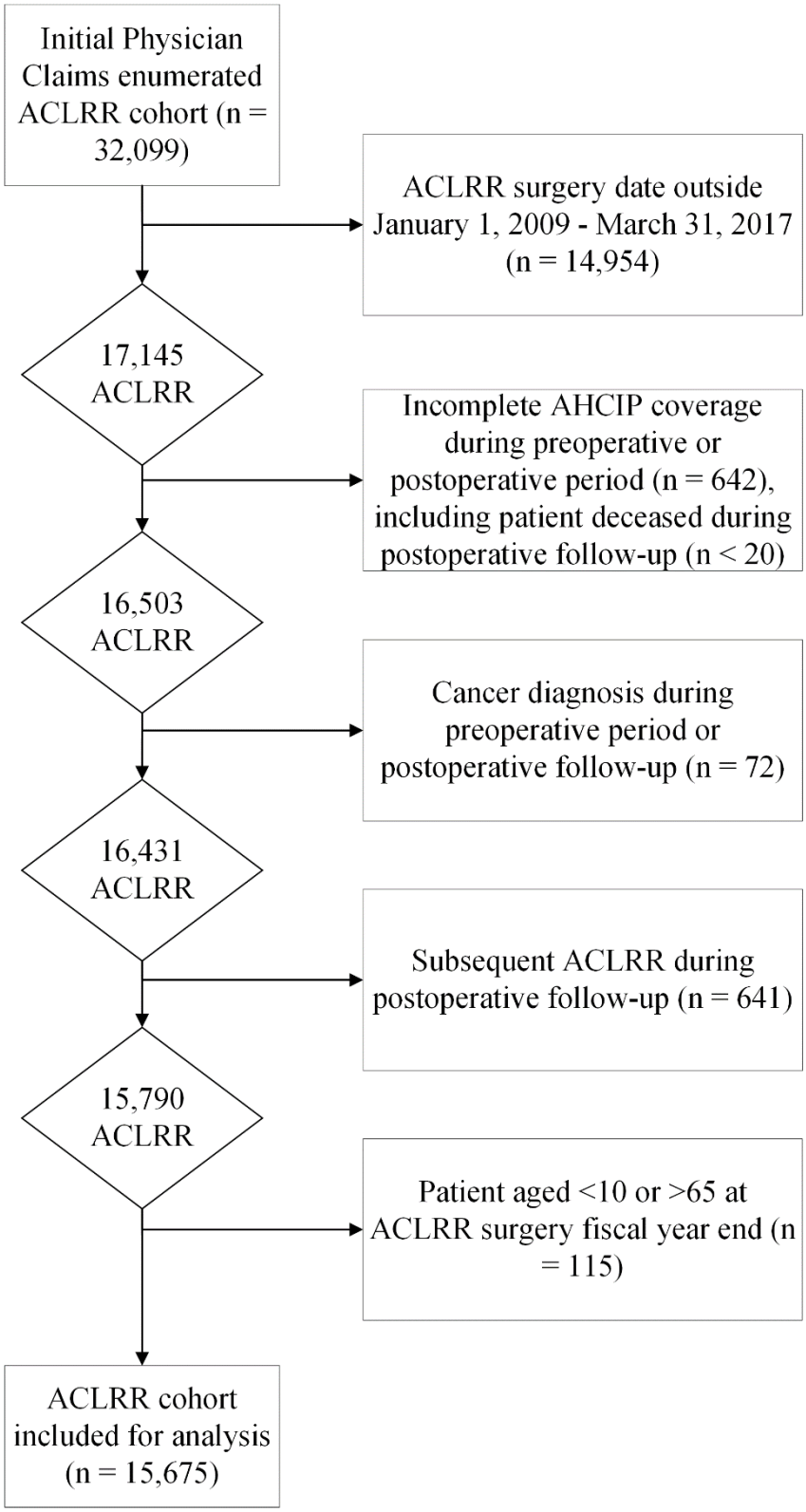
Cohort characteristics

15,675 ACLRRs were eventually included for analysis from an initial 32,099 enumerated ACLRR patients (Figure 8).

Patient demographic, comorbidity, and surgical baseline characteristics are presented in Table 11. Individuals aged 10-29 made up the largest group in the study, at 7,917 (50.5%) patients, and 6,447 patients (43.2%) were female. Apart from the combined 2016-17 surgical period, surgery count increased year-over-year from 1,730 (11.0% of the cohort) in 2009 to 2,061 (13.2% of the cohort) in 2015.

Preoperative non-opioid medication use ranged from 166 (1.1%) patients using antipsychotics to 1,215 (7.8%) patients using antidepressants. Alcohol and non-alcohol drug use disorder were identified respectively in 0.9% (145) and 1.4% (269) of ACLRR patients. Apart from 6.6% (1,031) of the ACLRR cohort having a preoperative chronic pain diagnosis, comorbidity was low, with counts < 20 (0.13%) for patients exhibiting 14 of 17 Charlson comorbidity subgroups, bipolar disorder, and schizophrenia. Only 402 patients (2.6%) had a weighted Charlson comorbidity index score of ≥1.

Figure 8: Flow diagram from initial enumerated ACLRR cohort to study-eligible cohort



ACLR with meniscectomy was indicated in over half (8,229) of the cohort and was more than twice as prevalent as any other procedure. Revision surgery patients made up under 8% (1,155) of the ACLRR cohort. 1.3% (202) of patients underwent ACL repair within 14 days of acute injury, and in 3.7% (584) of surgeries ACLRR had taken place in the two preceding years.

Table 11: Cohort characteristics of patients undergoing 15,675 ACLRR

Characteristic	No. of surgeries (%)
Demographic characteristics	
Female sex	6,774 (43.2)
Age category	
10-29	7,917 (50.5)
30-39	4,077 (26.0)
40-49	2,678 (17.1)
50-65	1,003 (6.4)
Preoperative characteristics (one year lookback unless noted)	
1-year longitudinal Charlson comorbidity index, weighted	
0	15,273 (97.4)
1	360 (2.3)
≥2	42 (0.3)
Pre-operative opioid exposure (90-day lookback)	1,293 (8.3)
Benzodiazepine use	559 (3.6)
Antidepressant use	1,215 (7.8)
Antipsychotic use	166 (1.1)
Anxiety	93 (0.6)
Stress / adjustment disorder	82 (0.5)
Depression	93 (0.6)
Alcohol use disorder	145 (0.9)
Other drug use disorder	269 (1.4)
Chronic pain	1031 (6.6)
Chronic pulmonary disease	201 (1.3)
Peptic ulcer disease	25 (0.2)
Uncomplicated diabetes	106 (0.7)
Perioperative characteristics	
Recent ACL surgery (any ACL reconstruction in two-year lookback)	584 (3.7)

Surgery type (mutually exclusive)	
ACL reconstruction with bone-patellar tendon graft	2,733 (17.4)
ACL reconstruction with meniscectomy	8,229 (52.5)
ACL reconstruction with meniscal repair	3,356 (21.4)
Early ACL repair, within 14 days	202 (1.3)
Revision ACL reconstruction	341 (2.2)
Revision ACL reconstruction with meniscectomy	597 (3.8)
Revision ACL reconstruction with meniscal repair	217 (1.4)
Individual patient characteristics excluded due to count of <20: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, connective tissue/rheumatic disease, mild liver disease, diabetes with complications, paraplegia/hemiplegia, renal disease, moderate/severe liver disease, metastatic carcinoma, HIV/AIDS, bipolar disorder, schizophrenia.	

Among the 11,491 opioid-naïve individuals who received an opioid dispensation within 30 days from the start of the postoperative period (Table 12), 26 (0.2%) received extended-duration formulations. First prescription daily MME was typically <50 (66.8%), initiating prescription duration was most often 5-7 days (46.7%), and 5,574 patients (48.5%) received prescription NSAIDs during their first postoperative month.

Table 12: Characteristics of 11,491 opioid initiations among preoperatively opioid-naïve ACLRR patients receiving opioids in their first 30 postoperative days

Characteristic	No. of patients (%)
Extended-release formulation	26 (0.2)
Daily dosage (MME)	
MME < 50	7,673 (66.8)
50 ≤ MME < 90	2,071 (18.0)
MME ≥90	1,747 (15.2)
Days' supply of first opioid prescription (days)	
<5	3,391 (29.5)
5-7	5,327 (46.7)
8-14	2,311 (20.1)
≥15	462 (4.0)
NSAID prescribed within 30 days postoperatively	5,574 (48.5)

Complete cohort LTOT prevalence

The primary definition LTOT outcome had a complete-cohort prevalence of 1.9%, in comparison to intermediate (2.2%) and prior studies' (10.9%) definitions (Table 13). Each of the three LTOT outcome prevalences were stratified significantly by preoperative opioid exposure via univariate analysis (Table 13).

Table 13: LTOT outcome proportions in the complete ACLRR cohort, with stratification by preoperative opioid exposure status

LTOT outcome definition	Total no. (%) of patients (cohort n = 15,675) with outcome	No. (subcohort %) of opioid-non-naïve patients (subcohort n = 1,293) with outcome	No. (subcohort %) of opioid-naïve patients (subcohort n = 14,382) with outcome
Primary[a]	304 (1.9)	245 (19.0)	59 (0.4)***
Intermediate[b]	346 (2.2)	261 (20.2)	85 (0.6)***
Prior Studies[c]	1,701 (10.9)	490 (28.8)	1,211 (8.4)***
Fisher's Exact test for equality of LTOT proportion in naïve versus non-naïve subcohort: *** indicates $p < 0.001$			
LTOT definitions: a) >90 days' supply during postoperative days 1–365 b) At least 1 days' supply per period, for at least three of the nine 30-day postoperative periods beginning on postoperative day 91 c) At least 1 opioid dispensation between postoperative days 91–365			

Measures of association with each LTOT outcome are presented for models using the complete ACLRR cohort (Table 14) and for models which included only opioid-naïve ACLRR patients who received opioids within their first 30 postoperative days (Table 15). Zero patients between ages 10-19 met the primary definition of LTOT within the opioid-naïve cohort; to allow for model convergence and comparability, age categories 10-19 and 20-29 were aggregated in all models.

Demographic risk factors

Female sex was not significantly associated with primary or intermediate LTOT and was negatively associated with prior studies' outcomes in both complete (aOR 0.85; 95% CI 0.76–0.95) and opioid-naïve (aOR 0.80; 95% CI 0.71–0.92) cohort models.

Patient ages 30-39, 40-49 and 50-65 were positively associated with primary and intermediate LTOT versus ages 10-29 in all complete cohort models, (maximum aOR 5.68; 95% CI 3.59–9.00). Similar associations were observed in naïve-cohort models, with the exception of patient age 40-49 using the prior studies' LTOT definition (maximum aOR 7.67; 95% CI 3.07–19.20). aOR point estimates progressively increased with increasing age category in both primary outcome LTOT models and the complete cohort intermediate outcome LTOT model (maximum $p < 0.02$).

Preoperative drug exposure risk factors

Preoperative opioid exposure exhibited the strongest association with LTOT in all complete cohort models, with a maximum aOR of 31.51 (95% CI 23.06–43.06) in the primary LTOT model. Preoperative benzodiazepine exposure was positively associated with LTOT in all six models, second only to preoperative opioid use in associative strength. Preoperative antipsychotic use was positively associated with LTOT for all models other than the complete cohort, primary LTOT outcome model, where it acted as a confounder. Preoperative antidepressant use was positively associated with LTOT in complete, but not opioid-naïve cohort models. Preoperative NSAID use was a confounder in both primary LTOT models and exhibited positive association in prior studies' LTOT models as well as the complete cohort intermediate LTOT model.

Preoperative mental health risk factors

Neither anxiety nor depression were significantly associated with LTOT in any model, but both were retained as confounders in the naïve-cohort models.

Alcohol use disorder and non-alcohol drug use disorder were both positively associated with all measures of LTOT in the complete cohort. In the opioid-naïve sub-cohort models they were respectively associated only with prior studies' LTOT (alcohol) or intermediate LTOT (non-alcohol) outcomes and were confounders for primary LTOT.

Preoperative chronic disease risk factors

Chronic pulmonary disease was positively associated with LTOT in all models. Diabetes without complications was retained in the complete cohort models, where it was positively associated with the prior studies' LTOT outcome; in the naïve cohort models, it was positively associated with primary and prior studies' LTOT outcomes.

Surgery type risk factors

ACL repair performed within 14 days of acute ACL injury was positively associated with LTOT in all six models. Revision surgery was retained as a confounder in all six models. ACLR with meniscal repair and ACLR with meniscectomy were retained as confounders only in naïve-subset cohort models.

First opioid dispensation risk factors in naïve-subset cohort

Among opioid-naïve patients with opioid dispensations in the first 30 postoperative days, initial dispensations which included an extended-release formulation opioid were positively associated with all three LTOT measures. Initiating prescription duration of ≥15 days versus 1-4 days was positively associated with primary- and intermediate-definition LTOT. First

prescription daily dosages of 50 ≤ MME < 90 and ≤90 MME versus <50 MME were positively associated with primary definition LTOT only, and no clear dose-response relationship among initiating dosage was observed.

Table 14: Measures of association of patient-level characteristics with LTOT outcomes in the full (n = 15,675) ACLRR cohort.

Characteristic	Multivariable-adjusted odds ratio (aOR) Point estimate (95% CI)		
LTOT outcome definition	1 (Primary)	2 (Intermediate)	3 (Prior studies)
Demographic characteristics			
Female sex	1.13 (0.86 – 1.50)	0.90 (0.70 – 1.17)	**0.85 (0.76 – 0.95)**
Age category			
10-29	Reference		
30-39	**2.63 (1.78 – 3.87)**	**2.72 (1.90 – 3.88)**	**1.36 (1.19 – 1.54)**
40-49	**4.37 (2.97 – 6.43)**	**4.09 (2.87 – 5.85)**	**1.40 (1.21 – 1.62)**
50-65	**5.68 (3.59 – 9.00)**	**4.76 (3.08 – 7.36)**	**1.46 (1.19 – 1.79)**
Trend	***p* < 0.001**	***p* < 0.006**	$p < 0.51$
Preoperative characteristics			
Preoperative opioid exposure (90-day lookback)	**31.51 (23.06 – 43.06)**	**23.51 (17.84 – 30.97)**	**4.33 (3.77 – 4.98)**
Benzodiazepine use	**3.36 (2.39 – 4.73)**	**2.96 (2.14 – 4.11)**	**2.23 (1.80 – 2.76)**
Antidepressant use	**2.03 (1.47 – 2.81)**	**2.52 (1.87 – 3.39)**	**1.72 (1.45 – 2.03)**
Antipsychotic use	1.70 (0.93 – 3.11)	**2.09 (1.19 – 3.68)**	**1.67 (1.14 – 2.45)**
NSAID use	1.31 (0.99 – 1.73)	**1.34 (1.03 – 1.74)**	**1.65 (1.47 – 1.85)**
Other drug use disorder	**2.31 (1.36 – 3.94)**	**3.07 (1.87 – 5.04)**	**1.58 (1.14 – 2.18)**
Alcohol use disorder	**2.61 (1.30 – 5.23)**	**2.39 (1.21 – 4.70)**	**2.07 (1.36 – 3.15)**
Chronic pulmonary disease	**2.52 (1.23 – 5.13)**	**2.91 (1.51 – 5.61)**	**2.24 (1.57 – 3.19)**
Uncomplicated diabetes	2.25 (0.98 – 5.16)	1.94 (0.85 – 4.47)	**2.16 (1.34 – 3.51)**
Intraoperative characteristics			

Surgery type			
Repair <14 days from injury	**4.22 (2.22 – 8.05)**	**3.96 (2.12 – 7.38)**	**2.95 (2.10 – 4.15)**
Revision surgery	1.35 (0.88 – 2.08)	1.44 (0.96 – 2.15)	1.21 (1.00 – 1.46)

Bolded aOR indicates $p < 0.05$.

LTOT Definitions:
1) >90 days' supply during postoperative days 1–365
2) At least 1 days' supply per period, for at least three of the nine 30-day postoperative periods beginning on postoperative day 91
3) At least 1 opioid dispensation between postoperative days 91–365

Table 15: Measures of association of patient-level characteristics with LTOT outcomes in the sub-cohort of opioid-naïve ACLRR patients who received an initial opioid dispensation in their first 30 postoperative days (n = 11,491).

Characteristic	Multivariable-adjusted odds ratio (aOR) Point estimate (95% CI)		
LTOT outcome definition	1 (Primary)	2 (Intermediate)	3 (Prior studies)
Demographic characteristics			
Female sex	1.33 (0.76 – 2.32)	0.98 (0.63 – 1.54)	**0.80 (0.71 – 0.92)**
Age category			
10-29	Reference		
30-39	**2.79 (1.22 – 6.37)**	**2.72 (1.48 – 4.99)**	**1.26 (1.08 – 1.47)**
40-49	**5.70 (2.58 – 12.56)**	**3.16 (1.67 – 6.00)**	1.15 (0.96 – 1.39)
50-65	**7.67 (3.07 – 19.20)**	**5.11 (2.44 – 10.71)**	**1.33 (1.02 – 1.73)**
Trend	***p* < 0.02**	$p < 0.07$	$p < 0.70$
Preoperative characteristics			
Benzodiazepine use	**4.40 (2.12 - 9.12)**	**4.23 (2.27 - 7.88)**	**1.76 (1.29 - 2.39)**
Antipsychotic use	**3.84 (1.18 - 12.53)**	**5.61 (2.24 - 14.08)**	**2.45 (1.49 - 4.02)**
NSAID use	1.65 (0.93 - 2.95)	1.61 (1.00 - 2.59)	**1.81 (1.57 - 2.09)**
Anxiety	0.08 (0.01 - 2.60)	0.60 (0.09 - 4.05)	0.96 (0.46 - 2.04)
Depression	3.89 (0.87 - 17.37)	1.89 (0.42 - 8.50)	1.71 (0.87 - 3.36)
Other drug use disorder	2.88 (0.81 - 10.27)	**4.77 (1.94 - 11.74)**	1.47 (0.92 - 2.34)

Alcohol use disorder	3.67 (0.84 - 16.13)	1.81 (0.41 - 8.04)	**2.04 (1.11 - 3.77)**
Chronic pulmonary disease	**5.22 (1.72 - 15.81)**	**3.26 (1.10 - 9.60)**	**1.91 (1.20 - 3.06)**
Uncomplicated diabetes	**4.78 (1.41 - 16.20)**	3.09 (0.90 - 10.66)	**1.94 (1.05 - 3.60)**
Intraoperative characteristics			
Surgery type			
Repair <14 days from injury	**7.47 (2.27 - 24.66)**	**5.55 (2.01 - 15.35)**	**3.64 (2.28 - 5.82)**
Revision surgery	1.84 (0.81 - 4.18)	1.29 (0.61 - 2.75)	1.15 (0.91 - 1.47)
Meniscal repair	0.75 (0.31 - 1.82)	0.53 (0.25 - 1.15)	0.97 (0.79 - 1.19)
Meniscectomy	0.71 (0.36 - 1.41)	0.71 (0.41 - 1.23)	0.98 (0.83 - 1.17)
First opioid dispensation characteristics			
Extended-release formulation	**5.47 (1.13 - 26.56)**	**5.35 (1.26 - 22.81)**	**2.86 (1.14 - 7.18)**
Duration (days' supply)			
1-4	Reference		
5-7	1.06 (0.53 - 2.10)	1.54 (0.85 - 2.78)	1.04 (0.89 - 1.22)
8-14	1.14 (0.50 - 2.59)	1.31 (0.65 - 2.64)	1.10 (0.92 - 1.33)
15+	**3.03 (1.02 - 9.01)**	**3.31 (1.33 - 8.23)**	0.89 (0.62 - 1.29)
Daily dosage (MME)			
MME < 50	Reference		
50 ≤ MME < 90	**2.10 (1.09 - 4.06)**	1.04 (0.57 - 1.91)	1.05 (0.88 - 1.25)
MME ≥ 90	**2.11 (1.03 - 4.31)**	1.57 (0.88 - 2.81)	1.15 (0.96 - 1.38)

Bolded aOR indicates $p < 0.05$.

LTOT Definitions:

1) >90 days' supply during postoperative days 1–365
2) At least 1 days' supply per period, for at least three of the nine 30-day postoperative periods beginning on postoperative day 91
3) At least 1 opioid dispensation between postoperative days 91–365

Discussion:

This study identified risk factors for a set of long-term postoperative opioid use outcomes—those reflecting long-term postoperative opioid dispensing—among a multiyear cohort of ACLRR patients. Importantly, and in line with prior surgical research not in ACLRR, we identified preoperative use of antidepressants, benzodiazepines, and antipsychotics use as associated with increased LTOT, in addition to initiating dispensation dosages of ≥50 MME and durations of ≥15 days. Specific to ACLRR, we also identified ACL repair within 14 days of injury versus ACL reconstruction as conferring significant increased risk of LTOT. These findings serve to support clinicians, who as providers of postoperative pain control are responsible to minimize reasonably foreseeable pain across a continuum of potential postoperative outcomes, in part through judicious prescribing of postoperative analgesia.

Outcome choice in LTOT

We observed more than a fivefold difference between primary (1.9%) and prior studies' (10.9%) definitions of LTOT prevalence in the overall ACLRR cohort, which ballooned to more than a twenty-fold difference in the preoperatively opioid-naïve sub-cohort. All three LTOT definitions identify maximal and submaximal opioid dispensations, where severe dose-dependent adverse effects may be more common. They additionally identify discontinuous but recurrent opioid dispensation, where acute opioid initiation effects may be of principal concern. In contrast, only the prior studies' LTOT definition broadly includes all patients who receive any late postoperative opioid dispensations. As a usage metric, this may better approximate baseline opioid prescribing rates in the underlying population[24], and lacks specificity towards cumulative long-term or frequent opioid use. Showcasing this point, among ACLRR patients meeting the prior studies' LTOT definition, 80% overall and 93% of preoperatively opioid-naïve patients had zero monthly opioid availability for at least seven of the nine late period postoperative months.

While this would be less remarkable if the models for all three LTOT outcomes produced comparable results, certain patient characteristics exhibited qualitatively different patterns of association with the prior studies' LTOT definition, including patient age, sex, as well as dosage and duration of initial dispensations among preoperatively opioid-naïve patients. Given the multitude of postoperative LTOT definitions in the literature[24], future research should consider whether associations with a less demanding LTOT outcome will necessarily generalize to outcomes representing cumulative or repeated postoperative opioid dispensations.

Patient age and LTOT

The present study observed positive associations between LTOT and patient ages >29, in agreement with Rao et al. who observed positive associations between late postoperative period prescription filling and patient ages >19. We also observed successive increases of LTOT by age in primary and intermediate LTOT definition models. Mohamadi et al. propose an inverse U-shaped postoperative LTOT-by-age relationship peaking between patient ages 50-70 years[25]; per such a relationship, our (≤65) study population does not necessarily meet an age where successively decreasing LTOT rates would be observed. Other reviews, however, concede that substantial study heterogeneity precludes a general postoperative LTOT risk stratification by age[26,27]. Research specific to ACLR shows that older patient age predicts conversion to total knee arthroplasty (TKA) within two years[28] and new post-traumatic knee osteoarthritis (PTOA) within five years[29], both of which are associated with high opioid use rates[30–33], whereas younger patient age predicts revision surgery, meniscal surgery and arthroscopic arthrofibrosis treatment[29]. How these temporally close health outcomes differentially contribute to ACLRR postoperative opioid use by age is not yet established. Further research elucidating these

relationships would provide prescribers with improved age-specific expectations of post-ACLRR opioid demand and better clinical decision-making capacity.

Patient sex and LTOT

Female sex was not significantly associated with primary or intermediate LTOT outcomes but was negatively associated with the prior studies' LTOT outcome, which departs from other research in ACLRR[12,14]. Our data identified certain patient comorbidities more wholly as compared to prior studies, as we controlled for preoperative dispensation of prescribed NSAIDs, commonly utilized for pain, and for drug classes typically utilized during active management of psychiatric conditions. These comorbidities likely confound the sex-LTOT relationship in ACLRR given their higher prevalence among female patients[34,35] and correlation with postoperative pain and postoperative opioid use in other sports medicine procedures[36–39]. Assuming this holds in ACLRR, their inclusion via drug dispensation data may have reduced our estimate of associative strength between female sex and LTOT. Despite our increased control for confounding, we still observed a negative association between female sex and late-period opioid dispensing. It may be speculated that female patients, owing to higher rates of opioid-induced adverse events[40], receive nontreatment or non-opioid pharmacotherapy for acute pain episodes in the late postoperative period more frequently than their male counterparts. To our knowledge, such research has not yet been conducted.

Preoperative drug use, psychiatric comorbidity, and LTOT

In agreement with surgical literature as a whole[26,27] as well as ACLRR-specific studies[12,14] the present study identified preoperative opioid dispensation as the single best predictor of LTOT in the complete ACLRR cohort. Showcasing this disparate outcome, patients

with preoperative opioid dispensations made up less than 10% of the overall ACLRR cohort but represented more than 80% of primary and 75% of intermediate LTOT outcomes. Single-institution studies in ACLRR have shown this association to persist in ACLRR even after accounting for preoperative pain[41]; for these reasons, it remains a key indicator for potentially outsized postoperative opioid demand.

Preoperative benzodiazepine dispensation, agreeing with most prior surgical research[26,27], predicted LTOT, and was furthermore robust to model selection alongside anxiety disorder. That anxiety disorder was neither significantly predictive of primary LTOT nor a confounder in the full ACLRR cohort suggests characteristics beyond common benzodiazepine treatment indications are needed to further explicate benzodiazepine-LTOT relationships. This is a conclusion we share with Rishel et al. following their study among general surgical patients[42].

This study is one of only a handful to control for preoperative antipsychotic dispensation in postoperative LTOT[27], which themselves have resulted in mixed findings. We found that preoperative antipsychotic dispensation only predicted primary LTOT among opioid-naïve patients, so might reflect patient susceptibility to incident LTOT versus a risk factor for continuation or escalation of opioid therapy among patients with preoperative opioid exposure.

We found that preoperative antidepressant dispensation was predictive of LTOT, and while these associations have frequently been reported in general surgical literature[26,27], our study only observed them in models which included patients with preoperative opioid exposure. Neuropathic pain and restless leg syndrome are both examples of relatively common chronic health conditions which may be symptomatically managed with antidepressants, opioids, or switching between both drug classes – the latter typically reserved for patients with treatment-

refractory symptoms[43,44]. Since postoperative LTOT among patients with preoperative opioid and antidepressant dispensations might reflect status quo treatment of these or other conditions, future studies may instead wish to identify whether enduring changes to polydrug consumption patterns take place following postoperative prescribing, and whether any such changes are sensitive to drug treatment indication. Given the potential for poor diagnostic sensitivity of these conditions in routinely collected health data[45,46], any such research would likely require targeted preoperative patient screening for cohort enumeration.

Similar to antidepressant use, we observed positive associations with primary LTOT for preoperative substance use disorders (SUD) which became nonsignificant when we excluded patients with preoperative opioid dispensations. Due in part to the commonness of comorbid SUD and hyperalgesia, which are viewed as outcomes from shared neurophysiological processes[47,48], acute postoperative pain management in SUD remains a clinical dilemma. Treatment difficulties are especially notable for opioid tolerant SUD patients, who with postoperative dosage escalation may experience only marginally stronger pain relief but correspondingly larger increases in their likelihood of adverse symptom development, overdose, or propensity to misuse[49]. To minimize these risks, as well as the risk of incident or intensified nonmedical substance use for supplemental postoperative analgesia, patients with SUD may benefit from pain management plans created preoperatively. Recent guidance recommends such treatment plans to maximize non-opioid pharmacotherapy, provide concrete opioid tapering schedules contingent upon pain relief, and consult pain specialists for persistent postoperative pain[50].

Preoperative chronic disease and LTOT

Chronic pulmonary disease was associated with LTOT in all models, aligning with findings by Rao et al.[12] and surgical literature altogether[26,27]. Asthma is overrepresented among patients who use opioids [51], and asthma patients exhibit more frequent contraindication to opioid-sparing pain regimens[52]. Alongside chronic obstructive pulmonary disease patients, who experience greater day-to-day musculoskeletal pain[53], these together might drive some of their observed associations with LTOT.

Diabetes without complication was associated with LTOT in the full ACLRR cohort, but these associations were attenuated in the opioid-naïve cohort models. This study's coding structure categorized patients who exhibited diabetic neuropathy separately—itself suppressed due to small sample size—so this finding may instead reflect symptomatic management of other painful conditions which are commonly comorbid in diabetes[54].

Surgery type and LTOT

Unique to the current study is the finding that ACL repair <14 days from acute ACL injury strongly predicted LTOT in all models. In contrast, Rao et al. found that ACL reconstruction surgery latency from acute ACL injury of ≤90 days predicted increased opioid dispensation up to postoperative day 90[12], but did not explicitly compare patients undergoing ACL repair versus reconstruction. While recent reviews present advanced ACL repair technique as a means towards comparable treatment outcomes versus graft ACL reconstruction, its non-inferiority may be limited to treating proximal ACL tears, which remain uncommon[55–57]. Furthermore, at a time to surgery of <14 days from acute ACL trauma, physiological biomarker data suggests the persistence of acute inflammation even compared to weeks just thereafter[58]. Taken together, more careful assessment of postoperative pain control adequacy and opioid

consumption patterns may be warranted for patients who undergo ACL repair within this early period.

First dispensation characteristics and LTOT in naïve-subset cohort

Initial dispensations which contained extended duration oral opioid formulations were rare within the preoperatively opioid-naïve sub-cohort but were associated with a strong increase in all LTOT outcomes. This increase in risk has been extensively described in nonsurgical opioid-naïve populations[15,59,60], and this study showcases the same risk increase among ACLRR patients in the postoperative period. Per recent guideline recommendations, these formulations are not typically considered appropriate when initiating opioid therapy for opioid-naïve patients[49].

As compared to initial dispensation durations of <5 days, only durations exceeding 14 days in length were associated with increased primary and intermediate LTOT. This contrasts with other studies in nonsurgical populations which exhibited progressively increasing LTOT association strength at ≥5 days duration[60] or an upwards LTOT risk inflection at 10 days duration[15]. Dispensation daily dosages exceeding <50 MME were also associated with increased LTOT, but we observed no further dose-response relationship. This result is congruent with prior research, which suggests that stronger associations with LTOT require daily dosages of >200 MME[60], which are exceedingly uncommon among preoperatively opioid-naïve patients. Importantly, we observed no statistically significant associations whatsoever between initial dispensation dosage or duration for the prior' studies LTOT outcome. Future research should acknowledge the potential for reduced generalizability of these associations between differing LTOT constructs.

Study strengths and limitations

We capitalized on broad data availability from a large population-representative healthcare system in our ascertainment of patient-level characteristics and LTOT in ACLRR. Specifically, owing to our granular community pharmacy dispensation data, we captured patient preoperative non-opioid drug exposures, initial opioid dispensation characteristics for preoperatively opioid-naïve patients, and an LTOT outcome based on cumulative day-to-day opioid supply, which are all novel among ACLRR-specific LTOT studies[12–14]. Furthermore, our use of three different LTOT constructs allowed for within-study comparisons of outcome prevalence, identification of contrasting risk factors between outcome constructs, and more direct comparison of findings with prior research.

There are multiple limitations to this study. We used routinely collected administrative data for exposure ascertainment, and lacked access to patient preoperative characteristics more typically detailed in individual-level chart data. As a result, this study does not report on ACL injury etiology or preoperative American Society of Anesthesiologists physical classification score, which have both shown positive associations with late-period opioid dispensation in prior research[12]. While the sum total of variables which residually confound these study results may not readily be known, compared to prior ACLRR-specific research[12–14], our study captured for model inclusion more preoperative characteristics identified by the surgical literature as a whole as having associations with LTOT[25–27].

Our study is also subject to biases specific to pharmacoepidemiology. Patient day-to-day measures of opioid availability and MME were calculated under the assumption that patients consumed dispensations beginning on dispensation date and in accordance with estimated days'

supply, and these assumptions do not necessarily hold for all patients. Furthermore, we did not identify prescription drug products obtained externally to community pharmacies, such as from in-hospital care or via diversion, or non-prescription pharmacotherapy, such as over-the-counter drugs or illicitly obtained drug products. Finally, while this study identified numerous patterns of association between patient-level characteristics and LTOT and we provided putative mechanisms for many of these findings, they should not be interpreted as causal relationships in the absence of confirmatory inferential research.

Conclusion

Numerous preoperative and intraoperative associations with increased LTOT were observed among patients in this ACLRR cohort. LTOT associations with preoperative drug exposure and with initial postoperative opioid dispensation characteristics are novel in ACLRR but agree with prior high-quality research in opioid pharmacoepidemiology. Preoperative opioid exposure remains, however, the most significant predictor of eventual postoperative LTOT. Given the substantial differences in patient-specific risk factors between LTOT outcome measures, future research should heed recommendations to use robust LTOT outcome measures where possible.

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Appendix B

Table 16: The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	A) ii b) ii	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.4) ii 1.5) ii 1.6) ii
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	72		

Objectives	3	State specific objectives, including any prespecified hypotheses	72-73		
Methods					
Study Design	4	Present key elements of study design early in the paper	73-76		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	73-74		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give	B) 73-74, Fig. 8	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to	6.1) Appendix B, Table 17 6.2) 74-75, Appendix B, Table 17 6.3) N/A

		matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	74-76, Appendix B, Table 17	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Appendix B, Table 17
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	74-76, Appendix B, Table 17		
Bias	9	Describe any efforts to address potential sources of bias	73, 74, 76, 77, 78, Appendix B, Table 18		
Study size	10	Explain how the study size was arrived at	Figure 8		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	77		
Statistical methods	12	(a) Describe all statistical methods, including those	a) 77-78 b) 76-78 c) 73-74, Figure 8		

		used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	d) 73-74, Figure 8		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1) 73 12.2) Appendix B, Table 18
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data	73

				linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	73-75, Figure 8
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 11, Table 12		
Outcome data	15	*Cohort study* - Report numbers of outcome events	Tables 12-13		

		or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	A) Tables 14-15 B) Table 11, Tables 14-15 C) N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Tables 14-15		
Discussion					
Key results	18	Summarise key results with reference to study objectives	87-94		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	94-96	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	94-96
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	96		
Generalisability	21	Discuss the generalisability (external validity) of the study results	87-89, 94-95		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	N/A

Table 17: Administrative health data codes used to ascertain study exposures and outcomes

Exposure/outcome category	Code structure
ACL reconstruction codes	
National Ambulatory Care Reporting System (NACRS) / Hospital Inpatient Data	*Canadian Classification for Health Interventions (CCI) codes:* 1.VL.80x, 1.VN.80x
Practitioner claims data	*Billing codes:* 93.45A, 93.45B, 93.45C, 93.45D, 93.45E, 93.45F, 93.45J
Charlson comorbidity index risk factor sub-codes (ICD-10-CA codes)*	
Myocardial infarction (weight 1)	I21.x, I22.x, I25.2
Congestive heart failure (weight 1)	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease (weight 1)	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease (weight 1)	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia (weight 2)	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease (weight 1)	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Connective tissue / rheumatic disease (weight 1)	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease (weight 1)	K25.x-K28.x
Mild liver disease (weight 1)	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without complications (weight 1)	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0,E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with complications (weight 2)	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Paraplegia and Hemiplegia (weight 1)	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9

Renal disease (weight 2)	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Cancer (weight 2)	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Moderate or severe liver disease (weight 3)	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic carcinoma (weight 6)	C77.x-C80.x
HIV/AIDS (weight 6)	B20.x-B22.x, B24.x
Other identified risk factors (ICD-10-CA codes)	
Chronic pain**	F45.4, M08.1, M25.50, M25.51, M25.55 - M25.57, M43.2 - M43.6, M45, M46.1, M46.3, M46.4, M46.9, M47, M48.0, M48.1, M48.8, M48.9, M50.8, M50.9, M51, M53.1 - M53.3, M53.8, M53.9, M54, M60.8, M60.9, M63.3, M79.0 - M79.2, M79.6, M79.7, M96.1
Mental health risk factors (ICD-10-CA codes)	
Anxiety	F40.0-F42.9
Depression	F32.0-F33.9, F34.1, F38.1
Bipolar disorder	F30.0-F31.9, F34.0
Schizophrenia	F20.0-F20.9
Substance use risk factors (ICD-10-CA codes)	
Alcohol use disorder	F10.0-F10.9
Other substance use disorder	F11.0-F16.9, F17.0-F17.9, F18-F19.9, F55
Opioid analgesic codes	
Initial identification of opioid	*Anatomical Therapeutic Chemical codes:* N02Ax , R05DAx

Opioid exclusion categories	*Anatomic Theraputic Chemical code-based exclusion:* i) Drugs containing only dextromethorphan (R05DA09) or combination (R05DA20) *via Drug Identification Number matched with Government of Canada Drug Product Database:* i) Opioid-naloxone combinations (A06AH04) ii) Liquid, nasal, rectal, parenteral formulation
Other drug product codes	
Benzodiazepine use	N05CAx, N05CDx, N05CFx, N03EA01
Antidepressant use	N06Ax
Antipsychotic use	N05Ax
Non-steroidal anti-inflammatory drug use	M01Ax
* codes obtained from Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining Comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov; 43(11): 1130-9 ** codes obtained from Tonelli, M., Wiebe, N., Fortin, M. et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak 15, 31 (2016). https://doi.org/10.1186/s12911-015-0155-5 *** weights obtained from Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8. PMID: 3558716.	

Table 18: Cleaning algorithm for Practitioner Claims database

Algorithm steps	i. Same-date ACLRR claims by multiple practitioners on a single patient were interpreted as a single ACLRR surgery. ii. Discrepancies in ACLRR billing code between practitioners were resolved by retaining the practitioner claim from the designated primary surgeon. iii. Discrepancies in surgery date during a single episode of care were resolved by retaining the earliest claim date. iv. Instances of billing code *93.45B*, representing early cruciate ligament repair, required the same-day NACRS or DAD-linked episode of care to document an ACLRR via CCI code.

Chapter 4: Conclusion

Overview of study objectives

This thesis had multiple objectives. First, it sought to contextualize perioperative opioid dispensing among a multi-year cohort of Canadian ACLRR patients, providing a more in-depth analysis compared to prior research in ACLRR[1], and in a consistent manner to other Canadian cohort studies of perioperative opioid dispensing in orthopedic surgery[2,3]. Second, it sought to identify associations between patient-level characteristics in ACLRR and specific long-term postoperative opioid dispensation patterns, address whether these associations were stable when using more robust LTOT outcome measures, and incorporate initial postoperative opioid dispensation characteristics as a putative risk factor for LTOT in ACLRR.

Overview of key findings

This thesis describes findings novel to Canadian and ACLRR-specific pharmacoepidemiology literature. A selection of noteworthy findings includes, but is not limited to:

1) The overall rate of primary-definition LTOT of 1.94% among the entire ACLRR cohort, and its significant stratification by preoperative opioid exposure;
2) Tramadol, by 2016–17, overtaking codeine as the most common postoperative initiating opioid choice in ACLRR, materializing as the result of an increasing dispensation trend seemingly in excess of those documented across Canada[2–4];
3) Transition probabilities for month-to-month opioid supply between postoperative months 6-12, where just 30-40% of preoperatively opioid-naïve ACLRR patients with

opioid supply in a given month were expected to receive opioids in the following postoperative month, versus more than 80% of patients with preoperative opioid exposure;

4) Differences in association pattern, dependent on LTOT outcome construct, of increasing patient age on long-term postoperative opioid dispensations;

5) Distinct patterns of association across primary LTOT models for antidepressants, antipsychotics, and benzodiazepines;

6) ACL repair occurring <14 days from acute injury exhibiting a strong association with long-term postoperative opioid dispensation.

Thesis strengths

This thesis benefited from high-quality patient data. Alongside enumeration of a population-representative ACLRR cohort, all diagnoses entered into administrative inpatient and outpatient care databases during the preoperative period were available to query, which permitted the identification of many relevant patient preoperative comorbidities using previously validated code structures[5,6]. Furthermore, the PIN dataset captured the entirety of perioperative drug dispensations to ACLRR patients in Alberta community pharmacies, which permitted the identification of patient preoperative exposure to four relevant non-opioid drug classes not previous used as risk factors among the large ACLRR-specific LTOT studies[1,7,8]. The wealth of individual dispensation-level data contained within the PIN dataset was utilized further to identify, on a day-to-day basis, patients' expected opioid type and strength during the postoperative period, which permitted the construction of detailed metrics regarding opioid naïve patients' first postoperative dispensations, whole cohort month-to-month postoperative dispensation patterns, and ascertainment of cumulative use-based LTOT measures.

Thesis limitations

It is important to emphasize limiting aspects of this thesis to minimize any overestimation in its scope and any incautious application of its conclusions.

While both Chapters 2 and 3 of this thesis assumed that opioids dispensed to ACLRR patients would be consumed beginning on the date of dispensation and in accordance with the presumed quantity of days the prescription would last (days' supply), this is only a proxy measure of actual opioid consumption. Patients might consume different day-to-day quantities of opioid drug over the course of their use periods, might discontinue opioid use prior to exhausting their opioid supply, might consume opioids obtained from prior dispensations, or might consume opioids which were not prescribed to them. These latter two categories—which represent higher-risk opioid consumption behaviors—cannot reliably be ascertained from the ACLRR cohort data, although it is possible that these behaviors cluster among patients with substance use disorders, which is an exposure this thesis did identify.

Some non-opioid preoperative exposures with previously-identified LTOT associations[7] could not be collected given data availability. These included ACL injury etiology, which was present only for a minute subset of patients diagnosed with acute ACL trauma in Alberta emergency departments, as well as American Society of Anesthesiologists patient classification score, which while subjective, remains an independent predictor of poor postoperative patient outcome in ambulatory surgery[9]. In addition, patient sociodemographic characteristics may have acted as residual confounders for models in Chapter 3, given their known relationship to poorer postoperative outcomes in ACLRR[10].

Multivariable logistic regression model performance becomes more limited as the ratio of outcome events to variables of interest—events per variable—decreases[11], which places the primary LTOT model using opioid-naïve-only ACLRR patient data at a not insignificant risk of poor performance. While this is a legitimate limitation which stems from outcome rarity and interconnectivity with many predictor variables, this thesis employed two countermeasures intended to mitigate its effects: augmented backwards elimination to increase model parsimony[12]; and Firth correction to improve regression coefficient accuracy[13].

Finally, neither prescriber intent nor clinical indication for any dispensed pharmacotherapy was available to assess within the ACLRR cohort. Since as a result, any opioid dispensation event may have occurred for reasons completely unrelated to ACLRR or to identified patient-level factors, the measures of association described in Chapter 3 of this thesis should not be misinterpreted as definitive causal inferences. They may, instead, be considered in future inferential research as component factors with a role in putative causal pathways ending in altered opioid consumption patterns. These causal effects remain difficult to confirm in opioid pharmacoepidemiology, given the complex interplay between clinicians' assessments of patient risk and intercommunication regarding patient risk tolerance on their eventual choice(s) of prescribed pharmacotherapy.

Implications and future research

This thesis emphasizes, as with other research on postoperative opioid use in Canada[2,3], that improved clinical guidance regarding acceptable postoperative analgesia is likely necessary before postoperative prescribing practices can change at a systemic level. Recent pain management documentation out of the United States[14] reiterates the potential harm of guideline

overreach and inflexible prescribing limits, and promotes patient- and procedure-specific opioid analgesia regimens. To accomplish these goals, further research remains necessary to better understand the implications of certain patient characteristics on opioid need and propensity for adverse outcomes. This thesis identifies some such research avenues:

1) The risk of adverse opioid use outcomes conferred onto surgical patients who receive postoperative dispensations containing more than one oral opioid formulation;

2) The potential mediating role of temporally close surgery on the relationship between patient age and LTOT in ACLRR;

3) The effect of surgical procedures on postoperative polydrug consumption pattern, alongside its sensitivity to preoperative treatment indication; and

4) The mechanisms behind increased LTOT among patients undergoing early ACL repair.

Conclusion

This thesis presents a nuanced picture of perioperative opioid dispensation among ACLRR patients in Alberta. While upwards trends in initial postoperative dispensation metrics may have matched or exceeded those observed among other surgical procedures across Canada, no equally clear uptick in postoperative LTOT rate occurred as a result of these trends, even as they remain unwarranted given current knowledge in postoperative pain management. Furthermore, though many patient-level risk factors for LTOT established in American ACLRR and other patient cohorts appear to translate into a Canadian setting, LTOT outcome measure choice does influentially alter their patterns of association.

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