Preoperative Opioids Influence on Outcomes After Total Knee Arthroplasty

by

Craig Michael Goplen

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Surgery

University of Alberta

Abstract

Background: Up to 40% of patients are prescribed opioids prior to total knee arthroplasty (TKA) in the USA. These patients prescribed preoperative opioids have increased complications and worse outcomes after surgery. But, the impact of preoperative opioid use on patient-reported outcome (PRO) scores after TKA has not been studied extensively. To our knowledge, the number of patients prescribed opioids before and after TKA in Canada also has never been reported. The purpose of this thesis is to estimate the prevalence of opioid use before and after TKA in Alberta, Canada, and to determine the impact of preoperative opioid use on PRO scores 12-months after TKA.

Methods: A systematic review evaluated the impact of preoperative opioid use on PRO pain and function scores after TKA. We then described three methods that can detect consistent opioid use with administrative health data. Applying this methodology to a cohort of patients that underwent primary, elective TKA between 2013 and 2015 in Alberta, Canada, we estimated the rate of opioid use before and after TKA, along with the dose, duration and most common opioid formulations dispensed. We also analyzed the relationship between preoperative opioid use and patient reported outcomes 12-months after TKA, adjusting for potentially confounding variables with multivariable linear regression. Potentially confounding variables included patient's age, sex, comorbidities including depression and preoperative score.

Results: The systematic review consisted of six studies that all reported patients prescribed opioid prior to surgery had worse clinical outcomes after surgery. The included studies had a moderate to high risk of bias as outcomes did not adjust for potential confounding factors such as

preoperative PRO score or a history of depression. All studies were published from centers in the USA.

In our retrospective, multicenter population-based study, 31% (n = 592) were prescribed opioids prior to TKA. Those patients (n = 124) that were considered long-term opioid users had worse adjusted Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC) pain and function scores 12-months after TKA compared to preoperative opioid naïve patients (pain score beta coefficient 7.7 [95% CI 4.0, 11.6], function score beta coefficient: 7.8 [95% CI 4.0, 11.6]; $p<0.001$. Few (<1%) patients that were not dispensed opioids prior to TKA became long-term opioid users between 180 and 360-days after surgery, but 44% (n=55) of preoperative long-term opioid users remained long-term opioid users 12-months after TKA. Tramadol, codeine and oxycodone were the most commonly prescribed opioids before and after TKA.

Conclusion: A significant number of patients were dispensed opioids before and after TKA in Alberta, Canada and patients dispensed preoperative opioids had worse pain and functional outcomes 12-months after TKA when compared to those who were not. These results substantiate previous work that suggested patients prescribed preoperative opioids should be judiciously counselled regarding expected outcomes after TKA as they have been observed to have more complications and worse outcomes after surgery. Future research is needed to define risk factors associated with persistent postoperative opioid use, and to determine whether weaning opioids preoperatively can optimize outcomes after surgery.

Preface

This thesis is an original work by Craig Michael Goplen. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "The Impact of Preoperative Opioids on Patient-Reported Outcomes following Primary Elective Total Joint Arthroplasty", Pro00076296, October 22, 2018.

Chapter 3 of this thesis: "Preoperative Opioid Use is Associated with Worse Patient Outcomes after Total Joint Arthroplasty: A Systematic Review and Meta-analysis" has been published in BMC Musculoskeletal Disorders. https://doi.org/10.1186/s12891-019-2619-8.

Chapter 4 of this thesis: "The influence of allowable refill gaps on detecting long-term opioid therapy: an analysis of population based administrative dispensing data among patients with knee arthritis awaiting total knee arthroplasty" has been reviewed at the Journal of Managed Care & Specialty Pharmacy and revised manuscript is currently under review.

Chapter 5 of this thesis: "Preoperative Long-term Opioid Therapy Negatively Impacts Patient Outcomes After Total Knee Arthroplasty: An Analysis of Multicenter Population-Based Administrative Data" is under review at the Canadian Journal of Surgery.

Acknowledgements

I would like to thank my supervisors, Drs. Beaupre and Churchill for their guidance and support helping me through my Masters. I would also like to extend my gratitude to my thesis committee; Drs. Voaklander and Jones, for their feedback, advice and expertise that greatly assisted in the development of this project. This work could have not been possible without the help from Dr. Randall and Mr. Sung Kang who provided me invaluable guidance, particularly around data management and statistics. I would also like to acknowledge the entire Division of Orthopedic Surgery who enabled me to take time off to complete the Masters and the Clinician Investigator Program that supported me for the past two years.

Finally, I would like to thank my family, and Monique for their endless inspiration and support.

Table of Contents

List of Tables

List of Figures

Abbreviations

AAOS	American Association of Orthopedic Surgeons
CNCP	Chronic non-cancer pain
LTOT	Long-term opioid therapy
MED	Morphine equivalents daily
NSAIDs	Non-steroidal anti-inflammatory drugs
OU	Opioid user
PRO	Patient reported outcomes
THA	Total Hip Arthroplasty
TJA	Total Joint Arthroplasty
TKA	Total Knee Arthroplasty
WOMAC	Western Ontario and MacMaster Universities Osteoarthritis Index

Chapter 1

Statement of the Problem

Over the past 20 years, opioid use has dramatically increased in Canada [1]. Physician-prescribed opioids are considered a driving factor as prescription rates nearly quadrupled during this same period [2]. Unfortunately, these prescribing practices have had substantial, unanticipated consequences. Opioid related poisoning increased more than 30% between 2007 and 2015, and in 2017 there were 3987 opioid related deaths in Canada [3]. For comparison, at the peak of the AIDs epidemic in Canada, there were 1764 deaths in one year [3,4]. Given these published numbers, the current opioid situation in Canada is now referred to as an epidemic [5].

The origins of the opioid epidemic are often traced back to three interrelated events. First, pain was labeled as the 5th vital sign by the American Pain Society in 1995 to encourage routine assessment as it was felt that pain was under-recognized and undertreated [6,7]. In addition, corporate marketing campaigns for novel semi-synthetic opioids failed to disclose many of the potential side effects, including addiction and overdose [8]. Finally, clinical guidelines were released that supported opioid use to manage chronic pain [9]. Unfortunately, these guidelines were largely based on expert opinion and industry-backed studies; a meta-analysis examining opioids for the treatment of chronic non-cancer pain (CNCP) reported that 90% of included studies were either funded by or had one or more coauthors affiliated with the pharmaceutical industry [10]. Collectively, these events resulted in health care systems in North America becoming largely dependent on opioids to manage chronic non-cancer pain, such as arthritis [11].

Opioid use among patients with arthritis awaiting total knee arthroplasty (TKA) has gained considerable clinical and research interest with the increasing pressure on physicians to justify opioid prescribing practices [12–16]. It has been reported that opioid use prior to TKA is associated with a more complicated hospital course and more complications after TKA [13,17,18]. Sing *et al.* (2016) reported that preoperative opioid users, stayed on average 1.6 days longer in hospital ($p = 0.05$), were more likely to be discharged to a subacute facility (odds ratio (OR) 6.7, 95% Confidence Interval (CI) 2.4, 19.0) and were associated with increased 90-day complications rates (OR 6.2, 95% CI 1.5, 26) compared to those who did not use opioids preoperatively [17]. Further, Ben-Ari *et al.* (2017) reported on 32,636 patients and found that patients who underwent revision surgery within one year were more likely to be taking opioids preoperatively, after controlling for other factors (1.4 OR, 95% CI 1.2, 1.6) [12].

To our knowledge, the prevalence of opioid use among patients with arthritis awaiting TKA has never been reported. But, 40% of patients are using opioids at the time of TKA in the USA despite national opioid guidelines that now suggest a much more limited, if any, role for opioids [11,13,19,20]. These updated guidelines are based on accumulating evidence that suggests opioids provide no benefit compared to ibuprofen or acetaminophen to manage pain associated with arthritis and have higher rates of adverse events such as addiction, poisoning and death [21,22]. In addition, these patients prescribed preoperative opioids have been observed to have less pain and functional improvements after TKA when compared to patients not prescribed opioids [16,19,23]. Opioid induced hyperalgesia (OIH) has been hypothesized to explain why preoperative opioid users have worse pain and functional outcomes after TKA [23].

OIH is a process by which patients taking long-term opioids have a paradoxical increased response to painful stimuli and may result in changes in the central endogenous opioid system

[24–26]. Chu *et al.* (2006) prospectively evaluated OIH in patients with chronic back pain and after one month of starting oral morphine therapy, patients reported positive hyperalgesia tests when compared to controls [26]. Further, Cohen *et al.* (2008) reported that patients on long-term opioid therapy (LTOT) had increased pain intensity and unpleasant scores when compared to patients who were not exposed to opioids [27]. However, other patient factors, such as depression, worse preoperative patient reported outcome (PRO) scores and patient comorbidities are associated with both opioid use and worse patient outcomes after surgery, but not accounted for in prior studies [19,23,25,28–30]. Without accounting for these potentially confounding variables, the independent impact of opioid use on outcomes after surgery remains unknown [25,29,31,32].

The overarching objective of this project was to investigate the relationship between preoperative opioid use and patient reported pain and function outcomes after TKA adjusting for patient factors such as age, sex, depression and comorbidities. Determining the extent that opioid use independently impacts PRO scores after TKA will provide valuable guidance for healthcare providers that manage these complex patients. Importantly, this objective aligns with North America's goal to reduce opioid consumption by emphasizing opioid stewardship that promotes evidence-based prescribing practices [11,33].

Thesis Objectives

1) To systematically review the literature to evaluate the current evidence on the association between preoperative opioid use and clinical outcomes after TKA.

2) To estimate the prevalence of preoperative opioid use among patients before and after TKA in Alberta, Canada.

3) To determine whether preoperative opioid use among patient awaiting TKA is associated with worse WOMAC (Western Ontario and MacMaster Universities Osteoarthritis Index) pain or function scores 12-months postoperatively when compared to patients who did not use opioids preoperatively, adjusting for potential confounders.

Chapter 2

Literature Review

History of Opioids

Opium is a milky white latex that is produced by *Papaver somniferum*, the opium poppy [34,35]. The Sumerians were the first group of people known to use opium for different ailments, including pain [34,35]. Over the next hundreds of years, knowledge of opium spread throughout Europe and Asia; opium was used to treat many different conditions, such as dysentery and infant colic [34–36]. Morphine, named after Morpheus, the Greek god of dreams was the first alkaloid purified from opium in 1804 by Fredrich Serturner, a German pharmacist [36]. Chemists continued to purify alkaloid compounds from opium throughout the 19th century as isolates were found to have superior pharmacological properties [37]. Purification and characterization allowed chemists to alter these compounds to minimize side effects and increase clinical effectiveness [36]. Alder Wright, a British chemist, was credited with producing the first semisynthetic opioid, diacetylmorphine (heroin) in 1874 [36]. It was thought to be a non-addictive alternative to morphine and was first marketed as a cough suppressant by Beyer pharmaceuticals in 1898 [36]. However, for most of the 20th century, there was little reliance on opioids in North America's as there was little evidence supporting its use to manage chronic pain [38].

Common Opioid Formulations

There are many different opioid formulations currently available in Canada (Table 2.1). The most common opioids prescribed in Canada are codeine, oxycodone, hydromorphone, morphine, tramadol and fentanyl [3]. These formulations accounted for 96% of all opioid prescriptions filled between 2012 and 2016 [3]. In Canada, all opioids except tramadol are registered under the Controlled Drugs and Substances Act [39]. Recently, the Canadian Pharmacist Association has stated that Tramadol should be reclassified as a Schedule 1 narcotic as there is no evidence supporting its exclusion given similar rates of adverse events and abuse potential [40].

Classification of Opioids

Opioids can be classified based on their synthetic process, pharmacokinetics or analgesic properties [41]. Traditionally, opioids are broadly classified based on the production process (Table 2.1) [41]. Codeine and morphine are classified as naturally occurring opioids as they are extracted directly from opium [42]. Chemically altered compounds that share structural similarities to morphine are referred to as semisynthetic opioids and include hydromorphone, hydrocodone and oxycodone [42]. Fully synthetic opioids share no structural relationship with opium resin, but still act on opioid receptors include tramadol, fentanyl and methadone [41]. Alternatively, opioids can be classified based on receptor affinity [42]. Pure opioid agonists, such as morphine bind to the receptor and produce a maximal response, while partial agonists such as buprenorphine partially activate the opioid receptor [42]. In comparison, opioid antagonists are compounds that bind to opioid receptors with a high affinity, but produce no functional response and prevent opioids from binding [42]. These antagonists, such as naloxone can help reverse the

undesirable and potentially lethal effects of opioids [42]. Finally, opioids can be classified as having either weak or strong based analgesic properties as described by the World Health Organization (WHO) pain ladder [43]. According to the WHO, weak opioids include codeine and tramadol, while strong opioids include morphine, fentanyl, hydromorphone, methadone and oxycodone [43]. Pharmacological properties of individual opioid compounds are discussed in Appendix 2.1.

Table 2-1 Opioid Classification by Synthetic Process [11,51]

Classification	**Generic Name**	**Trade Name**
Natural	Codeine	Codeine, Codeine-Contin
	Codeine/acetaphinophen	Tylenol 2,3,4
	Morphine	M-Eslon, MS Contin
Semi-Synthetic	Oxycodone	OxyNeo, Supeudol
	Oxycodone/ASA	Endoan, Percoan, Percodan-Demi, ratio Oxycodone
	Oxycodone/acetaminophen	Percoet, ratio-Oxycocet, PMS-Oxycodone-Acetaminophen, Endocet
	Hydromorphone	Dilaudid
	Hydrocodone	PDP-Hydrocodone
Fully Synthetic	Tramadol	Tridural
	Tramadol/acetaminophen	Tramacet
	Tapentadol	Nucynta
	Fentanyl	Abstral,Duragesic, Onsolis
	Buprenorphine	BuTrans
	Buprenorphine-naloxone	Suboxone
	Methadone	Methadose, Metadol
	Meperidine	Demerol

Morphine Equivalence

Opioid conversion factors have been developed to establish equianalgesic opioid doses (Table 2.2) [11]. These conversion ratios allow for direct comparison of opioids irrespective of the drugs potency [11]. The Canadian Guideline for Safe and Effective Use of Opioids for CNCP published opioid analgesic conversion tables based on the best available evidence to allow calculation of the analgesic equivalence of opioids [11]. For example, 1 milligram (mg) of oral hydromorphone had a similar analgesic effect as 5 mg of oral morphine and is reported as 5 mg oral morphine equivalent (OME). Different terms are often used to represent similar standardized equianalgesic opioid doses and include OME per day, milligrams morphine equivalents per day (MME/day), Morphine equivalent dose (MED) or morphine equivalents daily dose [11,23,44].

Table 2-2 Opioid Conversion Factors [11,45]

Opioid	**Conversion Factor**
Codeine	0.15
Hydromorphone	5.0
Morphine	1.0
Tramadol	0.3
Oxycodone	1.5

Indications for Opioids

Chronic Cancer Pain

The use of opioids in the treatment of chronic pain related to cancer is well established [46]. The WHO has published a comprehensive guideline for the management of chronic cancer-related pain that involves opioids [43]. It is still recommended that physicians use the WHO pain ladder to manage patients' pain related to malignancy [46].

Acute Postoperative Pain

Short-term opioid use is safe and effective for the management of acute postoperative pain [47]. A comprehensive pain strategy that includes opioids has been shown to improve patient's postoperative mobilization and decreases rates of deep vein thrombosis and pneumonia [48,49]. In 2015, the Washington State Agency Medical Directors' Group released evidence-based clinical recommendations for the treatment of postoperative pain [50]. These guidelines recommend opioids be part of multimodal pain regimes for moderate to severe postoperative pain [50]. Further, the American Pain Society with American Society of Anesthesiologists released 32 recommendations regarding the management of postoperative pain after a comprehensive, systematic review of the literature [51]. This review concluded that pain strategies targeted at multiple pain pathways lead to superior pain control compared to monotherapy alone [51]. After TKA, the American Pain Society recommends systemic pharmacotherapy with a combination of opioids, non-steriodal anti-inflammatory drugs (NSAIDs), acetaminophen, gabapentin be used in conjunction with intraarticular, regional and

neuraxial anesthetic techniques [51]. The duration of opioid treatment is dependent on both patient and procedure factors [47]. In a retrospective review of opioid-naïve patients who underwent a primary TKA, approximately 80% of patients were still taking opioids at 2 weeks follow up, and 32% of patients required at least one opioid prescription refill [52].

Chronic Noncancer Pain

CNCP is defined as pain lasting beyond 3 months that is not associated with malignancy [11]. The Canadian Guideline for Opioids for CNCP recently published a systematic review of the best available evidence and recommended opioids should not be used for first-line treatment in patients with CNCP, such as arthritis [11]. Opioids provide, little if any benefit when compared with other pharmacological and non-pharmacologic treatments, but are associated with a much more significant risk profile [11]. In a recent randomized control trial of 240 patients with chronic back, hip or knee osteoarthritis pain, opioid therapy did not result in significantly better pain-related functional improvements over 12-months when compared to non-opioid medication therapy (mean difference 0.1, 95% CI, −0.5 to 0.7) [22]. But, the opioid therapy group had increased adverse medication-related symptoms over 12 months (overall $p = 0.03$) [22]. These results are supported by a recent systematic review and meta-analysis of 96 randomized clinical trials involving more than 26,000 patients who received opioids or a non-opioid control [21]. Moderate-quality evidence from 7 trials suggested no difference in physical function when patients prescribed opioids were compared to those prescribed NSAIDs (mean difference, −0.90 points, 95%CI, −2.69 to 0.89 points) [21]. When compared to placebo, the authors reported patients who received opioids had small improvements in pain and physical functioning (mean

difference, −0.69 cm, 95% CI, −0.82 to −0.56 cm on a 10-cm visual analog scale for pain, mean difference 2.04 points, 95% CI, 1.41 to 2.68 points on the 100-point SF-36 physical component score) [21]. However, these patients prescribed opioids had a higher incidence of vomiting when compared to placebo (RR 2.50, 95% CI, 1.89-3.30, $p < 0.001$) [21]. In addition, opioids have been reported to be associated with a 5.5% (95%CI, 3.91 - 7.03%) risk of addiction; 8.9% (95%CI 3.7 - 20%) in patients with a history of active substance use disorder or psychiatric diagnosis [11]. Rare, but significant side effects such as non-fatal poisoning (0.2%) and fatal poisoning (0.1%) occur even with low dose opioids (<20 MED). At higher doses, the risk of fatal poisoning doubles (0.23%) and risk of non-fatal poisoning increased 9-fold (1.8%) [11]. The established dose-response relationship for fatal and non-fatal poisonings has led to the recommendation that prescriptions be limited to less than 90 mg MED [11].

Long-term Opioid Therapy

LTOT, also referred to as chronic opioid therapy is defined by daily, or near-daily use of opioids for at least 90 days, often indefinitely [47,53]. This definitional threshold was adopted from a study that reported patients that consumed opioids for longer than 90-days with 10 or more opioid prescriptions or 120 days or more supply of opioids dispensed used opioids for a mean duration of 1000 days[53]. However, there is still substantial variation in methods used to detect LTOT as many studies rely on administrative data as a source of pharmacological history [12,13,15,19]. While administrative data is readily available for large numbers of patients and relatively inexpensive to access, data formatting inconsistencies can make defining consistent medication use challenging [54]. Any disruption in dispensing, such as a refill gap can influence

the opioid utilization period and potentially misclassify a patient [54]. Refill gaps are a result of inconsistent prescription refill patterns, where there may be a small gap between the previous prescriptions calculated end-date and the dispensing date of the subsequent prescription [54,55]. A grace period is often utilized to account for these periods as patients appear to persistently use the prescribed medication despite these small gaps in medication dispensing [54]. Previous research relying on administrative data to detect LTOT has used arbitrary thresholds of 0 to 32 days to determine the maximum allowable gap between opioid prescriptions, with little supporting evidence [15,56,57]. To our knowledge, the influence of refills gaps on opioid utilization periods, and the impact these different methods have on the estimated rates of LTOT has never been reported.

Knee Arthritis

Arthritis is a chronic disease that can affect any synovial joint and results in joint pain and stiffness [58,59]. It is estimated that 3.6 million people in Canada are living with arthritis and this number is expected to grow to 6 million by 2031 given the aging population and increasing prevalence of obesity [60,61]. The estimated total economic burden in Canada is expected to reach 550 billion dollars in the next 30 years as many patients are of working age [62,63]. Globally, arthritis is ranked as the 11th highest contributor to disability and the 38th highest in disability-adjusted life years [61].

Osteoarthritis is the most common form of arthritis and etiology is not fully understood but is thought to be multifactorial with various genetic and patient factors implicated [64].

Modifiable risk factors include prior history of trauma and increased body mass [64]. Females are diagnosed more commonly than men, and certain races have been reported to develop arthritis more often [64]. Regardless of individual factors and etiology, arthritis results in a common pathway that causes biological and mechanical changes of the entire joint, including the subchondral bone, synovium and articular cartilage [58,65]. These changes lead to joint incongruity, instability, overloading of marginal structures and progressive cartilage loss [66]. The diagnosis of arthritis requires a combination of both clinical symptoms and radiographic findings [67]. Symptoms associated with arthritis include joint pain, stiffness and reduced function that have been reported to precede a formal diagnosis of arthritis by over seven years [63,68]. Radiographic changes associated with arthritis include joint space narrowing, osteophyte formation, sclerosis and subchondral cysts [69]. Initial management of arthritis involves strategies that reduce pain and improve function in an attempt to delay or prevent TKA[70].

Nonsurgical Management of Knee Arthritis

The American Academy of Orthopedic Surgeons (AAOS) released a comprehensive, evidence-based clinical guideline that provided recommendations for common non-surgical strategies for patients with knee arthritis [71]. There is strong evidence to support non-pharmacological strategies such as patient education, low-impact aerobic exercises, weight loss and rehabilitation [71]. Supervised exercise combined with home exercise programs results in the largest improvement in pain and function at 12-months follow up [72,73]. Bracing is recommended only for patients with passively correctable, unicompartmental disease with coronal deformity of less than 10 degrees [70,71].

Other management options involve intra-articular injections of corticosteroids, visco-supplementation such as hyaluronic acid and platelet-rich plasma (PRP). The AAOS could not recommend for or against the use of PRP or intra-articular corticosteroids, and recommended against the use of hyaluronic acid injections for the management of arthritis [71]. In addition to these nonpharmacological strategies, multimodal pharmacological regimes that involve Tylenol and NSAIDs may improve knee pain and function [74].

Acetaminophen

Acetaminophen has traditionally been recommended as a first line pharmacologic treatment for arthritis (18,19). However, evidence supporting the effectiveness of acetaminophen in arthritis is limited. A Cochrane review identified 5 placebo controlled randomized control trials that reported acetaminophen had a significant reduction in pain with a number needed to treat varying from 4 to 16 [77]. Using a more stringent search strategy, the AAOS identified only one study that compared acetaminophen to placebo for knee arthritis pain management [71]. This double-blind, placebo controlled trial failed to demonstrate a significant difference in the symptomatic effect of acetaminophen when compared to placebo [78]. Therefore, given the lack of evidence, the AAOS could not recommend acetaminophen for the treatment of knee arthritis [71].

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Oral or topical NSAIDs are the only pharmacological treatment recommended by the AAOS for the management of knee arthritis [71]. This recommendation was based on 19 studies that demonstrated that NSAID's were superior to placebo in 171 of 202 possible outcomes [71]. Compared to acetaminophen, patients taking NSAIDs had a significant reduction in pain and improvement of functional status [77]. In addition, compared to opioids, NSAIDs were reported to have similar improvements in physical function, pain relief and fewer GI side effects (relative risk 2.52, 95%CI, 1.54 - 4.13) [11]. Studies have also demonstrated that NSAIDs have a lower mean cost and higher effectiveness compared to opioids [11,79].

Opioids

The use of opioids to manage arthritis continues to evolve as new evidence suggests that opioids are ineffective at managing pain attributed to arthritis and may negatively influence outcomes [11,16,23]. In fact, the AAOS most recent position statement "agrees with the [Center of Disease Control] in recommending both non-pharmacologic and non-opioid pharmacologic treatment for various conditions, particularly for conditions such as arthritis of the knee." [80]. Further, the AAOS reinforced that the "effectiveness, risks, and role of long-term opioids for non-malignant pain are unclear" [80]. Canada recently released guidelines that outlined the role of opioids in CNCP management [11]. These guidelines were developed not only with clinical experts that evaluated the best available evidence using a systematic approach, but also patients or people who were directly impacted by opioids [11]. These guidelines initially set out to address 24

recommendations, but only 10 recommendations were eventually released based on the available evidence [11]. These guidelines recommended that patients without a history of psychiatric disorders or substance use could trial opioids only after non-opioid pharmacotherapy and non-pharmacological therapy were exhausted [11]. None of the recommendations suggested adding opioid therapy if patients had a psychiatric illness or substance use as these patients have an increased risk of opioid addiction, non-fatal and fatal overdose [11].

Total Knee Arthroplasty

Patients are offered a TKA when they have daily pain that limits function with radiographic evidence of end-stage knee arthritis [81,82]. The modern TKA, first introduced by Dr. Insall in 1974 replaced the diseased joint by resecting the distal femur and proximal tibia's articular surface and replacing it with metal implants [83]. The two metal implants articulate through a plastic polyethylene insert that attempts to restore the biomechanics of the knee [83]. The modern TKA appears similar to the original implants designed by Dr. Insall; however, there are now more options available to surgeons as many different companies now produce TKA systems [84,85]. In addition, polyethylene inserts are now highly-crossed linked with gamma radiation to improve longevity by decreasing wear, and inserts can be either fixed or rotating [86,87]. Fixed bearing inserts restrict TKA motion to flexion and extension, while mobile bearings introduce a second articular surface at the tibial baseplate [88,89]. By allowing rotation of the polyethylene insert, in addition to flexion and extension, the forces acting on the implant are decoupled that may decreases implant interface stresses [90]. There are also different metal alloys available for implant construction, such as cobalt chrome, titanium or oxidized zirconium that can be

implanted with or without cement [91,92]. Outside of highly crosslinked polyethylene, these different design features have yet to be established to improve patient outcomes or long-term survivorship [86,89,91,92].

Patients can walk immediately after surgery and are discharged home once their pain is adequately managed with oral analgesics and ambulate safely [93,94]. On average, patients stay 3 days in the hospital, but there has been a recent shift to decrease costs associated with TKA by promoting outpatient TKA, where patients are discharged home the same day of the surgery [94–96]. During the postoperative rehabilitation phase, patients report an improvement in pain prior to function, with the majority of improvements in both domains (pain and function) noted within 3 to 6 months [97,98]. A prospective study of patients undergoing TKA reported that patients had the most improvement in WOMAC pain and function scores within 3 months of surgery, with no statistically significant changes in WOMAC scores between 3 months and 12-months follow up [105]. Despite significant direct costs of a TKA (24,247 US dollars per patient), it is a cost-effective intervention that improves function and health-related quality of life for patients with arthritis. TKA's have the potential to eliminate pain caused by arthritis and enable patients to resume most activities including hiking, skiing, swimming and cycling [99,100].

Outcomes after Total Knee Arthroplasty

Many different metrics can measure outcomes after TKA [101]. Clinical parameters, such as infection rates, implant loosening or polyethylene bearing wear are often used to quantify postoperative events [102]. When these events are combined, composite outcomes such as

survivorship (using revision surgery as an endpoint) are used to establish surgical success [103]. These measures are objective, comparable across datasets and easily communicable to patients [101]. TKA have excellent results using these metrics, with reported 90-95% 15-year survival rates [104]. However, these outcomes overlook the principal objective of an elective TKA - pain relief and functional improvement [81]. Therefore, outcome measures that better reflect the patient's perspective have gained significant attention [105]. These patient reported outcome (PRO) instruments describe the patient's function, the degree of pain relief and overall patient satisfaction [106–109].

A PRO is a "measurement based on a report that comes directly from the patient, about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else"[110]. PRO's are generated by self-reported questionnaires that attempt to capture the patient's values [106]. There are now over 32 PRO instruments used for patients undergoing TKA [108]. However, not all PRO's are equivalent and each instrument's measurement properties needs to be carefully examined prior to use and includes the instruments reliability, validity, and, responsiveness [107,111] (Appendix 2.1). Based on these measures, the WOMAC is reported to be one of the best performing and comprehensive joint specific PRO's available for TKA [112].

The WOMAC was developed in 1982 for patients with hip or knee arthritis with input from patients, rheumatologists and epidemiologists [113]. It has been validated for use in patients with knee or hip arthritis to determine their response to TKA [113]. Multiple methods of administration have been validated including self-administrated, over the phone or electronically [111]. The instrument takes approximately 5-10 minutes and has a 48-hour recall period for the

items [114]. It is available in over 80 languages and has been validated for multiple language translations [111]. The instrument contains 3 different domains: pain, stiffness and function that have unique, but related individual questions (items) [114]. The pain domain contains 5 items, stiffness 2 items and the function domain 14 items; each response can be scored on a 5-point Likert Scale with "0" representing none and 4 as extreme [114]. The total score can be calculated by summing each domain with a higher score representing worse pain, stiffness or function (Pain = 20, Stiffness = 8, Function = 68, Total = 96) [111]. Alternatively, each domain can also be used in reverse and/or after scores are standardized to 100 so that 0 represents "worst" and 100 "best" [115]. The domain response is considered invalid if 2 or more pain items, either stiffness item or 4 or more physical function items are missing [114].

The minimum difference between PRO scores represents a detectable clinical difference is essential to interpret results [111,116]. The minimum clinically important difference (MCID) refers to "the minimum difference in the scoring measure that the patient perceives as beneficial or harmful after treatment or a change in their health status compared with those who perceive no change" [116]. In contrast, the minimum important change (MIC) refers to the "minimum difference in the scoring measure that the patient perceives as beneficial or harmful after treatment or a change in their health status compared with those who perceive no change" [116]. While individual change should be related to the MIC, the MCID is used for between group comparisons [116]. It has been reported the estimated MCID after TKA for WOMAC pain and function scores is 11 and 9 respectively, on a standardized 100-point WOMAC scale [116].

Determinants of Pain and Physical Function after Total Knee Arthroplasty

While the majority of patients do very well after TKA, up to 20% of patients are dissatisfied with their surgery [117,118]. To help clinicians identify patients at risk for poor outcomes, and develop strategies to optimize outcomes after TKA, there has been substantial interest to determine preoperative factors that can influence pain and functional improvement after TKA [119].

Demographic Determinants

There is increasing evidence that suggests advancing age does not independently contribute to worse pain and function outcomes after TKA [119]. A recent systematic found there is only low quality evidence to suggest age influenced WOMAC pain and function scores one year after TKA[119]. Among studies that adjusted for other patient factors, there were no statistically significant associations between age and one-year WOMAC pain or function scores [119]. It appears associations between age and worse outcome after TKA may be due to unmeasured factors, such as comorbidities that are also known to increase with age [119]. While Wylde *et al.* (2012) reported that age (continuous variable) predicted one-year WOMAC pain or function after TKA in univariate analysis, after adjusting for other factors age did was not significantly associated with one-year WOMAC scores [120]. Further, when age was analyzed as a categorical variable (<65 years ≥ 65 years), Papakostidou *et al.* (2012) that reported that age was not predictive of one-year WOMAC pain or function scores after adjusting gender, BMI, education, social support and location [121]. These results also align with Jones *et al.* (2003),

who reported there was no difference in 6-months WOMAC pain and function scores when patients ≥80 were compared to patients < 80 after TKA, after adjusting for other factors [122].

There is also limited evidence to suggest sex is associated with worse clinical outcomes after TKA. While Fisher *et al.* (2007) reported that female sex was associated with worse one-year outcomes after TKA (OR 2.6, p <0.01), there is growing evidence that suggests this association is not significant, or in the opposite direction[118]. Papakostidou *et al*. (2012) reported that after controlling for BMI, education, social support and residence (rural vs urban), gender was not associated with either one-year WOMAC pain or function score after TKA [121]. Wylde *et al.* (2012) also reported that gender did not predict one-year WOMAC pain or function scores after TKA after controlling for factors such as mental health and comorbidities[120]. These findings were summarized in a recent systematic review that concluded female gender is not associated with outcome scores one-year after TKA [119]. However, it is well established that females have increased pain sensitivity, are more likely to develop chronic pain and respond differently to oral analgesia [123]. Therefore, age, gender and patient reported outcomes after TKA may have a more complex framework involving neurobiological changes in both the peripheral and central nervous system that influence outcomes after surgery [25].

Clinical Determinants

Obesity is one of the most commonly investigated predictors for pain and function outcomes after TKA [124]. Fourteen studies were published between 1997 and 2012 used BMI as a predictor for pain greater than 3-months after TKA[124]. Of these studies, only 2 found a

significant association to suggest obesity predicts pain 3 months or longer after TKA [124]. In contrast, an updated review included 22 studies published between 2013 and 2016, found no significant associations between obesity and the development of pain after TKA [124]. In addition, Harmelink *et al.* (2017) reported that among 5021 patients included in studies investigating the influence of BMI on patient outcomes after TKA, no studies observed that BMI was associated with worse postoperative pain scores, and only two studies found BMI as a significant prognostic factor for physical function[119]. Therefore, there is a growing belief that other factors, previously unaccounted for may influence clinical outcomes after TKA more so than obesity[119].

Poor glycemic control is an established risk factor for postoperative complications and mortality after TKA [125]. However, little is known regarding the impact that diabetes has on pain and function outcomes. It is difficult to elucidate the individual effect of diabetes as it is often incorporated into cumulative comorbidity scores, or reduced to a binary variable (yes/no) [126]. Amusat *et al.* (2014) highlighted this limitation when they reported that patients who had a diagnosis of diabetes that did not impact their activities had similar pain and function outcomes when compared to controls [127]. However, patients with diabetes that impacted their daily activities had worse pain and function outcomes after TKA when compared to the other two groups. Renal dysfunction is also commonly associated with poor outcomes after TKA surgery due to surgery related complications. However, there are few studies aimed at determining if renal dysfunction or disease can predict pain and function scores after TKA. A multivariate analysis, as reported by Amusat *et al.* (2014) reported patients with kidney disease had worse 6-months TKA WOMAC pain and function scores after controlling for other factors [127].

However, more research is needed to further understand this association as more recent studies have presented conflicting results [128].

Index scores provide an alternative to analyzing individual patient comorbidities. These scores attempt to condense a physiological profile into a single score that reflects the overall health status of the patient. The most commonly used indices used in arthroplasty studies are the Charlson Index, Index of Coexistent Disease (ICED), the Charnley Classification and the Functional Comorbidity Index [126]. However, few of these scores have been studied to determine their reliability and validity in arthroplasty specific patient populations [126,129]. Escobar *et al.* (2007) quantified patient's cumulative comorbidity according to the Charlson Index and analyzed patients in three groups: no comorbidities, one, or more than one [130]. They found that 2 or more co-morbidities predicted worse TKA WOMAC pain or function scores after adjusting for other factors while patients with none, or one comorbidity did not reach statistical significance [130]. In contrast, Sharma *et al.* (1996) reported that comorbid disease, quantified by Cumulative Illness Rating Scale (CIRS) was only marginally significant when predicting SF-36 function score ($p = 0.054$) [131].

Psychological Determinants

There is a growing belief that patients' age, sex and medical comorbidities may not significantly contribute to pain and function outcomes after TKA. In fact, Wylde *et al.* (2012) suggested that pain and function outcomes after TKA may be influenced more by psychosocial factors such as depression rather than patients' individual comorbidities [120]. This assertion is supported by the

findings from Lopez-Olivo *et al*. (2010) that reported WOMAC function scores were negatively impacted by higher depression scores, measured by the Depression Anxiety and Stress Scales after controlling for other factors 60-months after TKA [132]. Hirschmann *et al.* (2013) also reported depression, as measured by the Beck Depression Inventory was significantly associated with worse one year WOMAC function and pain scores [117]. However, the extent that depression impacts pain and function after surgery is dependent on the method used to identify depression or quantify depression related symptoms. Physician diagnosed depression, pharmaceutical or administrative data based on health claims data, or depression specific scores have been used to classify patients as depressed prior to TKA [23,117]. Depression scores may allow the severity of symptoms to be investigated, but often do not align with Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria [133] . In contrast, relying on medication records are problematic as antidepressants can be used for other disorders such as chronic pain and migraines [134]. Algorithms have been published that reported increased accuracy if a combination of medication records and depression specific codes are used to flag patients as depressed, but have yet to be applied to arthroplasty specific studies [135].

Preoperative pain and function scores also influence postoperative scores after TKA. A study by Papakostidou *et al* (2012) reported that preoperative WOMAC pain and function scores were associated with one year postoperative WOMAC pain and function after adjusting for age gender, BMI, education, social support and residence (rural vs. urban) [121]. Further, Lingard *et al.* (2004), reported that after controlling for age and gender, preoperative WOMAC pain and function was also significantly associated with pain at one year follow up after TKA [136]. These reports align with the conclusions from a recent systematic review that included studies reporting on factors associated with one-year outcome measures after TKA [119]. The review

identified 11 studies and concluded that preoperative pain is associated with worse postoperative pain after TKA [119]. In addition, 6 studies were identified that reported preoperative function scores was associated with worse physical function one year after TKA [119].

Conclusions

Traditional biomedical models used to describe disease have failed to explain much of the variation in outcomes after TKA despite the technical aspects of the surgery considered a success [119]. Adoption of a biopsychosocial model of disease enables a patient's psychosocial profile to be included when conceptualizing factors that impact patient reported outcomes after TKA [120]. Recent studies the utilized a multidimensional approach led to the discovery that a patients' psychosocial profiles may play the strongest role in determining patient outcomes after surgery [32,120,137]. However, many preliminary studies investigating the association between preoperative opioids and pain and function outcomes after TKA have failed to account for these factors [19,23,28]. More research, considering these other factors will help clarify the complex relationship between preoperative opioid use and outcomes after TKA

Chapter 3

Preoperative Opioid Use is Associated with Worse Patient Outcomes after Total Joint Arthroplasty: A Systematic Review and Meta-analysis

C. Michael Goplen MD, Wesley Verbeek BSc, Sung Hyun Kang MSc, C. Allyson Jones PT, PhD, Donald C Voaklander PhD, Thomas A Churchill PhD, Lauren A Beaupre PT, PhD.

This systematic review outlined the current evidence that described the association between preoperative opioid use and clinical outcomes after TKA. In addition, we described the parameters that have been used to define opioid use before TKA, and determined patient factors associated with preoperative opioid use that could potentially impact outcomes after surgery. Given the paucity of literature published on this topic, our a priori search strategy included both THA and TKA as these outcomes are often reported together. The term total joint arthroplasty (TJA) is used when both THA and TKA are reported together. This chapter has been published in BMC Musculoskeletal Disorders. https://doi.org/10.1186/s12891-019-2619-8.

Abstract

Background: A significant number of patients use opioids prior to total joint arthroplasty (TJA) in North America and there is growing concern that preoperative opioid use negatively impacts postoperative patient outcomes after surgery. This systematic review and meta-analysis evaluated the current evidence investigating the influence of preoperative opioid use on postoperative patient-reported outcomes (PRO) after total joint arthroplasty.

Methods: A systematic search was performed using Ovid, Embase, Cochrane Library, Scopus, Web of Science Core Collection, CINAHL on February 15th, 2018. Studies reporting baseline and postoperative PRO among those prescribed preoperative opioids and those who were not prior to total knee and hip arthroplasty were included. Standardized mean differences (SMD) in absolute difference and relative change in PRO measures between the two groups was calculated using random effect models.

Results: Six studies were included (n=7356 patients); overall 24% of patients were prescribed preoperative opioids. Patients with preoperative opioid use had worse absolute postoperative PRO scores when compared to those with no preoperative opioid use (standardized mean difference (SMD) -0.53, 95% CI -0.75, -0.32, $p < 0.0001$). When relative change in PRO score was analyzed, as measured by difference between postoperative and preoperative PRO scores, there was no group differences (SMD -0.26, 95% CI -0.56, 0.05, $p = 0.10$).

Conclusion: Patients prescribed preoperative opioids may attain worse overall pain and function benefits after TJA when compared to opioid-naïve patients, but do still benefit from undergoing TJA. These results suggest preoperative opioid users should be judiciously counselled regarding potential postoperative pain and function improvements after TJA.

Introduction

Over the past 20 years, the number of opioids prescribed to manage patients with chronic non-cancer pain, such as arthritis has dramatically increased in North America [1,2]. The reported rise is thought to be related to American guidelines that supported opioids to manage pain associated with arthritis [3]. Unfortunately, these guidelines were largely based on expert opinion and industry-backed studies with little supporting evidence [4,5]. Emerging evidence now suggests that opioids provide no benefit when compared to ibuprofen or acetaminophen to manage pain associated with arthritis, but have higher rates of adverse events [6,7]. Nevertheless, physician prescribing practicchaptes have resulted in over 40% of patients being prescribed opioids prior to total joint arthroplasty (TJA) in the USA [8–11].

Opioid use prior to TJA use has gained significant clinical and research interest given its potential to prognosticate a patient's postoperative outcome [8,9,12,13]. Preoperative opioid use has been associated with a more complicated hospital course and more complications after TJA. Sing *et al*. (2016) reported that preoperative opioid users, stayed on average 1.6 days longer in hospital ($p = 0.05$), were more likely to be discharged to a subacute facility (OR 6.7, 95% CI 2.4, 19.0) and associated with increased 90-day complications rates (OR 6.2, 95% CI 1.5, 26.0) than those who did not use opioids preoperatively [12]. Further, Ben-Ari *et al.* (2017) reported on 32,636 patients who underwent total knee arthroplasty (TKA), of which 39% were using long-term opioids preoperatively [9]. Patients who underwent revision surgery within 1 year were more likely to be taking opioids preoperatively, after controlling for other factors (1.4 OR, 95% CI 1.2, 1.6) [9]. However, reports are conflicting regarding the extent that preoperative opioid use impacts postoperative patient-reported outcomes (PRO) after surgery [10,14,15].

The primary objective of this systematic review was to investigate the impact of preoperative opioid use on PRO's after TJA. Our secondary objectives were to: 1) determine the prevalence of preoperative opioid use and dose prior to TJA; 2) compare the parameters used to define preoperative opioid use, such as duration and dose among studies; 3) compare postoperative opioid use between those who were prescribed preoperative opioids and opioid-naïve patients; 4) describe differences in preoperative patient characteristics and postoperative discharge characteristics.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16].

Search Strategy

The search strategies were developed by a health research librarian in collaboration with the first author (CG) and the following databases were searched on February 15th, 2018: 1) Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R); 2) Embase; 3) Cochrane Library; 4) Scopus; 5) Web of Science Core Collection; 6) CINAHL Plus with Full-Text. Controlled vocabulary and text-word terms representing arthroplasty were combined with terms representing opiates/opioids

and terms representing the preoperative period. No date or language limits were applied. See Appendix A for the complete search strategy.

Inclusion and Exclusion Criteria

Peer-reviewed articles that met the following criteria were included in our review: 1) included patients who had undergone primary total hip or total knee arthroplasty; 2) reported disease or joint specific preoperative and postoperative PRO measures; 3) compared patients prescribed preoperative opioids (hereafter 'opioid users') to those who were not (hereafter 'opioid–naïve'); 4) written in English. All study designs eligible for inclusion except case reports and conference abstracts.

Primary Outcome

The primary outcome of this review was the differences in absolute postoperative PRO scores as well as relative change in PRO scores for opioid users when compared to opioid-naïve patients. Relative change in PRO score was calculated by determining the difference between preoperative and postoperative PRO score.

Secondary Outcomes

Our secondary outcomes were: 1) the prevalence of preoperative opioid use; 2) the parameters used to define preoperative opioid use, such as dose and duration; 3) postoperative opioid rates for those prescribed preoperative opioids and opioid-naïve patients; 4) postoperative health services utilization.

Data Extraction and Synthesis

One investigator (CG) imported all retrieved studies into RefWorks, a reference management software program and screened titles to remove duplicate studies. All remaining studies were imported into Covidence, a screening and data extraction tool, for abstract screening, full text review and data extraction [17]. Two reviewers (CG and WV) independently screened all abstracts, completed full-text review of potentially eligible studies and extracted data from included studies. Data extracted included study design, publication date, sample size, statistical methods, preoperative patient data including age, sex and comorbidities, opioid use case definition, the prevalence of preoperative opioid use, PRO measures and secondary outcomes. Secondary outcomes included the prevalence of opioid use before and after TJA, patient demographic information for each group and healthcare utilization information including length of stay and discharge characteristics. Each reviewer then cross-checked all data and any disagreements between reviewers were discussed and resolved by consensus; no third party was required to achieve consensus. If available data were not directly extractable, the original authors were contacted (Supplementary Table 3.1).

Statistical Analysis

PRO Scores

All extracted PRO scores and standard deviation (SD) were standardized to 100 and reversed if required so that a score of 100 indicated the best possible score. If available, total PRO score was used for all calculations, otherwise the pain scores were used. Change in PRO score for each study was calculated by calculating the difference between mean postoperative PRO score and mean preoperative PRO score for opioid users and opioid-naïve groups. The differences between groups were determined by calculating the difference between mean change in PRO score or absolute postoperative PRO score for each study. For studies reporting a mean and 95%CI, we used the formula CI = mean ± t x (SD / √n) to calculate the SD [18]. Change in score SD (Sdiff) was determined using the formula: $S_{diff} = \sqrt{(S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2)}$, where S_1 equals the groups mean preoperative PRO score SD, S_2 equals the group's postoperative score SD and r is the correlation between preoperative and postoperative scores [18]. If there was no prior information on the correlation coefficient (r), we used a value of 0.5. Our sensitivity analysis was robust when we compared the results with correlation coefficients varying from 0.3 (low) to 0.8 (high), so we used the mid-point of 0.5 for our main analysis. For the studies where the SD was not reported, the standard SD was calculated by converting the p-value to a t-score and solving for SD using the study sample size [18]. SMD was then calculated by entering either absolute mean PRO score or change in mean PRO score for each group into Review Manager 5.3 [19]. SMD enables continuous outcome scores that measure the same construct with different instruments to be pooled by expressing the intervention effect relative to SD rather than the original units of measurement [20]. Random effect models were used to compute pooled SMD and 95% CIs.

Random-effects models account for between study heterogeneity and provides a more conservative evaluation of the association than one based on fixed effects [18]. Interpretations of effect sizes were based on suggestions by Cohen where an effect size of 0.2 is small, 0.5 is medium and 0.8 is large [21,22]. Heterogeneity was assessed with the I2 statistic and interpreted as low (> 25%), moderate (> 50%), or high (> 75%) [23]. The level of significance was set at $p < .05$.

Prevalence of Opioid Use prior to TJA

The prevalence of preoperative opioid use was calculated by pooling the total number of patients prescribed preoperative opioids divided by the total number of patients in the studies that reported preoperative opioid use (n = 3 studies).

Assessment of Study Quality

Two reviewers (CG and WV) independently conducted a quality assessment of eligible studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort Studies (Appendix 3.3) [24]. This checklist contains 11 questions that assess specific domains of studies to determine the potential risk of bias and could be answered with ‘yes’, ‘no’ or ‘unclear’ (Appendix 3.3). Any disagreements between reviewers were discussed and resolved by consensus. The risk of bias of individual studies were determined with the following cutoffs: low

risk of bias if 70% of answers scored yes, moderate risk if 50% to 69% questions scored yes and high risk of bias if yes scores were below 50% [25,26].

Results

Study Selection

Of the 3044 studies identified from the primary search, 1830 studies were duplicates and removed, leaving 1214 studies to undergo abstract screening. After removing 1200 irrelevant studies, 14 studies were reviewed in full to determine potential eligibility for inclusion and 6 studies were included in our meta-analysis (7356 patients) [10,27–31]. The summary of study selection is presented within the PRISMA diagram (Figure 3.1).

Study Characteristics

All studies were retrospective cohort studies, conducted in the USA and published between 2010 and 2017 (Table 3.1). Five studies were a retrospective analysis of prospectively collected data while one study did not indicate specific details regarding source patient data (Table 3.1). Potentially confounding factors were controlled by using a matched cohort (n=3 studies), or risk adjustment (n=1 study); two studies did not control for other potentially confounding variables (Table 3.1). Three studies included only TKA patients, two studies combined both total hip arthroplasty (THA) and TKA patients, while one study was limited to THA patients (Table 3.1). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was reported

for three studies, two studies reported the Knee Society Score (KSS) and one study used the Harris Hip Score (HHS) (Table 3.1). Mean postoperative follow-up ranged from 6 months to 58 months (Table 3.1).

Risk of Bias

Three studies were considered to have a moderate risk of bias, while the remaining 3 studies were classified as high risk of bias according to the JBI Critical Appraisal Checklist for Cohort Studies (Table 3.2). Most studies lacked appropriate statistical methods or design to identify and control for differences noted between the two groups (Table 3.2).

Primary Outcome

All studies reported worse absolute postoperative scores among patients prescribed preoperative opioids compared to opioid-naïve patients (Table 3.3). Of the studies that reported a parameter of statistical significance comparing absolute postoperative PRO scores between the two groups, all reported worse scores among opioid users when compared to opioid-naïve patients (range 4.7 – 13 points, $p < 0.05$ for all) (Supplementary Table 3.2). When relative change in PRO score was analyzed, five of the six studies demonstrated that opioid users had a smaller change in PRO scores when compared to opioid-naïve patients (range 2.4 – 20.2 points). Of the three studies that performed statistical analysis comparing the change in PRO score between groups, all reported these differences to be statistically significant ($p < 0.05$ for all) (Supplementary Table 3.2).

Our meta-analysis found that opioid users had worse absolute postoperative PRO scores, compared to opioid-naïve patients (SMD -0.53, 95% CI -0.75, -0.32, p <0.0001) (Figure 3.2). Based on Cohen's coefficient, the effect size is moderate. Contrary to individual study results, relative change in PRO did not reach statistical significance between groups (SMD -0.26, 95% CI -0.55, 0.05, p =0.10) (Figure 3.3) in the meta-analysis; the effect size was also considered small. However, heterogeneity was statistically high between studies for both change in PRO score (I^2change = 88%), and absolute postoperative PRO score (I^2absolute = 75%). Subgroup analysis did not influence the magnitude or significance of the results when stratified by joint (knee or hip) or by WOMAC domain score.

Secondary Outcomes

Opioid Use Prior to TJA

The prevalence of opioid use prior to TJA was 24.4% when data from studies were pooled (range 24% to 29%) (Table 3.4). Only two studies reported a mean dose for opioid users; Zywiel *et al.* (2011) reported the mean preoperative dose was 58 mg morphine equivalents per day (MED) (range 20 – 300 mg MED), while Nguyen *et al*. (2011) reported 34% of patients' preoperative dose was <30 mg MED, 17% 31-60 mg MED, 15% 61-120 mg MED, and 34% had >120 mg MED [27,31].

Preoperative Opioid Use Definitional Parameters

Definitional parameters for preoperative use ranged from "any" documented opioid use within two years of the index surgery to "a minimum of six weeks" of opioid use prior to index procedure (Table 3.4). Three studies justified their case definition based on the minimum amount of time required to develop opioid induced hyperalgesia (OIH); the three remaining studies did not include a justification (Table 3.4). Two studies reported that the minimum preoperative dose for the patients to be classified as opioid users was 20 or 30 mg MED, respectively (Table 3.4). Of the three studies that outlined which opioids were included in their study, only two considered Tramadol as an opioid (Table 3.4).

Postoperative Opioid Use

Pivec *et al.* (2014) reported opioid users consumed significantly more opioids on postoperative days 0, 1 and 3, and at six weeks compared to opioid-naïve patients ($p < 0.05$ for all) [29]. But, Zywiel *et al.* (2011) reported that there were no significant differences in mean MED at discharge from TKA when comparing opioid users to opioid-naïve patients (85 mg vs 91 mg MED, $p = 0.95$). Opioid users were also found to have higher rates of persistent postoperative opioid use at long-term follow up after TJA compared to opioid-naïve patients (Supplementary Table 3.3). At six months' follow up, Goesling *et al*. (2016) noted 50.3% of TKA and 37.7% of THA preoperative opioid users were still prescribed opioids, compared to only 8.2% of TKA and 4.3% of THA opioid-naïve patients ($p < 0.01$ for both). At 12-months follow up, Franklin *et al.* (2010) reported that 14% of opioid users were still using opioids compared to 2.6% of opioid-

naïve patients ($p < 0.01$). At final follow up (mean 58 months), Pivec *et al.* (2014) reported that 19% of opioid users were still prescribed opioids, compared to 4% of opioid-naïve patients ($p = 0.04$).

Impact of Patient Characteristics

There were significant differences in preoperative patient characteristics between opioid users and opioid-naïve patients (Table 3.5). Of the three studies that did not match for age, two reported that opioid users were younger than opioid-naïve patients ($p < 0.01$ for both) (Table 3.5). All studies reported that opioid users had worse preoperative mental health when compared to opioid-naïve patients. Goesling *et al*. (2016) reported that opioid users had worse hospital anxiety and depression scale (HADS) depression scores, HADS anxiety scores and catastrophizing scores when compared to opioid-naïve patients ($p < 0.01$ for all). Likewise, Smith *et al.* (2017) reported that opioid users had worse pain catastrophizing scores and Franklin *et al.* (2010) found opioid users had worse SF-12 mental component scores preoperatively when compared to opioid-naïve patients ($p < 0.05$ for both). Finally, Zywiel *et al*. (2011) found significantly more opioid users prescribed antidepressants or anxiolytics preoperatively, compared to opioid-naïve patients (21 patients vs. 10 patients, $p = 0.014$) and Pivec *et al.* (2014) reported opioid users also had significantly higher numbers of a past psychiatric diagnosis than opioid-naïve patients (16 patients vs. 7 patients, $p = 0.03$). Despite these group differences, there was no difference in the number of patients with chronic back pain, actively smoking or reporting alcohol use when groups were compared in both studies ($p > 0.05$ for all).

Length of Stay and Discharge Characteristics

Two studies reported varying effects on postoperative health services (Supplementary Table 3.3). While both studies found the mean hospital length of stay increased when opioid users were compared to opioid-naïve patients, only one study reported a statistically significant result (Supplementary Table 3.3). Although preoperative opioid use did not affect discharge destination from the surgical hospital, opioid users were more likely to be referred to chronic pain clinic postoperative when compared to preoperative opioid-naïve patients (8 patients vs. 1 patient, $p<0.001$) [31].

Discussion

In our pooled analysis comparing preoperative opioid users to opioid-naïve patients, we found that opioid users had worse absolute postoperative PRO scores, but similar relative change in PRO scores when compared to opioid-naïve patients (Figure 3.2 and 3.3). These results suggest that patients prescribed opioids preoperatively experience the same level of improvement compared to their opioid-naïve counterparts but still have overall worse PRO scores. Morris *et al.* (2016) also reported that patients prescribed opioids prior to total shoulder arthroplasty achieved similar relative change in PRO scores postoperatively, but worse overall benefit when compared to opioid-naïve patients [14,32]. These two studies also reported that significantly fewer patients prescribed preoperative opioids were satisfied with their surgery postoperatively, compared to opioid-naïve patients (80% vs 91%, $p = 0.03$) [32]. It has been hypothesized that OIH may explain the differences between these two groups [27,29,31,33]. OIH is a process by

which patients taking long-term opioids have a paradoxical increased response to painful stimuli [33]. However, the reasons why these changes persist at long-term follow up (>6 months) is uncertain and likely relates to the complex relationship between chronic pain, opioid use and patient's psychological factors [34].

Patients with mental health conditions, such as depression and anxiety are more likely to be prescribed opioids, at higher doses and for longer durations [35,36]. Our results were consistent with these reports; more opioid users reported psychiatric conditions, antidepressant or anxiolytic use than those who were opioid-naïve (Table 3.5). Understanding the association between opioids use and depression is complex, as they often coexist and can be a cause, or result of the other [35,37,38]. Not only have studies reported prolonged opioid use can induce depression, but depressed patients more frequently seek medical attention for pain, and are three times more likely to be prescribed chronic opioid therapy (>90 days) [34,35,38]. Despite this association, Smith *et al.* (2017) reported that after adjusting for these group differences, preoperative opioid was still associated with worse postoperative PRO scores after TKA [10].

The search strategy was not designed to exhaustively review our secondary outcomes, but our results did highlight several important points regarding opioid prescribing practices among TJA patients. First, a substantial number of patients (24%) are prescribed opioids prior to TJA in the USA (Table 3.4). To our knowledge, only two studies have reported the prevalence of preoperative opioid use outside of the USA; 5% of patients awaiting TKA, and 6% of patients awaiting THA were considered opioid users prior to surgery in Australia [39,40]. Our critical analysis describing the parameters used to define opioid users demonstrated definitional differences are likely contributing to the variation in preoperative opioid prescription rates (Table

3.4). In addition, there was an inconsistent inclusion of Tramadol, one of the most commonly prescribed opioids (Table 3.4). This exclusion may be explained by previous American Academy of Orthopaedic Surgeons guidelines that recommended its use for the management of pain associated with knee osteoarthritis [8,41]. However, Tramadol is now routinely classified as an opioid in national prescribing guidelines as the drug shares similar abuse rates and side effects as traditional opioids [6,42,43]. Collectively, the observed variations in case definitions create uncertainty about the true prevalence of preoperative opioid rates among patients undergoing TJA.

We also noted that patients prescribed preoperative opioids are more likely to continue to use opioids at long-term follow up after surgery when compared to preoperative opioid-naïve patients (Supplementary Table 3.3). These results are consistent with a study that reported preoperative opioid use (>225 days), depression and pain catastrophizing was associated with persistent postoperative opioid use after THA [28,39]. These patient factors may explain the subset of preoperative opioid-naïve patients that go on to long-term opioid use postoperatively, and underscores the importance of opioid stewardship. Implementing standardized, evidence-based postoperative opioid prescribing protocols may optimize postoperative opioid prescriptions and are particularly important for patients at risk for transitioning from short-term to long-term opioid therapy postoperatively [39,44,45].

The main limitation of this systematic review was the low number of studies available that used different analytic approaches, outcomes measures and follow-up periods. Given these differences, we used a random effects model that accounts for statistical heterogeneity between the studies and provides a more conservative estimate of the significance than a fixed effects

model [18]. In addition, sensitivity analysis for the estimations, including score construct (pain or total score), surgical joint (hip or knee) were robust and did not significantly change the results.

Conclusions

To our knowledge, this is the first systematic review comparing the impact of preoperative opioid use on PRO after TJA. Our study demonstrated that patients prescribed preoperative opioids may attain worse overall pain and function benefits after TJA, compared to opioid-naïve patients, but do still benefit from undergoing TJA. However, without further research that considers other patient factors in the context of preoperative opioid use, our understanding of the independent impact of opioid use on outcomes after surgery remains uncertain.

References

[1] Canadian Institute for Health Information CC on SA. Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. 2016.

[2] Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ 2016;188:1240–4. doi:10.1503/cmaj.160356.

[3] Federation of State Medical Boards of the United States I. Model policy for the use of controlled substances for the treatment of pain. J Pain Palliat Care Pharmacother 2005;19:73–8.

[4] Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006;174:1589–94. doi:10.1503/cmaj.051528.

[5] Franklin G. Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology: Comments. Neurology 2014;84:1503. doi:10.1212/WNL.0000000000000839.

[6] Busse JW. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. Natl Pain Cent 2017:1–105. doi:10.1503/cmaj.170363.

[7] Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain. Jama 2018;320:2448. doi:10.1001/jama.2018.18472.

[8] Bedard NA, Pugely AJ, Westermann RW, Duchman KR, Glass NA, Callaghan JJ. Opioid Use After Total Knee Arthroplasty: Trends and Risk Factors for Prolonged Use. J Arthroplasty 2017;32:2390–4. doi:10.1016/j.arth.2017.03.014.

[9] Ben-Ari A, Chansky H, Rozet I. Preoperative opioid use is associated with early revision after total knee arthroplasty a study of male patients treated in the veterans affairs system. J Bone Jt Surg - Am Vol 2017;99:1–9. doi:10.2106/JBJS.16.00167.

[10] Smith SR, Bido J, Collins JE, Yang H, Katz JN, Losina E. Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes. J Bone Jt Surg 2017;99:803–8. doi:10.2106/JBJS.16.01200.

[11] Kim KY, Anoushiravani AA, Chen KK, Roof M, Long WJ, Schwarzkopf R. Preoperative Chronic Opioid Users in Total Knee Arthroplasty-Which Patients Persistently Abuse Opiates Following Surgery?. J Arthroplasty 2018;33:107–12.

[12] Sing DC, Barry JJ, Cheah JW, Vail TP, Hansen EN. Long-Acting Opioid Use Independently Predicts Perioperative Complication in Total Joint Arthroplasty. J Arthroplasty 2016;31:170–174.e1. doi:10.1016/j.arth.2016.02.068.

[13] Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, et al. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. Osteoarthr Cartil 2017;25:1399–406. doi:10.1016/j.joca.2017.04.002.

[14] Morris BJ, Mir HR. The Opioid Epidemic and Orthopedic Outcomes: Implications and Strategies. Tech Orthop 2016;31:215–7. doi:10.1097/BTO.0000000000000188.

[15] Cheah JW, Sing DC, McLaughlin D, Feeley BT, Ma CB, Zhang AL. The perioperative effects of chronic preoperative opioid use on shoulder arthroplasty outcomes. J Shoulder Elb Surg 2017;26:1908–14. doi:10.1016/j.jse.2017.05.016.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Med 2009;6:e1000097.

[17] Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org

[18] Borenstein, M., Hedges, L. V., Higgins, J. P. T. & Rothstein HR. Introduction to Meta-Analysis. John Wiley & Sons, Ltd; 2009. doi:10.1002/9780470743386.

[19] Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

[20] Higgins JPT GS (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.

[21] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale: Lawrence Erlbaum Associates; 1988.

[22] Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York: Academic Press; 1969.

[23] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ Br Med J 2003;327:557–60. doi:10.1136/bmj.327.7414.557.

[24] Briggs. TIJ. JBI Critical Appraisal Checklist for Cohort Studies. Adelaide: The Joanna Briggs Institute; 2016.

[25] Melo G, Dutra KL, Rodrigues Filho R, Ortega AOL, Porporatti AL, Dick B, et al. Association between psychotropic medications and presence of sleep bruxism: A systematic review. J Oral Rehabil 2018;45:545–54. doi:10.1111/joor.12633.

[26] Briggs. TIJ. Joanna Briggs Institute Reviewers' Manual. 2nd edn. Adelaide: The Joanna Briggs Institute; 2014.

[27] Nguyen L-CL, Sing DC, Bozic KJ. Preoperative Reduction of Opioid Use Before Total Joint Arthroplasty. J Arthroplasty 2016;31:282–7. doi:10.1016/j.arth.2016.01.068.

[28] Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain 2016;157:1259–65. doi:10.1097/j.pain.0000000000000516.

[29] Pivec R, Issa K, Naziri Q, Kapadia BH, Bonutti PM, Mont MA. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. Int Orthop 2014;38:1159–65. doi:10.1007/s00264-014-2298-x.

[30] Franklin PD, Karbassi JA, Li W, Yang W, Ayers DC. Reduction in narcotic use after primary total knee arthroplasty and association with patient pain relief and satisfaction. J Arthroplasty 2010;25:12–6. doi:10.1016/j.arth.2010.05.003.

[31] Zywiel MG, Stroh DA, Lee SY, Bonutti PM, Mont MA, Zywiel MG, et al. Chronic opioid use prior to total knee arthroplasty. J Bone Jt Surgery, Am Vol 2011;93:1988–93. doi:10.2106/JBJS.J.01473.

[32] Morris BJ, Sciascia AD, Jacobs CA, Edwards TB. Preoperative opioid use associated with worse outcomes after anatomic shoulder arthroplasty. J Shoulder Elb Surg 2016;25:619–23. doi:10.1016/j.jse.2015.09.017.

[33] Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. J Pain 2006;7:43–8. doi:10.1016/j.jpain.2005.08.001.

[34] Sullivan MD. Depression Effects on Long-term Prescription Opioid Use , Abuse , and Addiction 2018;34:878–84. doi:10.1097/AJP.0000000000000603.

[35] Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. Gen Hosp Psychiatry 2009;31:564–70. doi:10.1016/j.genhosppsych.2009.07.003.

[36] Morasco BJ, Duckart JP, Carr TP, Deyo RA, Dobscha SK. Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. Pain 2010;151:625–32. doi:10.1016/j.pain.2010.08.002.

[37] Wright EA, Katz JN, Abrams S, Solomon DH, Losina E. Trends in prescription of opioids from 2003-2009 in persons with knee osteoarthritis. Arthritis Care Res (Hoboken) 2014;66:1489–95. doi:10.1002/acr.22360.

[38] Scherrer JF, Salas J, Lustman PJ, Burge S, Schneider FD, Residency Research Network of Texas (RRNeT) Investigators. Change in opioid dose and change in depression in a longitudinal primary care patient cohort. Pain 2015;156:348–55. doi:10.1097/01.j.pain.0000460316.58110.a0.

[39] Inacio MCS, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: A retrospective cohort study. BMJ Open 2016;6. doi:10.1136/bmjopen-2015-010664.

[40] Hansen CA, Inacio MCS, Pratt NL, Roughead EE, Graves SE. Chronic Use of Opioids Before and After Total Knee Arthroplasty: A Retrospective Cohort Study. J Arthroplasty 2017;32:817.e1.

[41] American Academy of Orthopaedic Surgeons Academy A. Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline 2nd Edition Adopted by the American American Academy of Orthopaedic Surgeons Board of Directors. Am Acad Orthop Surg Board Dir 2013:973. doi:10.5435/JAAOS-21-09-577.

[42] Howlett, Karen; Baum KB. Health Canada eyes opioid restrictions for popular painkiller. Globe Mail 2017. https://www.theglobeandmail.com/news/national/health-canada-eyes-opioid-restrictions-for-popular-painkillertramadol/article37048483/.

[43] Canadian Institute for Health Information. Pan-Canadian Trends in the Prescribing of Opioids, 2012 to 2016. Ottawa, ON: 2017.

[44] Sabatino MJ, Kunkel ST, Ramkumar DB, Keeney BJ, Jevsevar DS. Excess Opioid Medication and Variation in Prescribing Patterns Following Common Orthopaedic Procedures. J Bone Jt Surg Am 2018:180–8. doi:10.2106/JBJS.17.00672.

[45] Earp BE, Silver JA, Mora AN, Blazar PE. Implementing a Postoperative Opioid-Prescribing Protocol Significantly Reduces the Total Morphine Milligram Equivalents Prescribed. J Bone Jt Surg Am 2018:1698–703. doi:10.2106/JBJS.17.01307.

Table 3-1 Characteristics of Included Studies

Study	Year	Country	n	Procedure	Study Design	Source of Patients	Control of Confounding	Factors Matched/Adjusted	PRO	Follow up
Zywiel *et al.*	2011	USA	90	TKA	Retrospective Cohort	Prospectively collected database at two institutions that specialize in lower extremity total joint arthroplasty	Matching	Center (exact match), procedure type (unilateral or bilateral procedure; exact match), sex (exact match), age (± 4 years) and BMI (± 4 kg/m^2)	KSS	38.5 months (mean)
Smith *et al.*	2017	USA	156	TKA	Retrospective Cohort	Secondary analysis of a randomized controlled trial evaluating motivational interviewing to enhance TKA outcomes	Risk Adjustment	Propensity Score (Pain Catastrophizing Scale score, Charlson Comorbidity Index and baseline WOMAC pain score), preoperative opioid use	WOMAC	6 months
Franklin *et al.*	2010	USA	6346	TKA	Retrospective Cohort	Prospectively data on a national sample of primary, unilateral TKA patients sponsored by Zimmer, Inc., Warsaw between 2000 and 2005	None	None	KSS	12 months
Pivec *et al.*	2014	USA	108	THA	Retrospective Cohort	Prospectively collected database at two institutions that specialize in lower extremity total joint arthroplasty	Matching	Gender, Unilateral or bilateral total hip arthroplasty (exact), Age (±5 years), BMI (± $4kg/m^2$), when possible: insurance type, tobacco use ≥0.5 packs per day, history of psychiatric disorders, history of back pain or surgery	HSS	58 months (mean)
Nguyen *et al.*	2016	USA	82	TKA, THA	Retrospective Cohort	A single institution database	Matching	Primary diagnosis, affected joint (hip/knee), American Society of Anesthesiologists' classification of physical health, sex, BMI (±10 kg/m^2), age (±10), daily morphine equivalent group	WOMAC	6 -12 months
Goesling *et al.*	2016	USA	574	TKA, THA	Retrospective Cohort	Secondary analysis of data from a prospective outcome study in patients undergoing TKA and THA	None	None [1]	WOMAC	6 months

Abbreviations
n – number of patients included from study, PRO – Patient-Reported Outcome, WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index, KSS – Knee Society Score, HHS – Harris Hip Score, TKA – Total Knee Arthroplasty, THA – Total Hip Arthroplasty, BMI – Body Mass Index

Notes
[1] Additional data provided that did not adjust for other patient factors

Table 3-2 JBI Risk of Bias Quality Assessment for Cohort Studies

Study	Q1[1]	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	% yes	Risk[2]
Zywiel *et al.*	×	✓	✓	✓	×	✓	✓	✓	?	×	×	55%	Moderate
Smith *et al.*	×	×	×	✓	✓	✓	✓	✓	?	×	✓	55%	Moderate
Franklin *et al.*	?	×	×	×	×	✓	✓	✓	×	×	×	27%	High
Pivec *et al.*	×	✓	✓	✓	?	✓	✓	✓	?	×	×	55%	Moderate
Nguyen *et al.*	?	✓	✓	×	×	✓	✓	✓	?	×	×	45%	High
Goesling et al.	×	✓	×	✓	×	✓	✓	✓	?	×	×	45%	High

Abbreviations
JBI – Joanna Briggs Institute
[1] Q1 – Q11 indicate questions 1 to 11 based on the JBI risk assessment (Appendix 3.3)

Notes
[2] The risk of bias was ranked as high when the study reached up to 49% of ‘‘yes’’ scores, moderate when the study reached from 50% to 69% of ‘‘yes’’ scores, and low when the study reached more than 70% of ‘‘yes’’ scores. ‘✓’ indicates yes, ‘✕’ indicates no and ‘?’ indicates unclear

Table 3-3 Comparison of scores between Patient Prescribed Preoperative Opioids and Opioid-Naïve Patients

Study	Patients	PRO	Statistic	Preoperative Score		Postoperative Score		Mean Change [1]		Difference [2]
				OU	nOU	OU	nOU	OU	nOU	(OU – nOU)
Zywiel *et al.*	OU (n) = 45 nOU (n) = 45	KSS	mean (SD)	38.0	37.0	79.0 (10.0)	92.0 (10.0)	41.0 (14.5)	55.0 (12.0)	14.0
Smith *et al.*	OU (n) = 36 nOU (n) = 120	WOMAC Pain	mean (SD)	55.4	56.3	82.9 (12.7)	89.5 (12.7)	27.0 (12.7)	33.6 (12.7)	6.6
Franklin *et al.*	OU (n) = 1544 nOU (n) = 4802	KSS	mean (SD)	34.8	37.1	81.3 (15.7)	86.0 (14.1)	46.5 (15.4)	48.9 (14.9)	2.4
Pivec *et al.*	OU (n) = 54 nOU (n) = 54	HHS	mean (SD)	43.0	45.0	84.0 (11.5)	91.0 (11.5)	41.0 (81.2)	46.0 (91.1)	5.0
Nguyen *et al.*	OU (n) = 41 nOU (n) = 41	WOMAC	mean (SD)	47.5	44.1	65.3 (35.1)	83.1 (35.1)	17.8 (41.8)	39.0 (41.8)	20.2
Goesling *et al.*	OU (n) = 111 nOU (n) = 313	WOMAC	mean (SD)	39.3	49.4.0	80.8 (17.3)	85.5 (12.8)	41.5 (16.2)	36.1 (13.8)	- 5.4

Abbreviations
PRO –Joint or Disease Specific Patient-Reported Outcome Score. All scores Transformed to a 0 to 100-point scale (100 indicating the best possible score), WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index, KSS – Knee Society Score, HHS – Harris Hip Score, OU – patients prescribed preoperative opioids, nOU – Preoperative Opioid-naïve patients
n – number of patients, SD – Standard deviations, CI – Confidence Interval

Notes
[1]Mean change calculated by the difference in preoperative and postoperative score
[2]Difference represents the mean difference between opioid users and non-opioid users with a positive indicating benefit for preoperative opioid-naïve patients

Table 3-4 Preoperative Opioid Use Definitional Parameters

Study	Definition of Opioid User	Justification	Opioid Use	Source of Pharmacy Data	Included Opioids	Preoperative Duration	Preoperative Dose (MED)
Zywiel *et al.*	Any documented opioid use (minimum ≥20 mg morphine equivalents per day) for minimum 6 weeks prior to index procedure	Chu *et al* (2006)	N/A	Prescription records, clinic notes and admission records	N/A	Minimum 6 weeks	58 mg
Smith *et al.*	At least 1 opioid prescription within 2 years of index surgery	N/A	23%	Clinical visit notes, anesthesiology reports, discharge notes, prescription history, and medication lists.	Oxycodone, hydrocodone, hydromorphone, morphine, tramadol, codeine	N/A	N/A
Franklin *et al.*	Any documented opioid prescription prior to index procedure	N/A	24%	Administrative Database	Percocet, Vicodin, Darvocet, Tylenol with codeine 'other'	N/A	N/A
Pivec *et al.*	Minimum of 6 weeks of narcotic use (minimum ≥30 mg morphine equivalents per day) prior to index TKA	Chu *et al* (2006)	N/A	Clinic charts, in-patient hospital medication administration records, prescription documentation, and phone interviews	Morphine, codeine, hydrocodone, hydromorphone, methadone, meperidine, oxycodone, propoxyphene, tramadol, transdermal fentanyl	Minimum 6 weeks	N/A
Nguyen *et al.*	Continuous opioid use for at least 4 weeks prior to index procedure	Chu *et al* (2006)	N/A	Clinic and referral notes	N/A	Minimum 4 weeks	[1] Low 34% Medium 17% High 15% Very High 34%
Goesling *et al.*	Patient-reported opioids use prior to index procedure	N/A	29%	Chart review, confirmed by patient	N/A	N/A	N/A
		Mean [2]	**24%**				

Abbreviations
N/A – data not available, MED – Morphine equivalent dose
Notes
[1]Classification of opioid user: Low (<30mg), Medium (31-60 mg) High (61 - 120mg) and Very High (>121 mg)
[2] Mean calculated by summing number of patients prescribed preoperative opioids (n = 1747) and dividing by total patients (n = 7163)
Chu *et al.* (2006) – minimum duration and dosage required of morphine required to develop opioid induced hyperalge

Table 3-5 Comparison of Preoperative Patient Demographic between Patient Prescribed Preoperative Opioids and Opioid-Naïve Patients

Study	Patient Characteristics	OU	nOU	p
Zywiel *et al.*	Mean age*	56	57	0.653
	% male*	31.1	31.1	-
	Mean BMI*	34	34	0.884
	Number of patients prescribed antidepressants or anxiolytics	21	10	0.014
	Number of patients with chronic back pain or prior back surgery	9	8	0.788
	Number of patients actively smoking	10	7	0.419
	Number of patients reporting alcohol use	0	1	0.316
	Number of patients with systemic corticosteroid use	8	7	0.777
Smith *et al.*	Mean age	67.5	65.2	0.13
	% female	23.7	76.3	0.81
	Mean BMI	31.0	31.1	0.84
	Mean comorbidities	0.81	0.81	0.91
	Preoperative Pain Catastrophizing Scale (SD)	15.3 (10.3)	10.7 (7.7)	0.006
	Mean unadjusted preoperative WOMAC Pain (SD)	53.1 (15.7)	57 (12.8)	0.12
	Mean unadjusted preoperative WOMAC Function (SD)	51.0 (14.1)	57.9 (13.8)	0.009
Franklin *et al.*	Mean age (SD)	65.3 (11.0)	68.1 (9.7)	<0.001
	% male	28.9	34.1	<0.001
	Mean BMI	32.6 (7.5)	31.7 (6.8)	<0.001
	Mean SF-12 PCS (SD)	28.2 (7.1)	30.6 (7.9)	<0.001
	Mean SF-12 MCS (SD)	48.7 (12.0)	53.0 (10.8)	<0.001
Pivec *et al.*	Mean age*	55	55	-
	% male*	54	54	-
	BMI*	30.2	29.9	-
	Number of patients with history of a psychiatric diagnosis	16	7	0.03
	Number of patients with history of alcohol abuse	7	6	0.77
	Number of patients reporting active smoking	14	12	0.83
	Number of patients with history of back pain	11	14	0.24
	Number of patients with history of back surgery	7	10	0.60
	Number of patients with systemic corticosteroid use	10	6	0.42
	Numbers of patients reporting worker's compensation	2	1	0.56
Nguyen *et al.*	Mean age*	60	58	-
	% male*	34	34	-
	Mean SF-12 MCS	42.8	49.1	-
	Mean SF-12 PCS	28.8	30.9	-
Goesling *et al.*	Mean age	59.3	63.6	<0.001
	% male	43.1	50.1	0.127
	BPI Overall Pain Severity (SD)	5.6 (1.8)	4.3 (12.0)	<0.001
	HADS Depression (SD)	5.9 (3.5)	4.2 (3.2)	<0.001
	HADS Anxiety (SD)	6.2 (3.8)	5.2 (3.6)	0.002
	CSQ Catastrophizing (SD)	6.5 (5.8)	4.2 (5.7)	0.001

Abbreviations
SD – Standard deviation, WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index, KSS – Knee Society Score, HHS – Harris Hip Score, OU – patients prescribed preoperative opioids, nOU – Preoperative opioid-naïve patients, BPI – Brief Pain Inventory, HADS - Hospital Anxiety and Depression Scale Depression, CSQ - Coping Strategies Questionnaire, '-' not reported in study.

Notes
* Matched Cohort

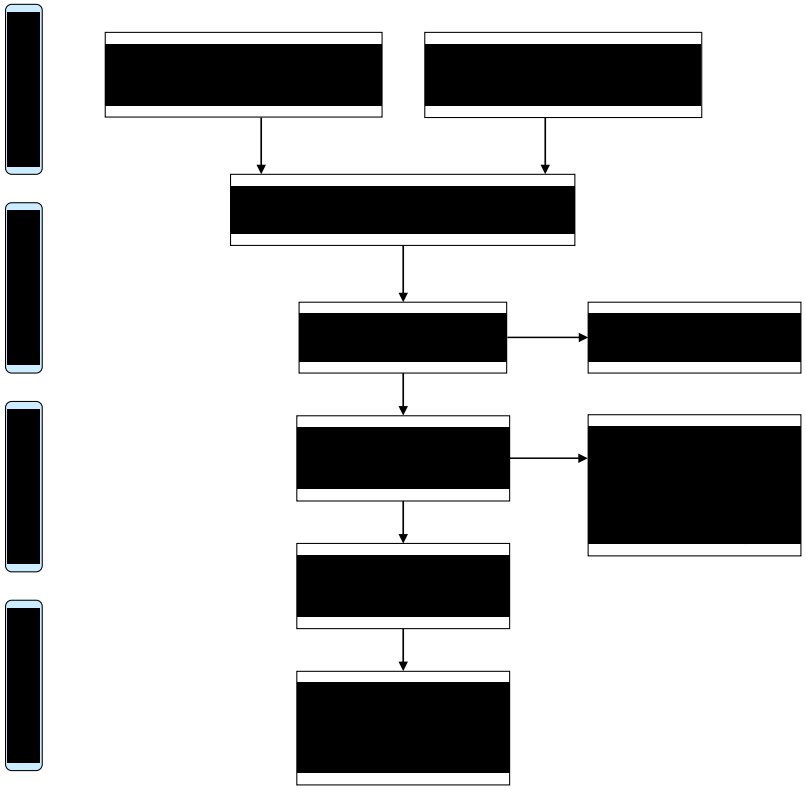


Figure 3.1 PRISMA flow diagram

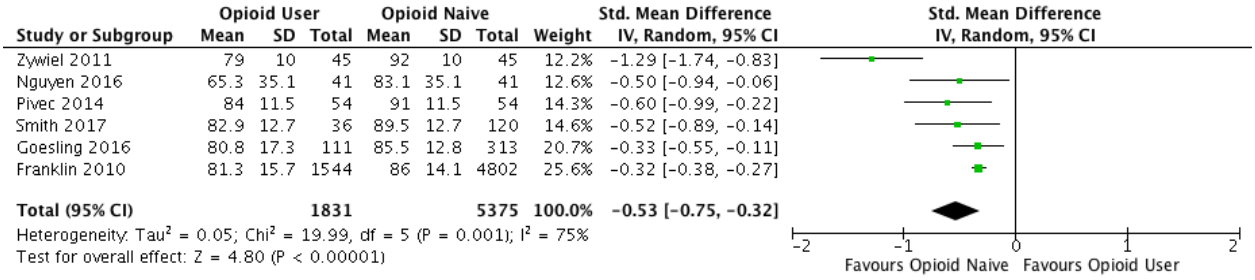


Figure 3.2 Forest plot comparing absolute PRO scores between opioid users and opioid-naïve-patients (CI, confidence interval; IV, Inverse variance; Random, random effects model; SMD, standard mean difference; SD, standard deviation. Individual studies SMD; pooled SMD).

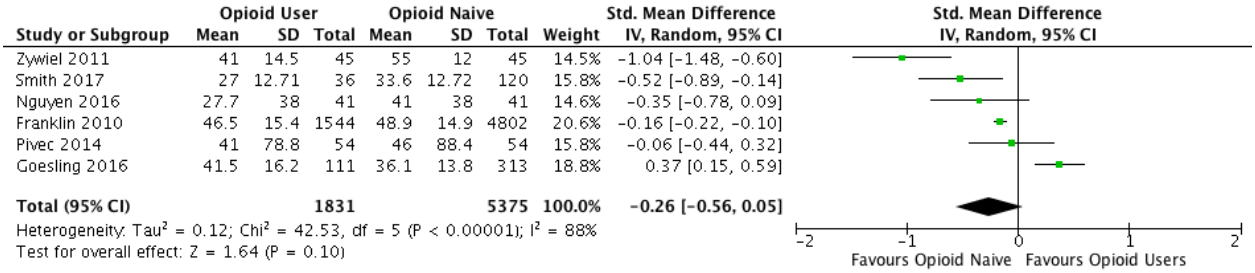


Figure 3.3 Forrest plot comparing change in PRO scores between opioid users and opioid-naïve patients. Change in PRO score calculated by the difference in preoperative PRO score and postoperative PRO scores (CI, confidence interval; IV, Inverse variance; Random, random effects model; SMD, standard mean difference; SD, standard deviation. Individual studies SMD; pooled SMD)

Chapter 4

The influence of allowable refill gaps on detecting long-term opioid therapy: an analysis of population based administrative dispensing data among patients with knee arthritis awaiting total knee arthroplasty

C. Michael Goplen MD, Jason Randall PhD, Sung Hyun Kang MSc, Fatemeh Vakilian MSc, C. Allyson Jones PT, PhD, Donald C. Voaklander PhD, Lauren A. Beaupre PT, PhD

This paper describes three different methods that can detect consistent opioid use with administrative data and the impact that the maximum allowable refill gap had on estimated rates of LTOT. We applied two previously described methods to a provincial wide pharmaceutical database and discussed the potential limitations of each method. We developed a third, hybrid mixed methodology that circumvented limitations of previous methods caused by opioid-specific prescribing. This novel mixed methodology enabled the median opioid dose, duration and most common opioid formulations to be described using Alberta's provincial pharmaceutical database. This chapter has been submitted to the Journal of Managed Care & Specialty Pharmacy and is revised manuscript is currently under review.

Abstract

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

Objective: The primary objective was to describe the effect of allowable refill gaps on detecting LTOT among a cohort of patients with arthritis awaiting total knee arthroplasty (TKA) using three different methods.

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

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

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

Introduction

Over the past two decades, the number of opioids prescribed for chronic non-cancer pain conditions, such as arthritis has dramatically increased [1–5]. These prescribing patterns are thought to be responsible for the increased prevalence of patients prescribed long-term opioid therapy (LTOT), that is "daily or near-daily use of opioids for at least 90 days, often indefinitely"[6–8]. LTOT among patients with symptomatic arthritis has gained substantial clinical and research interest as both Canadian and American opioid prescribing guidelines now suggest a much more limited, if any role of opioids for these patients [9–11]. These recommendations are based on the accumulating evidence that suggests opioids provide no improvement in pain or function when compared to acetaminophen or ibuprofen, but have increased rates of adverse events [12,13]. LTOT prior to surgery has also been associated with increased rates of postoperative complications and worse patient outcomes after elective surgery [14–16]. Our recent meta-analysis reported that patients with hip or knee arthritis prescribed opioids prior to surgery had worse patient reported outcomes after elective total joint arthroplasty [17]. However, the prevalence of LTOT in North America for this patient population is still unclear, as rates are not only dependent on regional prescribing practices, but are also affected by methodological parameters used to detect LTOT [18–22].

Pharmaceutical administrative databases containing medication dispensing records from community pharmacies are routinely used to analyze opioid prescriptions in both Canada and the USA as data are readily available for large numbers of patients, and relatively inexpensive to access [1,21,23–25]. However, it can be challenging to identify consistent opioid utilization episodes that meet the threshold for LTOT as any gaps between contiguous prescriptions disrupt

the classification episode [26–28]. These gaps are a result of inconsistent prescription refill patterns, where there may be a short period between the previous prescriptions calculated end-date and the dispensing date of the subsequent prescription [27]. A grace period, referred to as an allowable refill gap, is often utilized to analyze these pharmaceutical dispensing records as patients appear to consistently use the prescribed medication despite small gaps between prescriptions [21,27,28]. In other clinical areas, there has been significant interest to describe methods that account for allowable refill gaps and the different influence that these methods can have on estimating consistent medication use [27,28]. Current LTOT research uses arbitrary allowable refill gaps thresholds, with little understanding of how different methods and refill gaps might influence the estimated rates of LTOT or patient outcomes [20,23,29,30].

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

Methods

Study Design

A retrospective review of individual level data identified patients who underwent primary, elective unilateral TKA between January 1st, 2013 and December 31st, 2015 in Alberta, Canada. This patient cohort was selected as it was thought to represent a stable population of patients

with chronic non-cancer pain secondary to end-stage knee arthritis as confirmed by their requirement for TKA. Canada's socialized healthcare system does not restrict access to TKA, but patients wait on average six months for surgery [31]. Patients who underwent a subsequent contralateral TKA were included only once, for whichever procedure occurred first. Patients who underwent simultaneous bilateral TKA or revision TKA within one year of index procedure were excluded from the analysis. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in this observational study [32]. The study protocol was approved by the research ethics board at the University of Alberta, Edmonton, Alberta (Pro00076296).

Data Sources

Surgical data were obtained from the Alberta Bone and Joint Health Institute. This database contains patient demographic information, procedure details and clinical outcomes after TKA. Opioid dispensing data were obtained from the Pharmaceutical Information Network (PIN), a provincial pharmaceutical repository that maintains individual level pharmacotherapy records and dispensing information from all community pharmacies in Alberta, based on the provinces universal health insurance program. As Canada has universal healthcare coverage, these databases represent population-based dispensing practices within each Canadian province. A record was created in PIN each time a medication was dispensed from a community pharmacy in Alberta and contained the drug information number (DIN), anatomic therapeutic code (ATC), date dispensed, dose and duration (days supplied). Each PIN entry was linked to a patient's Unique Lifetime Identifier (ULI), a unique number assigned to all persons who receive health

services in Alberta. Each patient's PIN profile was queried for the 180-days prior to the index surgery to determine their opioid dispensing history. The end-date for each dispensing was then calculated by adding the duration to the dispensing date for each PIN entry. All datasets were deterministically linked using patients ULIs that were previously scrambled with an algorithm that de-identified each ULI, but still preserved the ability to link across datasets.

Allowable refill gap

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

We also applied a fraction method to determine the allowable refill gap between prescriptions [27]. This method used the length of the preceding prescription duration to determine the following allowable refill gap. We varied the fraction incrementally from 0.04 to 3.2. Previous work investigating cardiovascular medication adherence aligned 90-day prescription with a fraction of 1, as this was the maximum amount of days that health insurance

would compensate pharmacies [27]. In our study, we aligned the fraction and fixed method based on Canadian opioid guidelines that suggest opioid prescription be limited to less than 28 days [9]. Therefore, a fraction gap of 1 was aligned to a fixed refill gap of 28 days. In addition, a third method (mixed method) was developed that combined both fixed and fraction methods and defaulted to the largest refill gap calculated (Figure 1).

Primary Outcome: Long-term Opioid Use

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

Secondary Outcomes

1. Opioid Utilization Episode Duration

The duration of a patient's opioid utilization episode was determined by the difference between the first opioid dispensing date and the end-date of the last continuous opioid prescription. The

continuous opioid utilization episode terminated if the gap between the end date of the preceding prescription and the start date of the next opioid prescription exceeded the allowable refill gap, or a surgical date was encountered (Figure 1). Therefore, the total days in the opioid utilization episode contained both the number of active days a patient held an opioid prescription and the allowable refill gap (days) between prescriptions (Figure 1). If patients had multiple prescriptions, then the dispensation date and days supplied was used to adjust the end date of the prescriptions for each subsequent dispensation. If two or more overlapping prescriptions with the same dispensing date and days supplied were encountered, the prescriptions beyond the first would not extend the length of the episode, but would count towards the total dosage (MED) received. If a short prescription was received within a longer prescription (where the new prescriptions supply days did not extend past the predicted end of the prior prescription) then the total dosage (MED) was added to the treatment course, but the end date of the prescription course was not adjusted. In this instance, the fraction method would also continue to use the fraction of the prior, longer prescription. If a prescription was expected to end beyond the currently estimated end date then a new end date was estimated using the dispensation date and total days supplied of the prescription, and the fraction days were also adjusted to match the fraction of this prescription.

2. Daily Morphine Equivalent Dose

Patients' individual opioid dispensing were converted to a daily morphine equivalent dose (MED) by multiplying the daily dose (mg) by the corresponding MED [34]. Morphine conversion factors were based on the established conversion opioid factors [9]. The daily dose of

opioid was calculated by dividing the total MED for the opioid utilization episode by the corresponding duration of the episode, as calculated by the fixed, fraction or mixed method.

3. WOMAC Score 12-months after TKA

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

Statistical Analysis

Medians and interquartile range (IQR) were reported for nonparametric variables, while means and 95% confidence intervals (95% CI) were reported for variables that were normally distributed. Groups were compared using student's t-test for normally distributed variables and the Mann–Whitney test for nonparametric comparisons. Linear regression was performed using the patient's opioid classification as the independent variable and 12-month WOMAC score as

the dependent variable. Coefficients were interpreted compared to the defined reference group ('opioid naïve patients'). Significance was set at < 0.01. Data preparation and statistics were performed using SAS (SAS institute), version 9.4.

Results

Study Cohort

This cohort consisted of 14,252 patients with a mean age of 66.8+/-9.3 years; 60.4% were female (Table 4.1). Of these patients, 4,393 patients (31%) had an opioid prescription in the 180-days period before surgery with a median number of opioid prescriptions per patient of 3 (IQR 5). Of the 17,617 individual opioid prescriptions analyzed, the median length for prescriptions was 25 days (IQR 20). Codeine (38.3%), tramadol (23.9%) and oxycodone (16.1%) were the most commonly prescribed opioids (Table 4.1).

Long-term Opioid Use

As the allowable refill gap increased, the proportion of patients classified as an intermittent OU increased, while the number classified as long-term OU decreased for all three methods (Table 4.2). The number of patients classified as a long-term OU ranged from 4.4% to 14.6% (fixed method), 4.2% to 13.2% (fraction method) and 4.5 to 15.1% (mixed method), while the number of patients classified as intermittent OU varied from 26.4% to 16.2% (fixed method), 26.6% to 17.6% (fraction method) and 26.4% to 15.8% (mixed method) (Table 4.2). This represented a

232% (fixed method), 214% (fraction method) and 236% (mixed method) increase in the number of patients classified as a long-term. OU refill gap thresholds were varied from a minimum to maximum (Table 4.2). 'Opioid naïve' patients remained stable at 69% for all methods across all refill gaps thresholds. Between method variation (fixed, fraction and mixed) changed no more than 1.9% for both intermittent OU and long-term OU at all fraction or fixed day refill gap thresholds.

Active opioid days in 180-days prior to TKA

The fixed method minimized the maximum number of days that intermittent OU held an active opioid prescription in the 180-days prior to surgery, compared to the fraction method (Supplement Table 4.1). At a fraction of 0.5, the intermittent OU had a patient with an active opioid prescription for 178 days (fraction method), compared to 166 days using the fixed days method (Supplement Table 4.1). Again, at a fraction of 1, the intermittent OU group had a patient who held an active opioid prescription for 162 days, compared to 147 days using the fixed methodology (Supplement Table 4.1). In contrast, the fraction method maximized the minimum number of days that long-term OU held active opioid prescription in the 180-days prior to surgery (Supplement Table 4.1). Long-term OU had a minimum of 71 days at a fraction of 0.5, compared to 67 days at a refill gap of 14 days (Supplement Table 4.1). At a fraction of 1, the long-term OU group had a minimum of 40 days, compared to 32 days using the fixed days method (Supplement Table 4.1).

As the refill gap increased, the percent of days long-term OU held opioid prescriptions in the 180-days prior to surgery decreased. Long-term OU held an opioid prescription for 90.2% of the 180-day window for all three methods at the minimum allowable refill gap (Supplement Table 4.1). At the maximum allowable refill gap, long-term OU held an opioid prescription for 66% (fixed method), 70.2% (fraction method) and 65% (mixed method) of the entire 180-days window prior to TKA surgery (Supplement Table 4.1). The difference between the percent of days long-term OU and intermittent OU held opioid prescriptions in the 180-day period prior to surgery decreased as the allowable refill gap increased (Supplement Table 4.1).

Morphine Equivalent Dose

As the allowable refill gap increased, there was a decrease in median MED for long-term OU classification episode (Supplement Table 4.2). Median MED decreased 62.3% from 77.1 mg MED to 29.3 mg MED (fixed method), 53.5% from 74.2 mg MED to 34.5 mg MED 53.5% (fraction method) and 62.0% from 75.1 mg MED to 28.2 mg MED (mixed method) as the allowable refill gap varied from minimum to maximum (Supplement Table 4.2). No intermittent OU had a calculated MED classification episode; none of these patients met the parameters to be included as a long-term OU.

Impact of Opioid classification on WOMAC scores 12-months after TKA

The difference in WOMAC scores 12-months after TKA increased from -13.41 to -8.30 (40%) for long-term OU when the allowable refill gap increased from 1 to 90 days, compared to opioid naïve patients ($p < 0.001$) (Table 4.3). The difference in scores between long-term OU and opioid naive patients crossed the threshold considered clinically significant after TKA as the allowable refill gap moved from 1 to 1.5 (fraction method) or 28 days to 42 days (fixed method). Intermittent OU 12-months WOMAC scores increased from -4.80 to -3.58 points (17%) for long-term OU when the allowable refill gap increased from 1 to 90 days, compared to opioid naïve patients ($p < 0.001$) (Table 4.3). Similar trends were observed for the fraction and fixed methods (Table 3).

Discussion

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

and whether the difference in outcome scores between long-term OU and opioid naïve patients after TKA was considered clinically significant.

Developing standardized methods to detect consistent opioid use with pharmaceutical dispensing data that align with parameters of LTOT is of great interest as this threshold is associated with increased rates of adverse events and underlying physiological changes [41,42]. Long-term exogenous opioid exposure has been reported to change the endogenous opioid system in regions of the brain that regulate both patient's emotions and perception of chronic pain [41]. It is thought that change to the endogenous opioid system provides a framework to understand why certain high-risk patients with chronic pain, such as those with a history of arthritis and depression, self-select for LTOT [43]. These patients with a negative affect state are much more likely to transition from short-term to long-term opioid therapy at a higher dose compared to patients who do not have a history of depression or related conditions [44]. But, more work is needed to clarify this complex relationship to further understand these high-risk patients, which may help reduce the number of inappropriate opioid prescriptions, in keeping with current opioid North American prescribing guidelines [41]. The current study will inform future work, as it is based on established parameters for LTOT and adaptable to any pharmaceutical database that contain dispensing dates and prescription durations [20,21,24,45].

Our approach will enable investigators to determine rates of LTOT using consistent definitions, which will facilitate comparisons of opioid use among different patient populations. Unifying methods that define LTOT has the potential to clarify regional prescribing patterns, the effectiveness of opioid prescribing programs and variances among different patient populations. For example, Hadlandsmyth *et al.* (2018) reported 20% of patients were long-term OU prior to

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

In other clinical areas, the fixed method of determining refill gaps has been criticized as a static approach that does not consider the length of patient specific prescriptions [27]. These limitations in the fixed method were also noted when applied to opioid prescriptions in our cohort. Particularly, when applied to short opioid prescriptions, some patients were classified as long-term OU despite having more days without than with an active opioid prescription. In cardiovascular persistence medication studies, the fraction method appears to provide a better estimate of consistent medication use as each allowable refill gap is relative to the preceding prescription [27]. However, when applied to opioid prescriptions, we found that despite circumventing the fixed method limitations, missing a single day can disrupt the opioid classification episode at a threshold of less than one when daily dispensing of opioids is encountered. This limitation in the fraction approach can misclassify long-term high-dose patients who are often dispensed daily opioids to reduce the risk for opioid misuse and overdose [9]. In our results, a patient who was prescribed opioids for 178 days of a possible 180 days was classified as an intermittent OU at fractions less than one. To circumvent the limitations of both approaches for opioid prescriptions, we developed a mixed method that calculated both fixed and

fraction methods and defaulted to whichever refill gap was greatest (Figure 2). This method overcame the fraction methodological limitations and maximized the difference between intermittent and long-term OU mean episode duration and daily opioid dose.

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

Limitations

A limitation of our study was the assumption that opioid dispensing is a surrogate for patient consumption. Multiple methods have been used to determine opioid consumption including urine or blood tests, patient-reported use or refill data [48]. While blood serum levels or urine tests are expensive, and logistically complex if a large number of patients are required, patient-reported opioid use typically under-reports actual opioid use rates [49,50]. In a study of patients awaiting TKA, patients under-reported opioid use by as much as 46% when compared to an opioid

monitoring database [50]. While our study was restricted to patients from Alberta, our provincial wide database is likely representative of a general population of patients with symptomatic arthritis waiting for TKA as Canada provides universal healthcare to all residents and our findings were not restricted to one center or surgeon [45]. Additional research in other settings and disease states would help clarify the generalizability of our study results to determine if these effects are consistent in other prescribing environments or patient populations. Finally, we were not able to establish an allowable refill gap that best predicts LTOT. Nevertheless, we believe that our detailed analysis and described methodology provides valuable information regarding the effect of various allowable refill gaps and different methods that can be used to define LTOT to allow more consistent definition of opioid use and ensure that comparisons across groups are based on clear definitions.

Conclusions

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

References

[1] Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani MM. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Med 2011;5:e13-22.

[2] Wright EA, Katz JN, Abrams S, Solomon DH, Losina E. Trends in prescription of opioids from 2003-2009 in persons with knee osteoarthritis. Arthritis Care Res (Hoboken) 2014;66:1489–95. doi:10.1002/acr.22360.

[3] Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. Open Med 2012;6:e41-7.

[4] Canadian Institute for Health Information. Pan-Canadian Trends in the Prescribing of Opioids, 2012 to 2016. Ottawa, ON: 2017.

[5] Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ 2016;188:1240–4. doi:10.1503/cmaj.160356.

[6] Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain 2009;10:113-130.e22. doi:10.1016/j.jpain.2008.10.008.

[7] Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009;18:1166–75. doi:10.1002/pds.1833.

[8] Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM, et al. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions. Pain 2016;157:1525–31. doi:10.1097/j.pain.0000000000000557.

[9] Busse JW. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. Natl Pain Cent 2017:1–105. doi:10.1503/cmaj.170363.

[10] Dowell D, TM H, Chou R. Cdc guideline for prescribing opioids for chronic pain—united states, 2016. JAMA 2016;315:1624–45.

[11] American Academy of Orthopedic Surgeons. Opioid Use, Misuse, and Abuse in Orthopaedic Practice 2015:1–4.

[12] Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain. Jama 2018;320:2448. doi:10.1001/jama.2018.18472.

[13] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. JAMA - J Am Med Assoc 2018;319:872–82. doi:10.1001/jama.2018.0899.

[14] Ben-Ari A, Chansky H, Rozet I. Preoperative opioid use is associated with early revision after total knee arthroplasty a study of male patients treated in the veterans affairs system. J Bone Jt Surg 2017;99:1–9. doi:10.2106/JBJS.16.00167.

[15] Smith SR, Collins JE, Yang H, Katz JN, Losina E, Bido J, et al. Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes. J Bone Jt Surgery, Am Vol 2017;99:803–8. doi:10.2106/JBJS.16.01200.

[16] Morris BJ, Sciascia AD, Jacobs CA, Edwards TB. Preoperative opioid use associated with worse outcomes after anatomic shoulder arthroplasty. J Shoulder Elb Surg 2016;25:619–23. doi:10.1016/j.jse.2015.09.017.

[17] Goplen CM, Verbeek W, Kang SH, Jones CA, Voaklander DC, Churchill TA, et al. Preoperative opioid use is associated with worse patient outcomes after Total joint arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord 2019;20:234. doi:10.1186/s12891-019-2619-8.

[18] Hansen CA, Inacio MCS, Pratt NL, Roughead EE, Graves SE. Chronic Use of Opioids Before and After Total Knee Arthroplasty: A Retrospective Cohort Study. J Arthroplasty 2017;32:817.e1.

[19] Saïdi H, Pagé MG, Boulanger A, Ware MA, Choinière M. Effectiveness of long-term opioid therapy among chronic non-cancer pain patients attending multidisciplinary pain treatment clinics: A Quebec Pain Registry study. Can J Pain 2018;2:113–24. doi:10.1080/24740527.2018.1451252.

[20] Hadlandsmyth K, Weg MW Vander, McCoy KD, Mosher HJ, Vaughan-Sarrazin MS, Lund BC. Risk for Prolonged Opioid Use Following Total Knee Arthroplasty in Veterans. J Arthroplasty 2018;33:119–23. doi:10.1016/j.arth.2017.08.022.

[21] Korff M Von, Saunders K, Thomas Ray G, Boudreau D, Campbell C, Merrill J, et al. De Facto Long-term Opioid Therapy for Noncancer Pain. Clin J Pain 2008;24:521–7. doi:10.1097/AJP.0b013e318169d03b.

[22] Inacio MCS, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: A retrospective cohort study. BMJ Open 2016;6. doi:10.1136/bmjopen-2015-010664.

[23] Vanderlip ER, Sullivan MD, Edlund MJ, Martin BC, Fortney J, Austen M, et al. National study of discontinuation of long-term opioid therapy among veterans. Pain 2014;155:2673–9. doi:10.1016/j.pain.2014.09.034.

[24] Aroke H, Buchanan A, Wen X, Ragosta P, Koziol J, Kogut S. Estimating the Direct Costs of Outpatient Opioid Prescriptions: A Retrospective Analysis of Data from the Rhode Island Prescription Drug Monitoring Program. J Manag Care Spec Pharm 2018;24:214–24. doi:10.18553/jmcp.2018.24.3.214.

[25] Gomes T, Mamdani MM, Paterson JM, Dhalla IA, Juurlink DN. Trends in high-dose opioid prescribing in Canada. Can Fam Physician 2014;60:826–32.

[26] Vink NM, Klungel OH, Stolk RP, Denig P. Comparison of various measures for assessing medication refill adherence using prescription data. Pharmacoepidemiol Drug Saf 2009;18:159–65. doi:10.1002/pds.1698.

[27] Van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation. J Clin Epidemiol 2006;59:11–7. doi:10.1016/j.jclinepi.2005.05.005.

[28] Parker MM, Moffet HH, Adams A, Karter AJ. An algorithm to identify medication nonpersistence using electronic pharmacy databases. J Am Med Inform Assoc 2015;22:957–61. doi:10.1093/jamia/ocv054.

[29] Gressler. LE, Martin BC, Hudson TJ, Painter JT. The relationship between concomitant benzodiazepine-opioid use and adverse outcomes among U.S. veterans. Pain 2017;159:1. doi:10.1097/j.pain.0000000000001111.

[30] Landsman-Blumberg PB, Katz N, Gajria K, Coutinho AD, Yeung PP, White R. Burden of Alcohol Abuse or Dependence Among Long-Term Opioid Users with Chronic Noncancer Pain. J Manag Care Spec Pharm 2017;23:718–24. doi:10.18553/jmcp.2017.23.7.718.

[31] Canadian Institute for Health Information. Wait Times for Priority Procedures in Canada. Ottawa: 2017.

[32] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9. doi:10.1016/j.jclinepi.2007.11.008.

[33] Kaur AD, McQueen A, Jan S. Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use. J Manag Care Pharm 2016;14:186–94. doi:10.18553/jmcp.2008.14.2.186.

[34] Work Safe BC. Claims with Opioids, Sedative/Hypnotics or Other Prescribed Potentially Addictive Drugs. 2017.

[35] Collins NJ, Roos EM. Patient-Reported Outcomes for Total Hip and Knee Arthroplasty. Commonly Used Instruments and Attributes of a "Good" Measure. Clin Geriatr Med 2012;28:367–94. doi:10.1016/j.cger.2012.05.007.

[36] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.

[37] Clement ND, Bardgett M, Weir D, Holland J, Gerrand C, Deehan DJ. What is the Minimum Clinically Important Difference for the WOMAC Index After TKA? Clin Orthop Relat Res 2018;476:2005–14. doi:10.1097/CORR.0000000000000444.

[38] Calcaterra SL, Scarbro S, Hull ML, Forber AD, Binswanger IA, Colborn KL. Prediction of Future Chronic Opioid Use Among Hospitalized Patients. J Gen Intern Med 2018;33:898–905. doi:10.1007/s11606-018-4335-8.

[39] Kim KY, Anoushiravani AA, Chen KK, Roof M, Long WJ, Schwarzkopf R. Preoperative Chronic Opioid Users in Total Knee Arthroplasty-Which Patients Persistently Abuse Opiates Following Surgery? J Arthroplasty 2017:6–11. doi:10.1016/j.arth.2017.07.041.

[40] Bedard NA, DeMik DE, Dowdle SB, Callaghan JJ. Trends and risk factors for prolonged opioid use after unicompartmental knee arthroplasty. Bone Joint J 2018;100-B:62–7.

[41] Sullivan MD. Depression Effects on Long-term Prescription Opioid Use , Abuse , and Addiction 2018;34:878–84. doi:10.1097/AJP.0000000000000603.

[42] Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017;10:CD012509. doi:10.1002/14651858.CD012509.pub2.

[43] Sullivan MD. Why does depression promote long-term opioid use? Pain 2016;157:2395–6. doi:10.1097/j.pain.0000000000000658.

[44] Halbert BT, Davis RB, Wee CC. Disproportionate longer-term opioid use among U.S. adults with mood disorders. Pain 2016;157:2452–7. doi:10.1097/j.pain.0000000000000650.

[45] Bedard NA, Pugely AJ, Westermann RW, Duchman KR, Glass NA, Callaghan JJ. Opioid Use After Total Knee Arthroplasty: Trends and Risk Factors for Prolonged Use. J Arthroplasty 2017;32:2390–4. doi:10.1016/j.arth.2017.03.014.

[46] Martin BC, Fan M-Y, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med 2011;26:1450–7. doi:10.1007/s11606-011-1771-0.

[47] Braden JB, Fan M-Y, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. J Pain 2008;9:1026–35. doi:10.1016/j.jpain.2008.06.002.

[48] Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005;353:487–97. doi:10.1056/NEJMra050100.

[49] C. El Khoury A, Karlawish J, Andrews E, Caplan A. Pharmacoepidemiology, Fifth Edition. 2012. doi:10.1002/9781119959946.ch35.

[50] Hereford TE, Cryar KA, Edwards PK, Siegel ER, Barnes CL, Mears SC. Patients With Hip or Knee Arthritis Underreport Narcotic Usage. J Arthroplasty 2018;33:3113–7. doi:10.1016/j.arth.2018.05.032.

Table 4-1 Characteristics of the study cohort and opioid prescriptions

Variable	
Patients (n)	14,252
Mean age (SD)	66.8 (9.3)
Female, n (%)	8608 (60.4)
Total opioid prescriptions (n)	17617
Individual opioid prescription duration, median days (IQR)	24 (21)
Type of Opioid Prescriptions	n (%)
Codeine	6755 (38.3)
Tramadol	4203 (23.9)
Oxycodone	2836 (16.1)
Hydromorphone	1708 (9.7)
Morphine	1196 (6.8)
Fentanyl	319 (1.8)
[a] Other	600 (3.5)

Abbreviations
n – Number, SD – Standard deviation, IQR – Interquartile range
Notes
[a] Other: Tapentadol, Meperidine, Butorphanol, Opium and Buprenorphine

Table 4-2 Comparison of the prevalence of opioid use with fraction, fixed and mixed methods

		Intermittent Opioid User [a]			**Long-term Opioid User[a]**		
		Mixed[c]	Fraction[d]	Fixed	Mixed[c]	Fraction[d]	Fixed
Fraction	Fixed	Percent (n)	Percent (n)	Percent (n)	Percent (n)	Percent (n)	Percent (n)
0.04	1	26.4 (3758)	26.6 (3792)	26.4 (3763)	4.5 (635)	4.2 (601)	4.4 (630)
0.25	7	23.8 (3396)	24.1 (3438)	24.0 (3423)	7.0 (997)	6.7 (955)	6.8 (970)
0.5	14	22.5 (3210)	22.9 (3263)	23.0 (3278)	8.3 (1183)	7.9 (1130)	7.8 (1115)
0.75	21	21.4 (3044)	22.0 (3136)	21.9 (3121)	9.5 (1349)	8.8 (1257)	8.9 (1272)
1	28	20.5 (2927)	21.3 (3035)	21.0 (2998)	10.3 (1466)	9.5 (1358)	9.8 (1395)
1.5	42	19.1(2715)	20.2 (2872)	19.6 (2794)	11.8 (1678)	10.7 (1521)	11.2 (1599)
2	56	18.0 (2558)	19.2 (2740)	18.5 (2636)	12.9 (1835)	11.6 (1653)	12.3 (1757)
2.5	70	17.0 (2427)	18.6 (2647)	17.5 (2492)	13.8 (1966)	12.3 (1746)	13.3 (1901)
3	84	16.1 (2297)	17.9 (2551)	16.6 (2365)	14.7 (2096)	12.9 (1842)	14.2 (2028)
3.2	90	15.8 (2248)	17.6 (2514)	16.2 (2314)	15.1 (2145)	13.2 (1879)	14.6 (2079)

Notes
Reference group 'opioid naïve patients'
[a] Opioid Exposed defined as opioid prescriptions in 180-days prior to index TKA but does not meet criteria for an Opioid User
[b] Opioid User defined as 90 days of consistent opioid use in 180-days prior to index TKA
[c] Mixed method selection whichever refill gap is greater (fixed or fraction)
[d] Fraction gap based on % length of previous opioid prescription

Abbreviations
n - number of patients, SE – standard error

Table 4-3 Impact of opioid classification on 12-months WOMAC scores using different refill gaps

		Opioid Exposed[a]				**Opioid User[b]**			
Fraction[c]	Fixed[c]	n	Estimate	SE	p value	n	Estimate	SE	p value
0.04	1	3758	-4.80	0.87	<.0001	635	-13.41	2.19	<.0001
0.25	7	3396	-4.17	0.90	<.0001	997	-12.52	1.68	<.0001
0.5	14	3210	-3.94	0.91	<.0001	1183	-11.85	1.54	<.0001
0.75	21	3044	-3.72	0.93	<.0001	1349	-11.48	1.45	<.0001
1	28	2927	-3.90	0.94	<.0001	1466	-10.23	1.38	<.0001
1.5	42	2715	-3.76	0.97	0.0001	1678	-9.52	1.28	<.0001
2	56	2558	-3.66	1.00	0.0002	1835	-9.07	1.22	<.0001
2.5	70	2427	-3.54	1.02	0.0005	1966	-8.84	1.18	<.0001
3	84	2297	-3.62	1.04	0.0005	2096	-8.36	1.14	<.0001
3.2	90	2248	-3.58	1.05	0.0006	2145	-8.30	1.13	<.0001
Fraction[d]									
0.04		3792	-4.90	0.86	<.0001	601	-12.95	2.24	<.0001
0.25		3438	-4.30	0.89	<.0001	955	-12.33	1.72	<.0001
0.5		3263	-3.97	0.91	<.0001	1130	-12.09	1.57	<.0001
0.75		3136	-3.56	0.92	0.0001	1257	-12.65	1.50	<.0001
1		3035	-3.65	0.93	<.0001	1358	-11.51	1.43	<.0001
1.5		2872	-3.76	0.95	<.0001	1521	-10.25	1.35	<.0001
2		2740	-3.34	0.97	0.0006	1653	-10.40	1.28	<.0001
2.5		2647	-3.33	0.98	0.0007	1746	-10.03	1.25	<.0001
3		2551	-3.46	0.99	0.0005	1842	-9.43	1.22	<.0001
3.2		2514	-3.57	1.00	0.0004	1879	-9.06	1.20	<.0001
	Fixed								
	1	3763	-4.80	0.87	<.0001	630	-13.41	2.19	<.0001
	7	3423	-4.13	0.89	<.0001	970	-12.99	1.71	<.0001
	14	3278	-4.17	0.91	<.0001	1115	-11.46	1.58	<.0001
	21	3121	-3.83	0.92	<.0001	1272	-11.48	1.47	<.0001
	28	2998	-3.94	0.94	<.0001	1395	-10.40	1.41	<.0001
	42	2794	-3.99	0.96	<.0001	1599	-9.31	1.31	<.0001
	56	2636	-4.10	0.98	<.0001	1757	-8.58	1.25	<.0001
	70	2492	-3.90	1.00	0.0001	1901	-8.50	1.20	<.0001
	84	2365	-4.05	1.03	<.0001	2028	-7.99	1.17	<.0001
	90	2314	-4.00	1.03	0.0001	2079	-7.96	1.15	<.0001

Notes
Reference group 'opioid naïve patients'
[a] Opioid Exposed defined as opioid prescriptions in 180-days prior to index TKA but does not meet criteria for an Opioid User
[b] Opioid User defined as 90 days of consistent opioid use in 180-days prior to index TKA
[c] Mixed method selection whichever refill gap is greater (fixed or fraction)
[d] Fraction gap based on % length of previous opioid prescription

Abbreviations
n - number of patients, SE – standard error

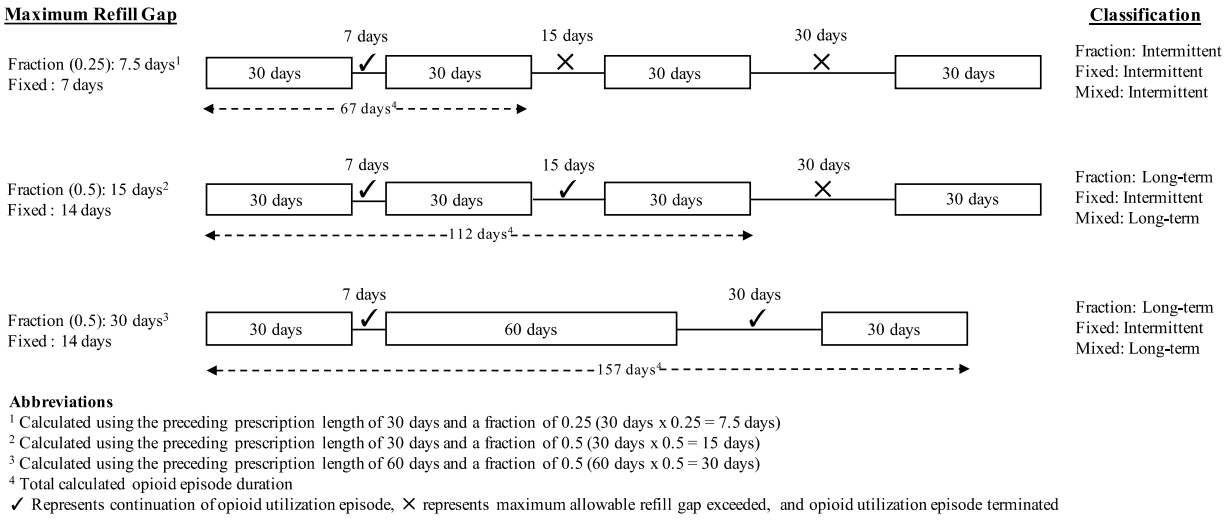


Figure 4.1 Overview of opioid classification episodes using different methods and refill gaps

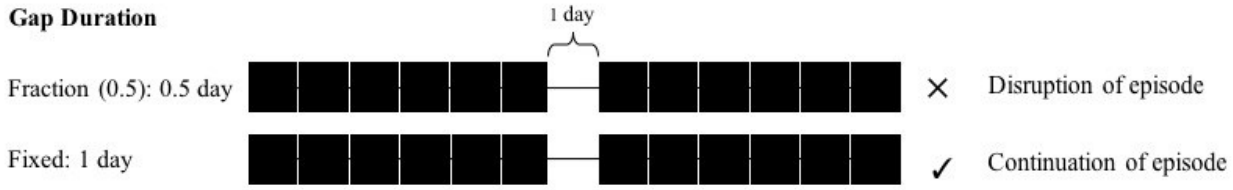


Figure 4.2 Impact of a one-day refill gap on opioid utilization episode duration using fixed (1 day) or fraction method (0.5)

Chapter 5

Preoperative Preoperative Long-term Opioid Therapy Negatively Impacts Patient Outcomes After Total Knee Arthroplasty: An Analysis of Multicenter Population-Based Administrative Data

C. Michael Goplen MD, Sung Hyun Kang MSc, Jason R. Randell PhD, C. Allyson Jones PT, PhD, Donald C. Voaklander PhD, Thomas A. Churchill PhD, Lauren A. Beaupre PT, PhD

This paper reports the rates of opioid use before and after TKA in Alberta, Canada by applying our novel, mixed methodology, as described in Chapter 4, to provincial administrative data. We also described the relationship between preoperative LTOT and WOMAC scores 12-months after primary, elective TKA. Outcomes were adjusted for potentially confounding variables with multivariable linear regression by linkage of pharmaceutical provincial data with clinical outcomes collected by the Alberta Bone and Joint Health Institute (ABJHI). This chapter is formatted to be submitted to the Canadian Journal of Surgery.

Abstract

Objective: Up to 40% of patients are using opioids at the time of total knee arthroplasty (TKA) in the USA despite evidence suggesting opioids are ineffective for pain associated with arthritis and have significant risks. Our primary objective was to determine whether preoperative opioid users had worse knee pain and function outcomes 12-months after TKA when compared to preoperative opioid naïve patients. Our secondary objective determined the prevalence of opioid use before and after TKA in Alberta, Canada.

Design: Retrospective analysis of population-based data identified patients that underwent TKA between 2013 and 2015 in Alberta, Canada. Multivariable linear regression examined the association between preoperative opioid use and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores 12-months after TKA, adjusting for potentially confounding variables.

Results: Of the 1907 patients; 31.0% had at least one opioid dispensed prior to TKA and 6.5% were classified as long-term opioid users. Long-term opioid users had worse adjusted WOMAC pain and function scores 12-months after TKA compared to preoperative opioid naïve patients (pain score beta: 7.7 [95% CI 4.0, 11.6], function score beta: 7.8 [95% CI 4.0, 11.6]; $p<0.001$ for all). Of the preoperative long-term opioid users, 72% of patients were still dispensed opioids between 180 and 360-days after TKA, compared to only 12% of preoperative opioid naïve patients.

Conclusion: A significant number of patients were dispensed opioids before and after TKA. Preoperative opioid users had worse adjusted pain and function outcomes at 12-months after TKA, compared to preoperative opioid naïve patients.

Introduction

Over the past 20 years, the number of opioids prescribed to manage patients with arthritis has dramatically increased in North America despite emerging evidence to suggest opioids provide no benefit when compared to other alternatives such as acetaminophen or ibuprofen [1–4]. These findings were also reflected in the most recent Canadian and American guidelines for chronic non-cancer pain that now recommend a much more limited role for opioids to manage pain associated with arthritis [1,5]. However, 40% of patients are reported to still be prescribed opioids prior to total knee arthroplasty (TKA) in the USA; we are unaware of any reports from Canada [6–8]. It is also unknown if TKA significantly reduces opioid consumption in these patients, and there is growing concern that TKA may be a risk factor for long-term opioid therapy (LTOT) as a result of excessive postoperative opioid prescribing practices [9–11].

As pressure to practice appropriate opioid stewardship grows, patients prescribed preoperative opioids have garnered substantial research and clinical interest [11–15]. Patients prescribed preoperative opioids had higher 90-day complication rates and higher rates of revision surgery within one-year than patients who were opioid naïve preoperatively [6,16]. These patients also had worse pain and lower functional improvement after TKA when compared to those who were not prescribed preoperative opioids [13,15,17]. However, these studies failed to account for important group differences, such as rates of depression and preoperative pain and functional scores between those prescribed preoperative opioids and those who were not [15]. Given that these additional patient factors are also associated with both long-term opioid use and worse clinical outcomes after TKA, the extent that opioid use independently impacts clinical outcomes remains uncertain [18–20].

The primary objective of this study was to determine if preoperative long-term opioid users (OU) had worse postoperative patient reported knee pain and functional outcome scores 12-months after TKA when compared to those who did not use opioids preoperatively after controlling for potential confounding factors. Our secondary objective was to determine the prevalence of preoperative opioid use before and after TKA in Alberta, Canada.

Methods

Study Design

A retrospective review of individual level data identified patients who underwent primary, elective unilateral TKA between January 1st 2013 and December 31st 2015 in one of thirteen hospitals in Alberta, Canada. Patients who underwent a contralateral TKA were included only once, for the first procedure. Patients were excluded if they underwent a contralateral TKA or revision TKA within 12-month follow-up from index procedure. Patients with missing data (comorbidity, preoperative or 12-month postoperative Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores) were also excluded (Figure 5.1). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in this observational study [21].

Data Sources

Surgical data were obtained from the Alberta Bone and Joint Health Institute (ABJHI), a nonprofit third-party organization that collects provincial data for all TKA completed in Alberta. All adult (18 years or older) patients who underwent elective TKA in the dataset were flagged using International Classification of Diseases 10 Canadian specific TKA codes (Supplementary Table 5.1). ABJHI captured pre-specified preoperative comorbidities from the Canadian Institute for Health Information electronic abstract for each patient (Supplementary Table 5.1). ABJHI also collected preoperative and 12-month postoperative WOMAC scores from Alberta's six centralized multidisciplinary Hip and Knee intake clinics within the province.

Opioid data were obtained from the Pharmaceutical Information Network (PIN). This provincial pharmaceutical repository maintains individual level pharmacotherapy records and includes dispensing information from all community pharmacies in Alberta, regardless of insurance coverage. A record was created in PIN each time a medication was dispensed from a pharmacy in the province and contained the drug information number (DIN), anatomic therapeutic code (ATC), date dispensed, dose and duration (days supplied). Each PIN entry was linked to patients Unique Lifetime Identifier (ULI), a unique number assigned to all persons who received health services in the province. Using opioid specific ATC codes, each patient's PIN profile was queried for the 365 days prior to and following the index surgery to determine their opioid dispensing history (Supplementary Table 5.2). The end-date for each dispensing was then calculated by adding the duration to the dispensing date for each PIN entry.

Individual opioid prescriptions were then converted to a daily morphine equivalent dose (MED) by multiplying the daily dose for each opioid by the corresponding MED to allow for standardized comparison across different opioid compounds [1]. Morphine conversion factors

were based on the published conversion factors that align Canadian opioid prescribing guidelines [1,22]. Opioid compounds were classified into weak (tramadol and codeine) and strong (all remaining opioids) [23]. All datasets were deterministically linked using patients ULIs that were previously scrambled with an algorithm that de-identified each ULI, but still preserved the ability to link across datasets.

Primary Outcome

The primary outcomes of interest were WOMAC pain and function scores 12-months after TKA. The WOMAC is a validated disease-specific patient-reported outcome instrument used to measure joint pain, stiffness and function [24]. Scores ranging from 0 to 100 are generated for each domain from a Likert scale with higher scores indicative of better outcome [24].

Classification of Opioid Use

Preoperative long-term OU were defined as patients who had 90-days or more of continuous opioid dispensing's within 180-days prior to TKA. These parameters were consistent with the definition of LTOT [25]. *Preoperative intermittent OU* had recorded opioid dispensing's within the 180-days prior to TKA, but did not meet the threshold parameters for a preoperative long-term OU. *Preoperative opioid naïve patients* did not have a recorded opioid dispensing within 180-days prior to TKA. The 180-day opioid free period had been previously used in studies investigating LTOT and is the established threshold for opioid discontinuation [26,27].

Postoperative long-term OU, postoperative intermittent OU and postoperative non-OU were defined using the same parameters as those used to define preoperative opioid use, but the medication utilization period was increased from 180 days to 360 days after index TKA. The maximum allowable refill gap between prescriptions in an opioid utilization episode was 14 days, or 0.5 times the preceding prescription length. This methodology and threshold were based on our work that described how to detect LTOT using administrative data (paper under review).

Covariates

Clinically meaningful demographic and medical variables were age, sex, preoperative WOMAC pain or function score, history of stroke, pulmonary disease, cardiac disease, liver disease, renal dysfunction, diabetes, obesity and depression. These covariates were chosen to include factors thought to influence postoperative clinical outcome scores after TKA and account for potential confounders.

Statistical Analysis

Descriptive statistics were used to characterize preoperative opioid dispensing patterns including dose (MED) and duration. Medians and interquartile range (IQR) were reported for nonparametric variables, while means, 95% confidence intervals (95% CI) or standard deviation (SD) were reported if variables were normally distributed. Continuous outcomes were compared using Student's t-test or one-way analysis of variance (ANOVA) for normally distributed

variables. A post-hoc Bonferroni correction determined pairwise differences between groups. Differences between preoperative and postoperative opioid prescriptions were presented as percent difference (PD) [28].

To examine the effects of preoperative opioid use and 12-month WOMAC pain or function scores, we developed separate multivariable regression models for each outcome. Final parsimonious models for 12-month WOMAC pain or function were determined using a purposeful selection procedure with predictors deemed significant ($p<0.2$) after univariate analysis carried forward to the multivariable model. Age and sex, deemed clinically meaningful, were forced entered in the model regardless of their statistical significance. Forward, backward, and stepwise selection using adjusted R-square, Akaike information criterion, Bayesian information criterion, Schwarz Bayesian Criterion, Mallows's Cp, cross validation as criteria demonstrated the final models were robust to the selection procedure used. Model diagnostics and influential plot based on Cook's Distance were produced to check model assumptions and fit. No collinearity among continuous predictors was noted using Pearson's correlation coefficient. Significance was set at $p < 0.05$ and statistics were performed using SAS (SAS institute), version 9.4 for data linkage and preparation and Stata Statistical Software (StataCorp LP), version 13 for final regression models.

Results

Study Population

Of the 16,049 patients that underwent primary, elective TKA between 2013 and 2015 in Alberta, Canada, 1,907 patients were eligible for inclusion into our final study cohort (Figure 5.1). Excluded patients had comparable patient characteristics when compared to the study population (Supplementary Table 5.3 and 5.4).

The mean age of the study population was 66.6 years (SD 8.7) and 64.7% (n = 1234 patients) were female, 28.8% (n=540 patients) were obese, 20.4% (n=388 patients) had a history of diabetes and 15.8% (n=301) had a history of depression (Table 5.1). Of the 1907 patients who met inclusion criteria, 31.0% (n=592 patients) had at least one opioid prescription dispensed within 180-days of surgery and 6.5% (n=124) were classified as long-term OU (Table 5.1). There were 1,970 individual preoperative opioid prescriptions analyzed within 180-days of TKA; preoperative long-term OU had 918 opioid prescriptions, while preoperatively intermittent OU had 1052 opioid prescriptions. Preoperative long-term OU had more strong opioids dispensed preoperatively (n =420), compared to preoperative intermittent OU (n = 144). In contrast preoperative intermittent OU had more weak opioids dispensed (n= 908) compared to long-term OU (n = 498). Compared to preoperative opioid naïve patients, preoperative long-term OU were younger (mean age 64.0 SD 8.5 vs 66.9 SD 8.5, $p < 0.001$) and group differences were observed in rates of obesity, depression, history of stroke, liver, cardiac or pulmonary disease, but not rates of diabetes or renal disease (Table 5.1). There were also significant differences among the three groups' preoperative WOMAC pain and function scores (Table 5.1). Preoperative opioid naïve patients had better preoperative WOMAC pain and function scores when compared to both preoperative long-term OU and preoperative intermittent OU ($p <0.001$ for both) (Table 5.1).

Primary Outcome: 12-months postoperative WOMAC pain and function scores

Preoperative long-term OU had a mean 12-months WOMAC pain score of 69.0 (95% CI 64.5, 73.5) and function score of 67.9 (95% CI 63.5, 72.4), while preoperative intermittent OU had a mean 12-months WOMAC pain score of 73.0 (95% CI 71.7, 76.1) and function score of 71.3 (95%CI 69.3, 73.3). Preoperative opioid naïve patients had a mean 12-months WOMAC pain score of 80.3 (95% CI 79.2, 81.5) and function score of 72.2 (95% CI 70.1, 74.2), which was significantly better than both preoperative long-term OU and preoperative intermittent OU ($p < 0.001$ for all).

The unadjusted parameter estimates in Table 5.2 demonstrate that preoperative opioid use was associated with worse 12-months WOMAC pain and function outcomes after TKA when compared to preoperative opioid naïve patients. Age, worse preoperative WOMAC scores, cardiac, liver and pulmonary disease, diabetes and a history of depression were also associated with worse 12-months WOMAC pain scores in univariable analysis. Worse preoperative WOMAC function scores, were associated with worse 12-months WOMAC function scores as were obesity, history of cardiac or pulmonary disease and depression.

After adjusting for preoperative pain or function scores, age, sex, depression, pulmonary, cardiac and liver disease, intermittent OU and long-term OU were still associated with worse 12-months pain scores when compared to opioid naïve patients (Table 5.2). Similarly, 12-months postoperative WOMAC function scores were on average of 5.2 units worse (95% CI 3.1, 7.4) for intermittent OU, and 7.8 units worse (95% CI 4.0, 11.6) for long-term OU when compared to opioid naïve patients after controlling for age, sex, depression, diabetes, pulmonary and cardiac disease.

Significant interactions ($p < 0.05$) were found between opioid use and depression in both pain and function models (Supplementary Table 5.5 and 5.6). Preoperative long-term OU who had a history of depression were on average 13.3 (95% CI 5.9, 20.7) points worse for 12-months WOMAC pain scores and 14.9 (95% CI 7.8, 22.0) points worse for WOMAC function scores compared to preoperative opioid naïve patients without a history of depression.

Persistent Postoperative Opioid Use

Postoperatively, there were 1,609 individual opioid prescriptions analyzed between 180 and 360-days postoperatively; preoperative long-term OU had 871 opioid prescriptions, while preoperative intermittent OU had 735 opioid prescriptions. Of the 1,907 patients, 23.5% (n = 448) were dispensed opioids between 180 and 360-days after TKA. Stratified by group, 12.0% (n = 158) of the preoperative opioid naïve patients were dispensed opioids after more than 180-days post-TKA, compared to 42.8% (n = 201) preoperative intermittent OU and 71.8% (n=89) preoperative long-term OU (Table 5.3). Codeine (40.2%), tramadol (31.1%) and oxycodone (11.2%) were the most commonly dispensed opioid preoperatively and postoperatively (Table 5.4). There were no differences in the mean duration between preoperative and postoperatively prescriptions (23.4 days vs. 25.8 days, $p = 0.57$).

Discussion

These findings substantiate findings from existing studies that observed patients prescribed preoperative opioids had worse clinical outcomes after TKA when compared to those who were not, even after risk adjustment [13,15,17,29,30]. Previous studies used crude parameters to classify preoperative opioid use and failed to adjust for important group differences, such as worse preoperative pain and function scores and higher rates of depression among those prescribed preoperative opioids [13,17,29]. Using established parameters for LTOT and adjusting for significant differences in patient characteristics including a history of depression and preoperative pain and functional scores, we found that preoperative long-term OU still had worse pain and function outcomes 12-months after TKA when compared to those who did not use preoperative opioids. The difference between these two groups approached the threshold considered clinically important for WOMAC pain and function scores after TKA [31].

Opioid induced hyperalgesia (OIH) has been hypothesized to explain why preoperative opioid users have worse pain and functional outcomes after TKA [15]. OIH is a process by which patients taking long-term opioids have a paradoxical increased response to painful stimuli [20,32,33]. Chu *et al*. (2006) prospectively evaluated OIH in patients with chronic pain and after one month of starting oral morphine therapy, patients reported positive hyperalgesia tests when compared to controls [33]. Further, Cohen *et al*. (2008) reported that patients on LTOT had increased pain intensity and unpleasant scores when compared to patients who were not exposed to opioids [34]. It is thought that LTOT can disrupt the endogenous opioid system in regions of the brain such as the limbic system and alter how an individual interprets pain and perceives disability [20,35].

To our knowledge, this is the first report of the prevalence of opioid use prior to TKA in Canada. Similar to that reported in the USA, a substantial proportion (31.0%) of patients were dispensed opioids within 180-days prior to TKA and 6.5% were long-term OU [7,11,36]. Outside North America, an Australian based study reported 5% of patients awaiting TKA were considered opioid users [37,38]. While it may appear that Australia had lower rates of preoperative opioid use compared to the USA, careful consideration of each case definition highlights the influence definitional parameters may have on the reported rates, in addition to possible physician and geographic specific prescribing practices [7,11,30,37,38]. Hansen *et al*. (2017) used parameters that aligned more closely to our definition of long-term OU, compared to crude refill based definitions used in studies based in the USA, that aligned more closely to our reported overall preoperative dispensing rate of 31% [6,37–39].

We also observed that while TKA reduced the total number of opioids dispensed in our cohort postoperatively, the number of strong opioid prescriptions dispensed increased postoperatively when compared to preoperative prescriptions. In addition, few preoperative opioid naïve patients transitioned from short-term to long-term use after TKA, but 44% of preoperative long-term OU remained long-term OU after TKA. These results align with previous studies that observed 2% of preoperative opioid naïve patients go onto long-term OU after TKA, and 57% of preoperative long-term OU continued LTOT one-year after TKA in the USA [40]. There was also a substantial number of patients had intermittent opioid dispensing postoperatively. This raises concerns as every extra day that a patient is prescribed opioids, the likelihood of transitioning to LTOT increases [41].

Strengths and Limitations

A strength of our study is our ability to detect opioid use within a provincial wide database that represents a general population as Canada provides universal healthcare to all residents and our findings were not restricted to one center or surgeon. In addition, our comprehensive database and methodology enabled detailed analysis of not only individual prescription's formation, dose and duration both preoperative and postoperatively, but allowed us to relate preoperative opioid use to adjusted postoperative WOMAC scores.

A limitation of our results is the assumption that opioid dispensing is a surrogate for patient consumption. However, it has been reported that administrative data is more accurate when compared to patient reported use; patients under-reported opioid use by as much as 46% prior to TKA due to the perceived stigma of disclosing opioid use to physicians [42,43]. There was a substantial number of patients who had incomplete WOMAC scores excluded from our cohort. These findings are not unexpected as Alberta is the fourth largest Canadian province in both geographical size and population with approximately four million residents distributed across more than 600,000 square kilometers. This causes follow-up challenges for Alberta's centralized hip and knee clinics as patients are often asked to travel long distances to attend appointments [44]. However, we demonstrated that patients with incomplete WOMAC data had comparable preoperative characteristics when compared to those that were included in the study (Supplementary Table 5.3 and 5.4). These findings are consistent with previous reports that observed that patients who attended follow-up after TKA had similar patient characteristics and postoperative WOMAC scores to those that did not [45].

Conclusions

A significant number of patients are still dispensed opioids prior to TKA in Canada despite narrowing indications for such medications. Our results support North America's movement to transition away from opioids to manage chronic pain associated with arthritis, as these patients were shown to have worse patient-reported outcomes after TKA and are more likely to remain long-term opioid users post-operatively [1,5]. With the introduction of opioid stewardship, postoperative opioid prescribing practices are increasingly scrutinized in recognition that a subset of patients are at risk for persistent opioid use after TKA. However, more research is needed to further understand risk factors associated with persistent postoperative opioid use, and if standardized, evidence-based postoperative opioid prescribing programs can reduce the duration and dose postoperatively.

References

[1] Busse JW. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. Natl Pain Cent 2017:1–105. doi:10.1503/cmaj.170363.

[2] Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain. Jama 2018;320:2448. doi:10.1001/jama.2018.18472.

[3] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. JAMA - J Am Med Assoc 2018;319:872–82. doi:10.1001/jama.2018.0899.

[4] Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ 2016;188:1240–4. doi:10.1503/cmaj.160356.

[5] Dowell D, TM H, Chou R. Cdc guideline for prescribing opioids for chronic pain—united states, 2016. JAMA 2016;315:1624–45.

[6] Ben-Ari A, Chansky H, Rozet I. Preoperative opioid use is associated with early revision after total knee arthroplasty a study of male patients treated in the veterans affairs system. J Bone Jt Surg - Am Vol 2017;99:1–9. doi:10.2106/JBJS.16.00167.

[7] Bedard NA, Pugely AJ, Westermann RW, Duchman KR, Glass NA, Callaghan JJ. Opioid Use After Total Knee Arthroplasty: Trends and Risk Factors for Prolonged Use. J Arthroplasty 2017;32:2390–4. doi:10.1016/j.arth.2017.03.014.

[8] Kim KY, Anoushiravani AA, Chen KK, Roof M, Long WJ, Schwarzkopf R. Preoperative Chronic Opioid Users in Total Knee Arthroplasty-Which Patients Persistently Abuse Opiates Following Surgery? J Arthroplasty 2017:6–11. doi:10.1016/j.arth.2017.07.041.

[9] Hernandez NM, Parry JA, Taunton MJ. Patients at Risk: Large Opioid Prescriptions After Total Knee Arthroplasty. J Arthroplasty 2017;32:2395–8. doi:10.1016/j.arth.2017.02.060.

[10] Scully RE, Schoenfeld AJ, Jiang W, Lipsitz S, Chaudhary MA, Learn PA, et al. Defining Optimal Length of Opioid Pain Medication Prescription After Common Surgical Procedures. Jama Surg 2018;153:37–43. doi:10.1001/jamasurg.2017.3132.

[11] Rozell JC, Courtney PM, Dattilo JR, Wu CH, Lee G-CC-C, Hasenauer M, et al. Preoperative Opiate Use Independently Predicts Narcotic Consumption and Complications After Total Joint Arthroplasty. J Arthroplasty 2017;32:2658–62. doi:10.1016/j.arth.2017.04.002.

[12] Agrawal Y, Smith RM, Garbuz DS, Masri BA. Opioids in Arthroplasty: Mind the Gap Between North America and the Rest of the World. J Bone Joint Surg Am 2018;100:2162–71. doi:10.2106/JBJS.17.01422.

[13] Nguyen L-CL-CL, Sing DC, Bozic KJ. Preoperative Reduction of Opioid Use Before Total Joint Arthroplasty. J Arthroplasty 2016;31:282–7. doi:10.1016/j.arth.2016.01.068.

[14] Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain 2016;157:1259–65. doi:10.1097/j.pain.0000000000000516.

[15] Zywiel MG, Stroh DA, Lee SY, Bonutti PM, Mont MA, Zywiel MG, et al. Chronic opioid use prior to total knee arthroplasty. J Bone Jt Surgery, Am Vol 2011;93:1988–93. doi:10.2106/JBJS.J.01473.

[16] Sing DC, Barry JJ, Cheah JW, Vail TP, Hansen EN. Long-Acting Opioid Use Independently Predicts Perioperative Complication in Total Joint Arthroplasty. J Arthroplasty 2016;31:170–174.e1. doi:10.1016/j.arth.2016.02.068.

[17] Franklin PD, Karbassi JA, Li W, Yang W, Ayers DC. Reduction in narcotic use after primary total knee arthroplasty and association with patient pain relief and satisfaction. J Arthroplasty 2010;25:12–6. doi:10.1016/j.arth.2010.05.003.

[18] Lavernia CJ, Alcerro JC, Contreras JS. Knee arthroplasty: Growing trends and future problems. Int J Clin Rheumtol 2010;5:565–79. doi:10.2217/ijr.10.49.

[19] Wylde V, Trela-Larsen L, Whitehouse MR, Blom AW. Preoperative psychosocial risk factors for poor outcomes at 1 and 5 years after total knee replacement. Acta Orthop 2017;88:530–6. doi:10.1080/17453674.2017.1334180.

[20] Sullivan MD. Depression Effects on Long-term Prescription Opioid Use , Abuse , and Addiction 2018;34:878–84. doi:10.1097/AJP.0000000000000603.

[21] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9. doi:10.1016/j.jclinepi.2007.11.008.

[22] Work Safe BC. Claims with Opioids, Sedative/Hypnotics or Other Prescribed Potentially Addictive Drugs. 2017.

[23] Cancer pain relief. Geneva, Switzerland: World Health Organization; 1986.

[24] Collins NJ, Roos EM. Patient-Reported Outcomes for Total Hip and Knee Arthroplasty. Commonly Used Instruments and Attributes of a "Good" Measure. Clin Geriatr Med 2012;28:367–94. doi:10.1016/j.cger.2012.05.007.

[25] Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain 2009;10:113–130.e22. doi:10.1016/j.jpain.2008.10.008.

[26] Vanderlip ER, Sullivan MD, Edlund MJ, Martin BC, Fortney J, Austen M, et al. National study of discontinuation of long-term opioid therapy among veterans. Pain 2014;155:2673–9. doi:10.1016/j.pain.2014.09.034.

[27] Calcaterra SL, Scarbro S, Hull ML, Forber AD, Binswanger IA, Colborn KL. Prediction of Future Chronic Opioid Use Among Hospitalized Patients. J Gen Intern Med 2018;33:898–905. doi:10.1007/s11606-018-4335-8.

[28] Politzer CS, Kildow BJ, Goltz DE, Green CL, Bolognesi MP, Seyler TM. Trends in Opioid Utilization Before and After Total Knee Arthroplasty. J Arthroplasty 2017. doi:10.1016/j.arth.2017.10.060.

[29] Pivec R, Issa K, Naziri Q, Kapadia BH, Bonutti PM, Mont MA. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. Int Orthop 2014;38:1159–65. doi:10.1007/s00264-014-2298-x.

[30] Smith SR, Collins JE, Yang H, Katz JN, Losina E, Bido J. Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes. J Bone Jt Surgery, Am Vol 2017;99:803–8. doi:10.2106/JBJS.16.01200.

[31] Clement ND, Bardgett M, Weir D, Holland J, Gerrand C, Deehan DJ. What is the Minimum Clinically Important Difference for the WOMAC Index After TKA? Clin Orthop Relat Res 2018;476:2005–14. doi:10.1097/CORR.0000000000000444.

[32] Carullo V, Fitz-James I, Delphin E. Opioid-Induced Hyperalgesia: A Diagnostic Dilemma. J Pain Palliat Care Pharmacother 2015;29:378–84. doi:10.3109/15360288.2015.1082006.

[33] Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. J Pain 2006;7:43–8. doi:10.1016/j.jpain.2005.08.001.

[34] Cohen SP, Christo PJ, Wang S, Chen L, Stojanovic MP, Shields CH, et al. The Effect of Opioid Dose and Treatment Duration on the Perception of a Painful Standardized Clinical Stimulus. Reg Anesth Pain Med 2008;33:199–206. doi:10.1016/j.rapm.2007.10.009.

[35] Sullivan M, Tanzer M, Stanish W, Fallaha M, Keefe FJ, Simmonds M, et al. Psychological determinants of problematic outcomes following Total Knee Arthroplasty. Pain 2009;143:123–9. doi:10.1016/j.pain.2009.02.011.

[36] Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, et al. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. Osteoarthr Cartil 2017;25:1399–406. doi:10.1016/j.joca.2017.04.002.

[37] Inacio MCS, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: A retrospective cohort study. BMJ Open 2016;6:Arte Number: e010664. ate of Pubaton: 2016. doi:10.1136/bmjopen-2015-010664.

[38] Hansen CA, Inacio MCS, Pratt NL, Roughead EE, Graves SE. Chronic Use of Opioids Before and After Total Knee Arthroplasty: A Retrospective Cohort Study. J Arthroplasty 2017;32:817.e1.

[39] Jain N, Brock JL, Malik AT, Phillips FM, Khan SN. Prediction of Complications, Readmission, and Revision Surgery Based on Duration of Preoperative Opioid Use: Analysis of Major Joint Replacement and Lumbar Fusion. J Bone Joint Surg Am 2019;101:384–91. doi:10.2106/JBJS.18.00502.

[40] Hadlandsmyth K, Weg MW Vander, McCoy KD, Mosher HJ, Vaughan-Sarrazin MS, Lund BC. Risk for Prolonged Opioid Use Following Total Knee Arthroplasty in Veterans. J Arthroplasty 2018;33:119–23. doi:10.1016/j.arth.2017.08.022.

[41] Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. MMWR Morb Mortal Wkly Rep 2017;66:265–9. doi:10.15585/mmwr.mm6610a1.

[42] Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med 2015;5:470–82. doi:10.1007/s13142-015-0315-2.

[43] Hereford TE, Cryar KA, Edwards PK, Siegel ER, Barnes CL, Mears SC. Patients With Hip or Knee Arthritis Underreport Narcotic Usage. J Arthroplasty 2018;33:3113–7. doi:10.1016/j.arth.2018.05.032.

[44] Alberta G of. 2011 Census metropolitan areas. Treas Board Financ n.d. https://open.alberta.ca/dataset/953ebd2f-dabd-4141-bb75-f4d558f6f7b0/resource/91c3234a-3a53-43f2-b0b6-a48759c35fda/download/map-overview-alberta-census-metropolitan-areas.pdf (accessed March 22, 2019).

[45] Choi JK, Geller JA, Patrick Jr DA, Wang W, Macaulay W. How are those "lost to follow-up" patients really doing? A compliance comparison in arthroplasty patients. World J Orthop 2015;6:150–5. doi:10.5312/wjo.v6.i1.150.

Table 5-1 Baseline patient factors by preoperative opioid classification

		Preoperative Classification			
	Total Cohort (n = 1907)	**Opioid Naive (n = 1315)**	**Intermittent Opioid Users (n = 468)**	**Long-term Opioid Users (n = 124)**	**p-value**
Age (SD)	66.6 (8.7)	66.9 (8.5)	66.1 (9.2)	64.0 (8.5) [a, b]	0.002
Sex, n (%)					
Female	1234 (64.7)	845 (64.3)	309 (66.0)	80 (64.5)	
Male	673 (35.3)	470 (35.7)	159 (34.0)	44 (35.5)	0.789
Comorbidities, n (%)					
Depression	301 (15.8)	176 (13.4)	87 (18.6)	38 (30.7)	<.0001
Stroke	28 (1.5)	18 (1.4)	7 (1.5)	3 (2.4)	<.0001
Pulmonary disease	168 (8.8)	105 (8.0)	41 (8.8)	22 (17.7)	0.001
Cardiac disease	456 (23.9)	295 (22.4)	122 (26.1)	39 (31.5)	0.036
Diabetes	388 (20.4)	253 (21.8)	102 (21.8)	33 (26.6)	0.100
Renal disease	48 (2.5)	29 (2.2)	15 (3.2)	4 (3.2)	0.432
Obesity	549 (28.8)	356 (27.1)	149 (31.8)	44 (35.5)	0.035
Liver disease	22 (1.2)	13 (1.0)	8 (1.7)	1 (0.8)	0.031
Mean Preoperative WOMAC Score					
Pain [95% CI]	45.9 [45.0, 46.7]	47.6 [46.6, 48.5]	42.4 [40.8, 44.0]	40.6 [37.4, 43.9] [a]	<0.001
Function [95% CI]	45.5 [44.8, 46.3]	47.0 [46.0, 47.0]	42.9 [41.3, 44.4]	40.5 [37.5, 43.6] [a]	<0.001
Preoperative Opioid Use					
Median MED (IQR)	3.3 (15.3)	0	4.6 (9.4)	58.2 (79.3)	<0.001
Opioid Use in past 180 days, mean, [95% CI]	45.4 [41.7, 49.1]	0	34.4 [31.5, 37.3]	152.6 [148.0, 157.2]	<0.001

ANOVA analysis for cohort and Bonferroni corrections used for multiple pairwise comparisons for normally distributed continuous variables
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; CI Confidence Interval; SD Standard deviation; IQR interquartile range
[a] Comparisons of scores between preoperative opioid naïve patients and preoperative long-term opioid user is significant $p < 0.05$
[b] Comparisons of scores between preoperative intermittent opioid users and preoperative long-term opioid user is significant $p < 0.05$

Table 5-2 Unadjusted and adjusted parameter estimates for 12-months postoperative WOMAC pain and function scores

	WOMAC Pain [95% CI]				WOMAC Function [95% CI]			
Variable	**Crude beta**	**p-value**	**Adjusted beta**	**p-value**	**Crude beta**	**p-value**	**Adjusted beta**	**p-value**
Female	*1 [Reference]*		*1 [Reference]*		*1 [Reference]*		*1 [Reference]*	
Male	1.2 [-0.9, 3.3]	0.255	-0.1 [-2.0 2.0]	0.988	1.6 [-0.4, 3.6]	0.125	0.6 [-1.4, 2.5]	0.574
Age	0.2 [0.1, 0.3]	0.003	0.1 [-0.1 0.2]	0.084	0.1 [-0.1, 0.1]	0.799	0.1 [-0.1, 0.1]	0.845
Preoperative WOMAC Score	0.4 [0.3, 0.4]	<0.001	0.3 [0.3 0.4]	<0.001	0.4 [0.4, 0.5]	<0.001	0.4 [0.3, 0.4]	<0.001
Opioid Use								
Opioid Naïve	*1 [Reference]*		*1 [Reference]*		*1 [Reference]*		*1 [Reference]*	
Intermittent	-6.4 [-8.7, -4.1]	<0.001	-4.3 [-6.6 -2.1]	<0.001	-7.0 [-9.3, -4.8]	<0.001	-5.2 [-7.4, -3.1]	<0.001
Long-term	-11.4 [-15.4, -7.3]	<0.001	-7.7 [-11.6 -3.7]	<0.001	-11.3 [-15.2, -7.4]	<0.001	-7.8 [-11.6, -4.0]	<0.001
Comorbidities								
Depression	-5.2 [-7.9, -2.4]	<0.001	-2.6 [-5.3 0.1]	0.056	-5.5 [-8.0, -2.7]	<0.001	-2.8 [-5.3, -0.3]	0.031
Diabetes	-5.4 [-7.8, -2.9]	<0.001	-3.7 [-6.0 -1.3]	0.002	-4.5 [-6.8, -2.0]	<0.001	-2.5 [-4.8, -0.2]	0.032
Cardiac disease	-3.2 [-5.5, -0.8]	0.008	-2.3 [-4.7 -0.1]	0.048	-3.9 [-6.2, -1.6]	0.001	-2.2 [-4.4, 0.1]	0.057
Liver disease	-9.2 [-18.6, 0.1]	0.053	-8.0 [-16.9 0.9]	0.079	-6.5 [-15.5, 2.6]	0.161	-	-
Pulmonary disease	-4.6 [-8.1, -1.1]	0.011	-3.3 [-6.7 0.1]	0.054	-5.3 [-8.7, -1.9]	0.002	-2.9 [-6.2, 0.3]	0.075
Obesity	-2.1 [-4.3, 0.2]	0.069	-	-	-2.2 [-4.4, -0.1]	0.042	-	-
Stroke	-2.9 [-11.2, 5.5]	0.502	-	-	-3.6 [-11.6, 4.5]	0.384	-	-
Renal disease	-3.9 [-10.3, 2.5]	0.235	-	-	-4.7 [-10.8, 1.5]	0.140	-	-

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; CI Confidence Interval

Table 5-3 Comparison of the proportion of patients dispensed opioids preoperatively and postoperatively

	Preoperative Opioid Classification		
Postoperative Opioid Use, n (%)	**Opioid Naive (n = 1504)**	**Intermittent Opioid Users (n = 498)**	**Long-term Opioid Users (n = 124)**
Postoperative non-opioid user	1157 (88.0)	267 (57.0)	35 (28.2)
Postoperative intermittent opioid user	148 (11.3)	164 (35.0)	34 (27.4)
Postoperative long-term opioid user	10 (0.8)	37 (7.9)	55 (44.4)

Table 5-4 Preoperative and postoperative opioid use, stratified by opioid formulation

	Total Cohort			Intermittent Opioid Users			Long-term Opioid Users		
Opioid	Preoperative	Postoperative	PD	Preoperative	Postoperative	PD	Preoperative	Postoperative	PD
Codeine (%)	40.25	37.04	-3.21	50.76	53.06	2.30	28.21	23.62	-4.59
Tramadol (%)	31.12	27.97	-3.15	35.55	32.93	-2.62	26.03	23.74	-2.29
Oxycodone (%)	11.22	18.58	7.36	5.32	8.98	3.66	17.97	26.61	8.64
Morphine (%)	6.45	2.86	-3.59	1.81	1.36	-0.45	11.76	4.13	-7.63
Hydromorphone (%)	5.53	7.40	1.87	3.23	2.86	-0.37	8.17	11.24	3.07
Fentanyl (%)	0.76	4.60	3.00	0.76	0	-0.76	0.76	8.49	7.73
Other (%)	4.67	1.55	-3.12	2.58	0.81	-1.77	7.08	2.17	-4.91

PD Percent Difference (Postoperative - Preoperative)
Other – Opium, buprenorphine, meperidine-pethidine and tapentado

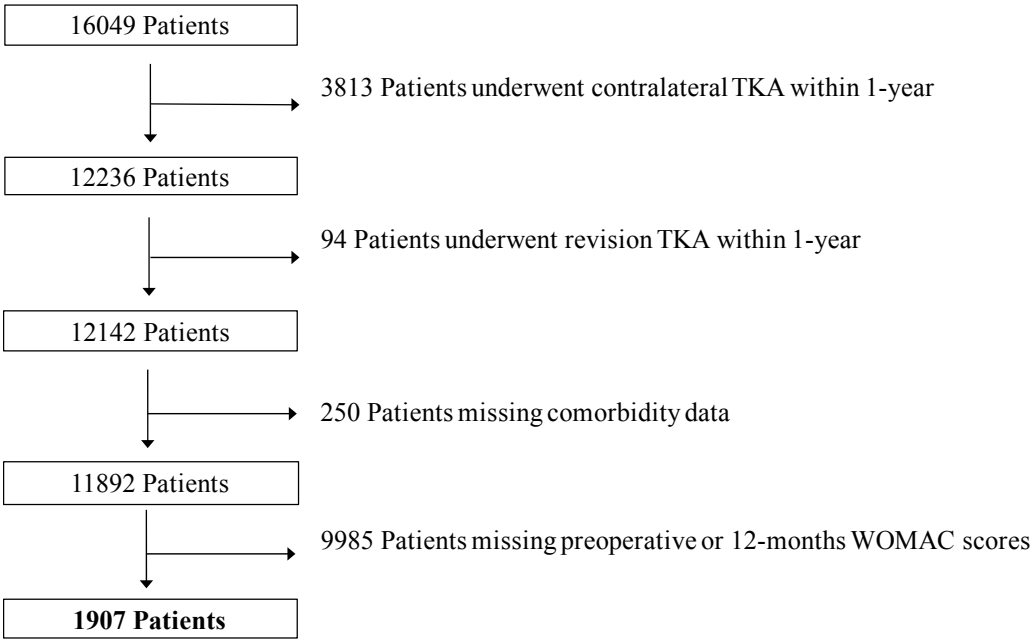


Figure 5.1 Cohort of patients that underwent unilateral TKA between 2013 and 2015 in Alberta, Canada

Chapter 6

General Discussion

The overarching objective of this thesis was to investigate the influence of preoperative opioid use on pain and function outcomes after TKA. To address this objective, we first systematically reviewed the literature to evaluate the evidence that described the association between preoperative opioid use and clinical outcomes after TKA. Of the studies included in the review, three used a matched cohort to control for potentially confounding variables, one study reported adjusted outcomes and two reported unadjusted outcomes [16,19,23,28,138,139]. Based on the published literature reviewed, it was clear that more research was needed using robust study designs and statistical analyses, but some patterns were emerging.

All six studies reported preoperative opioid use was associated with worse clinical outcomes scores after either total hip or knee arthroplasty regardless of the PRO instrument used [16,19,23,28,138,139]. This trend should be interpreted with caution as there are other factors associated with both opioid use and outcomes after surgery that were unaccounted for within the analysis [118]. All of the studies reported that patients prescribed preoperative opioids had higher rates of depression, anxiety, anti-depressant use, or lower SF-12 mental health score, but only one study adjusted for these group differences [16,19,23,28,138,139]. Smith *et al.* (2017) utilized propensity matching and found that outcomes measures persisted after adjusting for group difference. But, this study was limited by the small sample size and a crude definition to define preoperative opioid use [16]. Also, among the included studies, there were no standardized parameters used to define preoperative opioid use [16,19,23,28,138]. Most studies used crude parameters to define preoperative opioid use, based on the number of opioid refills,

that did not allow for the overall duration or dose to be analyzed [16,19,138]. None of the case definitions aligned with the established definition of LTOT; 90 days or more of daily, or near daily opioid use [25,47]. The 90-day threshold used to define LTOT was based on the report that once individuals pass this threshold, they tend to use opioids indefinitely [53].

Interestingly, the majority of patients prescribed opioids for CNCP, such as arthritis do not transition from short-term to LTOT [10,140]. Most patients started on opioids for CNCP, such as arthritis discontinue opioids prior to reaching the 90-day threshold despite the natural history of the disease that is characterized by a stepwise deterioration in pain and function [10,140,141]. Patients appear to self-discontinue opioid therapy due to minimum benefits and unwanted side-effects [10,57,140]. But, there is a consistent subset of patients, specifically those with a history of depression or other negative affect states, such as anxiety or catastrophizing that are more likely to transition from short-term to LTOT [25,138,142,143]. LTOT is also 2 to 3 times more likely in depressed patients and these patients have higher doses prescribed for longer durations despite lower pain intensity levels and higher levels of function than non-depressed patients [144,145]. Based on the accumulating evidence, it appears that patients with CNCP who transition from short-term to LTOT are a self-selected group with high rates of affective disorders and worse catastrophizing characteristics [25]. The endogenous opioid system is thought to provide a framework for understanding this complex relationship and may help explain why this subset of high-risk patients transition to LTOT [25].

The endogenous opioid system not only provides analgesia for physical pain, mediated by endorphins and mu receptors, but also influences social behavior and mood [25,146–148]. Recent studies have demonstrated Mu receptors are found within the affect regions of the brain, such as the anterior cingulate, and dysregulation has been associated various mental health

conditions such as depression, anxiety, and PTSD [25,147–149]. It is now thought that both physical pain and emotional pain share similar neurobiological pathways that can be influenced by exogenous opioids [25,146]. This discovery may help explain the observation that patients prescribed preoperative opioid have higher rates of depression, anxiety and pain catastrophizing [23,150]. But, underlying physiological mechanisms that explain why patients with a negative affect self-select for LTOT remains uncertain [25]. It was initially hypothesized that patients with depression might experience increased opioid effectiveness for CNCP and/or be treating concomitant depressive symptoms with exogenous opioids [25,146]. However, studies have now shown that patients with depression have less pain relief despite higher doses of opioids, and depression symptoms worsen with exogenous opioids [151–153]. More research is needed to understand this complex relationship and the influence healthcare providers may have on how, and why patients with a negative affect are more likely to transition from short-term to LTOT [25].

Based on previous research that focused on LTOT, it appeared key to align our exposure, preoperative opioid use, with established parameters of LTOT [25,47]. But, we discovered that there was little published evidence that outlined how to define consistent opioid use with administrative data, and no reports outlining how to justify the maximum allowable refill gap between opioid prescriptions. Refill gaps are a result of small gaps between prescription refills despite patients consistently using the medication [54]. To further investigate this area and help justify our case definition, we first evaluated different methods used to detect LTOT with administrative data to determine the impact of each method on estimated LTOT rates, opioid dose and duration, and outcomes after TKA (Chapter 4) [47,57,154]. We found that as the duration of the maximum allowable refill gap was extended, the overall rate of LTOT decreased

and the difference between the two groups (long-term OU and intermittent OU) dose, duration and WOMAC scores 12-months after TKA diminished for all methods. We also reported, that despite each method's theoretical limitations, there was minimal difference between each method's estimated LTOT rates, dose and duration. Applying our novel mixed methodology that circumvented potential limitations of previous methods to population based administrative data, we estimated the rates of LTOT before and after TKA in Alberta, Canada. Our detailed analysis also enabled us to determine the median dose, mean duration, and most common prescriptions prescribed in Alberta, Canada. By linking provincial pharmaceutical data to clinical outcome data, we were able to describe the influence of preoperative LTOT on WOMAC pain and function scores 12-months after TKA using a large cohort of patients, controlling for potentially confounding factors, including a history of depression. The major findings of this study is summarized below.

Of the 1907 patients included in the study, 31% (n = 592) of patients had at least one opioid prescription prior TKA and 6.5% (n = 124) patients were classified as preoperative long-term opioid users. These results fall within the rates published from US datasets (range 16% - 39%) [12,13,16,18–20]. Outside North America, two Australian studies reported 5% of patients awaiting TKA, and 6% of patients awaiting THA were considered chronic opioid users prior to surgery [143,155]. While it may appear that Australia had lower rates of preoperative opioid use compared to the USA, careful consideration of each case definition highlights the influence of definitional parameter on the reported rates [16,143,155]. These two Australian studies used parameters that aligned more closely to our definition of LTOT; in comparison, the broad definitions used in USA-based studies aligned more closely to our reported overall preoperative dispensing rate of 31% [12,13,143,155].

There was a reduction in the total number of opioid prescriptions after TKA, but a significant number of patients were dispensed opioids between 6 and 12 months after TKA. In our study, 44% (n = 55) of preoperative long-term OUs continued to consistently use opioids at 12-months follow up, compared to less than 1% (n = 10) of preoperative opioid naïve patients. Our findings are consistent with prior reports that suggest a significant number of patients continue to use opioid after surgery, while a subset of patients who were not on LTOT preoperatively, transitioned to LTOT postoperatively [19,28,143,150]. It has been reported that among patients undergoing THA, pain catastrophizing and a history of depression were associated with persistent postoperative opioid use [143].

Consistent with previous studies, preoperative opioid users had higher rates of comorbidities and lower preoperative pain and functional scores [16,19,23,28]. After adjusting for these differences, preoperative opioid use remained significantly associated with worse adjusted WOMAC scores 12-months after TKA, when compared to opioid naïve patients. Similar differences were observed for both WOMAC function and pain scores between those who were prescribed preoperative opioids and those who were not. These group differences approached the difference considered clinically significant for WOMAC pain and function scores after TKA [116]. There was also a significant interaction noted between depression and preoperative opioid use in both pain and function models. This finding underscores the complex relationship between depression, LTOT and CNCP that may be mediated by the endogenous opioid system and result in OIH or centralized sensitization [25,31,137,146,156–158]. While our methods enabled adjustment for potentially confounding factors, we were limited by the observational study design that cannot completely eliminate the potential for residual confounding factors. Future prospective studies that utilize validated depression or pain

catastrophizing instruments, and opioid specific interventions, such as preoperative weaning, would further our understanding of the relationship between opioid use and outcomes after surgery.

Conclusions and Future Directions

A significant number of patients continue to be dispensed opioids before and after TKA in Alberta, despite limited indications [11]. We also observed that LTOT is associated with worse pain and function outcomes after TKA, and that a significant number of patients continued to use opioids after TKA. These results provide valuable information to clinicians who manage patients awaiting TKA and surgeons who counsel patients prior to surgery regarding expected outcomes and potential complications. Based on the available evidence, patients prescribed preoperative opioids should be judicially counselled regarding their increased risk for complications, including revision surgery, high rates of persistent postoperative opioid use and worse overall pain and function improvements when compared to opioid naïve patients [12,13].

A notable limitation of our data was that we were not able to determine the indication for opioid prescriptions, which may have been for unrelated conditions. But we believe that the perioperative window may provide an opportunity for healthcare providers to practice opioid stewardship with the goal of reducing, or eliminating non-therapeutic opioid prescriptions. In addition, the introduction of standardized postoperative opioid prescribing practices will provide an opportunity to determine if these protocols can reduce the number of opioids prescribed, and if these changes in prescribing patterns impact patient recovery and satisfaction after surgery. Our results also give rise to an important question: is preoperative opioid use merely a prognostic

factor, or also a modifiable risk factor? Future research aimed at determining if a reduction in opioid use preoperatively improves pain and function outcomes after surgery would provide valuable information that has the potential to improve outcomes after TKA and enable a better understanding of the relationship between preoperative opioid use and outcomes after surgery.

.

References:

[1] Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ 2016;188:1240–4. doi:10.1503/cmaj.160356.

[2] Mack, Karin, Jones, Christopher, Laulozzi L. Morbidity and Mortality Weekly Report Morbidity and Mortality Weekly Report Vital Signs: Overdoses of Prescription Opioid Pain Relievers and Other Drugs Among Women — United States. Source Morb Mortal Wkly Rep Centers Dis Control Prev 2013;62:537–42.

[3] Canadian Institute for Health Information. Pan-Canadian Trends in the Prescribing of Opioids, 2012 to 2016. Ottawa, ON: 2017.

[4] HIV and Aids in Canada, Surveillance Report To December 31, 2012. 2013.

[5] Morris B. The Opioid Epidemic: Impact on Orthopaedic Surgery. J Am Acad Orthop Surg 2015;23:267–71. doi:10.5435/JAAOS-D-14-00163.

[6] Lanser P, Gesell S. Pain management: the fifth vital sign. Healthc Benchmarks 2001;8:68—70, 62.

[7] Morone NE, Weiner DK. Pain as the fifth vital sign: exposing the vital need for pain education. Clin Ther 2013;35:1728–32. doi:10.1016/j.clinthera.2013.10.001.

[8] Franklin G. Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology: Comments. Neurology 2014;84:1503. doi:10.1212/WNL.0000000000000839.

[9] Ferrell B, Argoff C, Epplin J. Pharmacological Management of Persistent Pain in Older Persons. J Am Geriatr Soc 2009;57:1331–46. doi:10.1111/j.1532-5415.2009.02376.x.

[10] Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006;174:1589–94. doi:10.1503/cmaj.051528.

[11] Busse JW. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. Natl Pain Cent 2017:1–105. doi:10.1503/cmaj.170363.

[12] Ben-Ari A, Chansky H, Rozet I. Preoperative opioid use is associated with early revision after total knee arthroplasty a study of male patients treated in the veterans affairs system. J Bone Jt Surg 2017;99:1–9. doi:10.2106/JBJS.16.00167.

[13] Bedard NA, Pugely AJ, Westermann RW, Duchman KR, Glass NA, Callaghan JJ. Opioid Use After Total Knee Arthroplasty: Trends and Risk Factors for Prolonged Use. J Arthroplasty 2017;32:2390–4. doi:10.1016/j.arth.2017.03.014.

[14] Kim KY, Anoushiravani AA, Chen KK, Roof M, Long WJ, Schwarzkopf R. Preoperative Chronic Opioid Users in Total Knee Arthroplasty-Which Patients Persistently Abuse Opiates Following Surgery? J Arthroplasty 2017:6–11. doi:10.1016/j.arth.2017.07.041.

[15] Hadlandsmyth K, Weg MW Vander, McCoy KD, Mosher HJ, Vaughan-Sarrazin MS, Lund BC. Risk for Prolonged Opioid Use Following Total Knee Arthroplasty in Veterans. J Arthroplasty 2018;33:119–23. doi:10.1016/j.arth.2017.08.022.

[16] Smith SR, Collins JE, Yang H, Katz JN, Losina E, Bido J, et al. Impact of Preoperative

Opioid Use on Total Knee Arthroplasty Outcomes. J Bone Jt Surgery, Am Vol 2017;99:803–8. doi:10.2106/JBJS.16.01200.

[17] Sing DC, Barry JJ, Cheah JW, Vail TP, Hansen EN. Long-Acting Opioid Use Independently Predicts Perioperative Complication in Total Joint Arthroplasty. J Arthroplasty 2016;31:170–174.e1. doi:10.1016/j.arth.2016.02.068.

[18] Rozell JC, Courtney PM, Dattilo JR, Wu CH, Lee G-CC-C, Hasenauer M, et al. Preoperative Opiate Use Independently Predicts Narcotic Consumption and Complications After Total Joint Arthroplasty. J Arthroplasty 2017;32:2658–62. doi:10.1016/j.arth.2017.04.002.

[19] Franklin PD, Karbassi JA, Li W, Yang W, Ayers DC. Reduction in narcotic use after primary total knee arthroplasty and association with patient pain relief and satisfaction. J Arthroplasty 2010;25:12–6. doi:10.1016/j.arth.2010.05.003.

[20] Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, et al. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. Osteoarthr Cartil 2017;25:1399–406. doi:10.1016/j.joca.2017.04.002.

[21] Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain. Jama 2018;320:2448. doi:10.1001/jama.2018.18472.

[22] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. JAMA - J Am Med Assoc 2018;319:872–82. doi:10.1001/jama.2018.0899.

[23] Zywiel MG, Stroh DA, Lee SY, Bonutti PM, Mont MA, Zywiel MG, et al. Chronic opioid use prior to total knee arthroplasty. J Bone Jt Surgery, Am Vol 2011;93:1988–93. doi:10.2106/JBJS.J.01473.

[24] Carullo V, Fitz-James I, Delphin E. Opioid-Induced Hyperalgesia: A Diagnostic Dilemma. J Pain Palliat Care Pharmacother 2015;29:378–84. doi:10.3109/15360288.2015.1082006.

[25] Sullivan MD. Depression Effects on Long-term Prescription Opioid Use , Abuse , and Addiction 2018;34:878–84. doi:10.1097/AJP.0000000000000603.

[26] Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. J Pain 2006;7:43–8. doi:10.1016/j.jpain.2005.08.001.

[27] Cohen SP, Christo PJ, Wang S, Chen L, Stojanovic MP, Shields CH, et al. The Effect of Opioid Dose and Treatment Duration on the Perception of a Painful Standardized Clinical Stimulus. Reg Anesth Pain Med 2008;33:199–206. doi:10.1016/j.rapm.2007.10.009.

[28] Pivec R, Issa K, Naziri Q, Kapadia BH, Bonutti PM, Mont MA. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. Int Orthop 2014;38:1159–65. doi:10.1007/s00264-014-2298-x.

[29] Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009;18:1166–75. doi:10.1002/pds.1833.

[30] Reid MC, Henderson CR, Papaleontiou M, Amanfo L, Olkhovskaya Y, Moore AA, et al. Characteristics of Older Adults Receiving Opioids in Primary Care: Treatment Duration and Outcomes. Pain Med 2010;11:1063–71. doi:10.1111/j.1526-4637.2010.00883.x.

[31] Sullivan M, Tanzer M, Stanish W, Fallaha M, Keefe FJ, Simmonds M, et al. Psychological determinants of problematic outcomes following Total Knee Arthroplasty. Pain 2009;143:123–9. doi:10.1016/j.pain.2009.02.011.

[32] Wylde V, Trela-Larsen L, Whitehouse MR, Blom AW. Preoperative psychosocial risk factors for poor outcomes at 1 and 5 years after total knee replacement. Acta Orthop 2017;88:530–6. doi:10.1080/17453674.2017.1334180.

[33] Dowell D, TM H, Chou R. Cdc guideline for prescribing opioids for chronic pain—united states, 2016. JAMA 2016;315:1624–45.

[34] Norn S, R Kruse P, Kruse E. History of opium poppy and morphine. Dan Medicinhist Arbog 2005;33:171–84.

[35] Brook K, Bennett J, Desai SP. The Chemical History of Morphine: An 8000-year Journey, from Resin to de-novo Synthesis. J Anesth Hist 2017;3:50–5. doi:10.1016/j.janh.2017.02.001.

[36] Sneader W. Department of medical history The discovery of heroin. Med Hist 1998;352:1697–9.

[37] L Schiff P, Schiff PL. Opium and Its Alkaloids. Am J Pharm Educ 2002;66:186–94.

[38] Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of

the Opioid Epidemic and Strategies for Pain Medicine. Pain Ther 2018;7:13–21. doi:10.1007/s40122-018-0097-6.

[39] Controlled Drugs and Substances Act. 2017.

[40] Kirkup K. Health Canada's position on opioid Tramadol is indefensible n.d. https://www.theglobeandmail.com/news/national/health-canadas-position-on-opioid-tramadol-is-indefensible-doctor/article34138299/ (accessed December 6, 2017).

[41] Pathan H, Williams J. Basic opioid pharmacology: An update. Br J Pain 2012;6. doi:10.1177/2049463712438493.

[42] Andrea M. MT, Sukdeb MD, Marion ML, Hans MH. Opioid Pharmacology. Pain Physician 2008;1975:S133–53. doi:https://www.ncbi.nlm.nih.gov/pubmed/18443637.

[43] Cancer pain relief. Geneva, Switzerland: World Health Organization; 1986.

[44] Calculating total daily dose of opioids for safer dosage. Cent Dis Control n.d. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf (accessed November 20, 2017).

[45] Work Safe BC. Claims with Opioids, Sedative/Hypnotics or Other Prescribed Potentially Addictive Drugs. 2017.

[46] Quigley C. The role of opioids in cancer pain. BMJ 2005;331:825–9. doi:10.1136/bmj.331.7520.825.

[47] Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain

2009;10:113–130.e22. doi:10.1016/j.jpain.2008.10.008.

[48] Pashikanti L, Von Ah D. Impact of early mobilization protocol on the medical-surgical inpatient population: an integrated review of literature. Clin Nurse Spec 2012;26:87–94. doi:10.1097/NUR.0b013e31824590e6.

[49] Lewis C, Gunta K, Mitchell K, Bobay K. Effectiveness of multimodal pain management protocol in total knee arthroplasty patients. Orthop Nurs 2012;31:153–9. doi:10.1097/NOR.0b013e3182558d0b.

[50] Interagency Guideline on Prescribing Opioids for Pain, 3rd Edition. 2015.

[51] Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Commi. J Pain 2016;17:131–57. doi:10.1016/j.jpain.2015.12.008.

[52] Hernandez NM, Parry JA, Taunton MJ. Patients at Risk: Large Opioid Prescriptions After Total Knee Arthroplasty. J Arthroplasty 2017;32:2395–8. doi:10.1016/j.arth.2017.02.060.

[53] Korff M Von, Saunders K, Thomas Ray G, Boudreau D, Campbell C, Merrill J, et al. De Facto Long-term Opioid Therapy for Noncancer Pain. Clin J Pain 2008;24:521–7. doi:10.1097/AJP.0b013e318169d03b.

[54] Van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation. J

Clin Epidemiol 2006;59:11–7. doi:10.1016/j.jclinepi.2005.05.005.

[55] Vink NM, Klungel OH, Stolk RP, Denig P. Comparison of various measures for assessing medication refill adherence using prescription data. Pharmacoepidemiol Drug Saf 2009;18:159–65. doi:10.1002/pds.1698.

[56] Calcaterra SL, Scarbro S, Hull ML, Forber AD, Binswanger IA, Colborn KL. Prediction of Future Chronic Opioid Use Among Hospitalized Patients. J Gen Intern Med 2018;33:898–905. doi:10.1007/s11606-018-4335-8.

[57] Vanderlip ER, Sullivan MD, Edlund MJ, Martin BC, Fortney J, Austen M, et al. National study of discontinuation of long-term opioid therapy among veterans. Pain 2014;155:2673–9. doi:10.1016/j.pain.2014.09.034.

[58] Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, et al. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. Arthritis Res Ther 2013;15:223. doi:10.1186/ar4405.

[59] Oliveria S, Felson D, Reed J, Cirillo P, Walker A. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995;38:1134–41.

[60] Sharif B, Kopec J, Bansback N, Rahman MM, Flanagan WM, Wong H, et al. Projecting the direct cost burden of osteoarthritis in Canada using a microsimulation model. Osteoarthr Cartil 2015;23:1654–63. doi:10.1016/j.joca.2015.05.029.

[61] Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of

hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73:1323–30. doi:10.1136/annrheumdis-2013-204763.

[62] Arthritis Alliance of Canada. The impact of arthritis in Canada: today and over the next 30 years. Arthritis Alliance of Canada 2011;Fall:52.

[63] Macdonald K V, Sanmartin C, Langlois K, Marshall DA. Symptom onset, diagnosis and management of osteoarthritis. Stat Canada 2014;25:10–7.

[64] Neogi T, Zhang Y. Epidemiology of Osteoarthritis. Rheum Dis Clin North Am 2013;39:1–19. doi:https://doi.org/10.1016/j.rdc.2012.10.004.

[65] Loeser R. Age-related changes in the muscoskeletal system and the development of osteoarthritis. Clin Geriatr Med 2010;26:371–86. doi:10.1016/j.cger.2010.03.002.Age-Related.

[66] van der Kraan P, van den Berg W. Osteophytes: relevance and biology. Osteoarthr Cartil 2007;15:237–44. doi:10.1016/j.joca.2006.11.006.

[67] Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49. doi:10.1002/art.1780290816.

[68] Case R, Thomas E, Clarke E, Peat G. Prodromal symptoms in knee osteoarthritis: A nested case-control study using data from the Osteoarthritis Initiative. Osteoarthr Cartil 2015;23:1083–9. doi:10.1016/j.joca.2014.12.026.

[69] Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised.

vol. 15. 2007. doi:10.1016/j.joca.2006.06.017.

[70] Feeley BT, Gallo RA, Sherman S, Williams RJ. Management of Osteoarthritis of the Knee in the Active Patient. J Am Acad Orthop Surg 2010;18:406–16. doi:18/7/406 [pii].

[71] American Academy of Orthopaedic Surgeons Academy A. Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline 2nd Edition Adopted by the American American Academy of Orthopaedic Surgeons Board of Directors. Am Acad Orthop Surg Board Dir 2013:973. doi:10.5435/JAAOS-21-09-577.

[72] Ackerman I. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Aust J Physiother 2009;55:213. doi:10.1016/S0004-9514(09)70088-1.

[73] McCarthy CJ, Mills P, Pullen R, Richardson G, Hawkins N, Roberts C, et al. Exercise programmes for people with osteoarthritis of the knees. Business 2004;8:iii.

[74] Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthr Cartil 2008;16:137–62. doi:10.1016/j.joca.2007.12.013.

[75] Bono J V, Robbins CE, Mehio AK, Aghazadeh M, Talmo CT. Before and After Total Joint Replacement of the Hip and Knee. CGM 2012;28:459–70. doi:10.1016/j.cger.2012.05.004.

[76] Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the medical management of osteoarthritis. Arthritis Rheum 1995;38:1535–

40. doi:10.1002/art.1780381103.

[77] Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006:CD004257. doi:10.1002/14651858.CD004257.pub2.

[78] Miceli-Richard C. Paracetamol in osteoarthritis of the knee. Ann Rheum Dis 2004;63:923–30. doi:10.1136/ard.2003.017236.

[79] Katz JN, Smith SR, Collins JE, Solomon DH, Jordan JM, Hunter DJ, et al. Cost-effectiveness of nonsteroidal anti-inflammatory drugs and opioids in the treatment of knee osteoarthritis in older patients with multiple comorbidities. Osteoarthr Cartil 2016;24:409–18. doi:10.1016/j.joca.2015.10.006.

[80] American Academy of Orthopedic Surgeons. Opioid Use, Misuse, and Abuse in Orthopaedic Practice 2015:1–4.

[81] Gademan MGJ, Hofstede SN, Vliet Vlieland TPM, Nelissen RGHH, Marang-van de Mheen PJ. Indication criteria for total hip or knee arthroplasty in osteoarthritis: a state-of-the-science overview. BMC Musculoskelet Disord 2016;17:463. doi:10.1186/s12891-016-1325-z.

[82] Van Manen M, Nace J, Mont M. Management of primary knee osteoarthritis and indications for total knee arthroplasty for general practitioners. J Am Osteopath Assoc 2012;112:709–15.

[83] Scuderi GR, Scott WN, Tchejeyan GH. The Insall Legacy in Total Knee Arthroplasty.

Clin Orthop Relat Res 2001:3–14.

[84] Morgan H, Battista V, Leopold SS. Constraint in primary total knee arthroplasty. J Am Acad Orthop Surg 2005;13:515–24.

[85] Nguyen L-CL, Lehil MS, Bozic KJ. Trends in total knee arthroplasty implant utilization. J Arthroplasty 2015;30:739–42. doi:10.1016/j.arth.2014.12.009.

[86] Brown TS, Van Citters DW, Berry DJ, Abdel MP. The use of highly crosslinked polyethylene in total knee arthroplasty. Bone Joint J 2017;99–B:996–1002. doi:10.1302/0301-620X.99B8.BJJ-2017-0028.R1.

[87] Callaghan JJ, Insall JN, Greenwald AS, Oxon D, Dennis DA, Komistek RD, et al. Mobile-Bearing Knee Replacement: Concepts and Results. AAOS Instr Course Lect 2001;50:431–49.

[88] Carr BC, Goswami T. Knee implants – Review of models and biomechanics. Mater Des 2009;30:398–413. doi:https://doi.org/10.1016/j.matdes.2008.03.032.

[89] Huang C-H, Liau J-J, Cheng C-K. Fixed or mobile-bearing total knee arthroplasty. J Orthop Surg Res 2007;2:1. doi:10.1186/1749-799X-2-1.

[90] Vertullo CJ, Easley ME, Scott WN, Insall JN. Mobile bearings in primary knee arthroplasty. J Am Acad Orthop Surg 2001;9:355–64.

[91] Franceschetti E, Torre G, Palumbo A, Papalia R, Karlsson J, Ayeni OR, et al. No difference between cemented and cementless total knee arthroplasty in young patients: a review of the evidence. Knee Surg Sports Traumatol Arthrosc 2017;25:1749–56.

doi:10.1007/s00167-017-4519-5.

[92] Ajwani SH, Charalambous CP. Availability of Total Knee Arthroplasty Implants for Metal Hypersensitivity Patients. Knee Surg Relat Res 2016;28:312–8. doi:10.5792/ksrr.16.018.

[93] Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Med 2009;7:32. doi:10.1186/1741-7015-7-32.

[94] Same-day Mobilization following Total Hip and Total Knee Arthroplasty. Alberta Bone & Joint Health Institute: 2009.

[95] Lucic AP, Chelly J. Total knee arthroplasty as ambulatory surgery: Proof of concept. Reg. Anesth. Pain Med., 2011.

[96] Krause A, Sayeed Z, El-Othmani M, Pallekonda V, Mihalko W, Saleh KJ. Outpatient Total Knee Arthroplasty: Are We There Yet? (Part 2). Orthop Clin North Am 2018;49:7–16. doi:10.1016/j.ocl.2017.08.003.

[97] Ethgen O, Bruyere O, Richy F, Dardennes C, Reginster J-Y. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. J Bone Joint Surg Am 2004;86–A:963–74.

[98] Lenguerrand E, Wylde V, Gooberman-Hill R, Sayers A, Brunton L, Beswick AD, et al. Trajectories of pain and function after primary hip and knee arthroplasty: The adapt cohort study. PLoS One 2016;11:1–16. doi:10.1371/journal.pone.0149306.

[99] Ruiz DJ, Koenig L, Dall TM, Gallo P, Narzikul A, Parvizi J, et al. The direct and indirect costs to society of treatment for end-stage knee osteoarthritis. J Bone Joint Surg Am 2013;95:1473–80. doi:10.2106/JBJS.L.01488.

[100] Witjes S, Gouttebarge V, Kuijer PPFM, van Geenen RCI, Poolman RW, Kerkhoffs GMMJ. Return to Sports and Physical Activity After Total and Unicondylar Knee Arthroplasty: A Systematic Review and Meta-Analysis. Sports Med 2016;46:269–92. doi:10.1007/s40279-015-0421-9.

[101] Dunbar MJ. Subjective outcomes after knee arthroplasty. Acta Orthop Scand 2001;72:1–63. doi:10.1080/000164701753739124.

[102] Kim YH, Park JW, Kim JS, Park SD. The relationship between the survival of total knee arthroplasty and postoperative coronal, sagittal and rotational alignment of knee prosthesis. Int Orthop 2014;38:379–85. doi:10.1007/s00264-013-2097-9.

[103] Robertsson O, Knutson K, Lewold S, Lidgren L. The Swedish Knee Arthroplasty Register 1975-1997: an update with special emphasis on 41,223 knees operated on in 1988-1997. Acta Orthop Scand 2001;72:503–13. doi:10.1080/000164701753532853.

[104] Schiavone Panni A, Falez F, D'Apolito R, Corona K, Perisano C, Vasso M. Long-term follow-up of a non-randomised prospective cohort of one hundred and ninety two total knee arthroplasties using the NexGen implant. Int Orthop 2017;41:1155–62. doi:10.1007/s00264-017-3438-x.

[105] Lyman S, Yin KL. Patient-reported Outcome Measurement for Patients With Total Knee Arthroplasty. J Am Acad Orthop Surg 2017;25:S44–7. doi:10.5435/JAAOS-D-16-00637.

[106] Collins NJ, Roos EM. Patient-Reported Outcomes for Total Hip and Knee Arthroplasty. Commonly Used Instruments and Attributes of a "Good" Measure. Clin Geriatr Med 2012;28:367–94. doi:10.1016/j.cger.2012.05.007.

[107] Rolfson O, Eresian Chenok K, Bohm E, Lübbeke A, Denissen G, Dunn J, et al. Patient-reported outcome measures in arthroplasty registries: Report of the Patient-Reported Outcome Measures Working Group of the International Society of Arthroplasty Registries: Part I. Overview and rationale for patient-reported outcome measures. Acta Orthop 2016;87:3–8. doi:10.1080/17453674.2016.1181815.

[108] Gagnier JJ, Mullins M, Huang H, Marinac-Dabic D, Ghambaryan A, Eloff B, et al. A Systematic Review of Measurement Properties of Patient-Reported Outcome Measures Used in Patients Undergoing Total Knee Arthroplasty. J Arthroplasty 2017;32:1688–1697.e7. doi:10.1016/j.arth.2016.12.052.

[109] Ayers DC. Implementation of Patient-reported Outcome Measures in Total Knee Arthroplasty. J Am Acad Orthop Surg 2017;25:S48–50. doi:10.5435/JAAOS-D-16-00631.

[110] Guidance for Industry Use in Medical Product Development to Support Labeling Claims Guidance for Industry. Food Drug Adm 2009:1–39. doi:10.1111/j.1524-4733.2009.00609.x.

[111] Collins N, Misra D, Felson D, Crossley K, Roos E. Measures of Knee Function. Arthritis Care Res (Hoboken) 2011;63:S208–28. doi:10.1002/acr.20632.Measures.

[112] Giesinger JM, Hamilton DF, Jost B, Behrend H, Giesinger K. WOMAC, EQ-5D and Knee Society Score Thresholds for Treatment Success After Total Knee Arthroplasty. J

Arthroplasty 2015;30:2154–8. doi:10.1016/j.arth.2015.06.012.

[113] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.

[114] Bellamy N. WOMAC Osteoarthritis Index user guide. 1995.

[115] Escobar A, Garc?a P?rez L, Herrera-Espi?eira C, Aizpuru F, Sarasqueta C, Gonzalez S?enz de Tejada M, et al. Total knee replacement; minimal clinically important differences and responders. Osteoarthr Cartil 2013;21:2006–12. doi:10.1016/j.joca.2013.09.009.

[116] Clement ND, Bardgett M, Weir D, Holland J, Gerrand C, Deehan DJ. What is the Minimum Clinically Important Difference for the WOMAC Index After TKA? Clin Orthop Relat Res 2018;476:2005–14. doi:10.1097/CORR.0000000000000444.

[117] Hirschmann MT, Testa E, Amsler F, Friederich NF. The unhappy total knee arthroplasty (TKA) patient: higher WOMAC and lower KSS in depressed patients prior and after TKA. Knee Surg Sports Traumatol Arthrosc 2013;21:2405–11. doi:10.1007/s00167-013-2409-z.

[118] Fisher DA, Dierckman B, Watts MR, Davis K. Looks good but feels bad: factors that contribute to poor results after total knee arthroplasty. J Arthroplasty 2007;22:39–42. doi:10.1016/j.arth.2007.04.011.

[119] Harmelink KEM, Zeegers AVCM, Hullegie W, Hoogeboom TJ, Nijhuis-van der Sanden MWG, Staal JB. Are There Prognostic Factors for One-Year Outcome After Total Knee Arthroplasty? A Systematic Review. J Arthroplasty 2017;32:3840–3853.e1. doi:10.1016/j.arth.2017.07.011.

[120] Wylde V, Dixon S, Blom AW. The Role of Preoperative Self-Efficacy in Predicting Outcome after Total Knee Replacement. Musculoskeletal Care 2012;10:110–8. doi:10.1002/msc.1008.

[121] Papakostidou I, Dailiana ZH, Papapolychroniou T, Liaropoulos L, Zintzaras E, Karachalios TS, et al. Factors affecting the quality of life after total knee arthroplasties: a prospective study. BMC Musculoskelet Disord 2012;13:116. doi:10.1186/1471-2474-13-116.

[122] Jones C, Voaklander D, Johnston W, Suarez-Almazor M. The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. Arch Intern Med 2001;161:454–60.

[123] Paller CJ, Campbell CM, Edwards RR, Dobs AS. Sex-Based Differences in Pain Perception and Treatment. Pain Med 2009;10:289–99. doi:10.1111/j.1526-4637.2008.00558.x.

[124] Lindberg MF. Factors that predict the trajectories of acute pain, pain with walking, and self-rated health after total knee arthroplasty – a longitudinal study. University of Oslo, 2017.

[125] Weaver F, Hynes D, Hopkinson W, Wixson R, Khuri S, Daley J, et al. Preoperative risks

and outcomes of hip and knee arthroplasty in the Veterans Health Administration. J Arthroplasty 2003;18:693–708.

[126] Bjorgul K, Novicoff WM, Saleh KJ. Evaluating comorbidities in total hip and knee arthroplasty: available instruments. J Orthop Traumatol 2010;11:203–9. doi:10.1007/s10195-010-0115-x.

[127] Amusat N, Beaupre L, Jhangri GS, Pohar SL, Simpson S, Warren S, et al. Diabetes that impacts on routine activities predicts slower recovery after total knee arthroplasty: An observational study. J Physiother 2014;60:217–23. doi:10.1016/j.jphys.2014.09.006.

[128] Lizaur-Utrilla A, Martinez-Mendez D, Collados-Maestre I, Marco-Gómez L, Lopez-Prats FA. Elective Total Knee Arthroplasty in Patients With End-Stage Renal Disease: Is It a Safe Procedure? J Arthroplasty 2016;31:2152–5. doi:10.1016/j.arth.2016.03.049.

[129] De Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: A critical review of available methods. J Clin Epidemiol 2003;56:221–9. doi:10.1016/S0895-4356(02)00585-1.

[130] Escobar A, Quintana JM, Bilbao A, Azkarate J, Guenaga JI, Arenaza JC, et al. Effect of patient characteristics on reported outcomes after total knee replacement. Rheumatology 2007;46:112–9. doi:10.1093/rheumatology/kel184.

[131] Sharma L, Sinacore J, Daugherty C, Kuesis DT, Stulberg SD, Lewis M, et al. Prognostic factors for functional outcome of total knee replacement: a prospective study. J Gerontol A Biol Sci Med Sci 1996;51:M152-7.

[132] Lopez-Olivo MA, Landon GC, Siff SJ, Edelstein D, Pak C, Kallen MA, et al. Psychosocial determinants of outcomes in knee replacement. Ann Rheum Dis 2011;70:1775–81. doi:10.1136/ard.2010.146423.

[133] Spettell CM, Wall TC, Allison J, Calhoun J, Kobylinski R, Fargason R, et al. Identifying physician-recognized depression from administrative data: consequences for quality measurement. Health Serv Res 2003;38:1081–102. doi:10.1111/1475-6773.00164.

[134] Townsend L, Walkup JT, Crystal S, Olfson M. A systematic review of validated methods for identifying depression using administrative data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:163–73. doi:10.1002/pds.2310.

[135] Spettell CM, Wall TC, Allison J, Calhoun J, Kobylinski R, Fargason R, et al. Identifying physician-recognized depression from administrative data: consequences for quality measurement. Health Serv Res 2003;38:1081–102. doi:10.1111/1475-6773.00164.

[136] Lingard EA, Katz JN, Wright EA, Sledge CB. Predicting the outcome of total knee arthroplasty. J Bone Joint Surg Am 2004;86–A:2179–86.

[137] Grosu I, Thienpont E, Lavand'Homme P. Role of catastrophising in the intensity of postoperative pain after TKA. Eur J Anaesthesiol Eur Anaesthesiol Congr EUROANAESTHESIA 2013Barcelona SpainConference Publ 2013;30:206.

[138] Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain 2016;157:1259–65. doi:10.1097/j.pain.0000000000000516.

[139] Nguyen L-CL, Sing DC, Bozic KJ. Preoperative Reduction of Opioid Use Before Total Joint Arthroplasty. J Arthroplasty 2016;31:282–7. doi:10.1016/j.arth.2016.01.068.

[140] Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010. doi:10.1002/14651858.CD006605.pub2.

[141] Felson D, Zhang Y, Hannan M, Naimark MD A, N. Weissman MD B, Aliabadi MD P, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. vol. 38. 1995. doi:10.1002/art.1780381017.

[142] Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of Chronic Opioids: A Survey of Chronic Pain Patients. J Pain 2017;18:360–5. doi:10.1016/j.jpain.2016.11.001.

[143] Inacio MCS, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: A retrospective cohort study. BMJ Open 2016;6. doi:10.1136/bmjopen-2015-010664.

[144] Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. Gen Hosp Psychiatry 2009;31:564–70. doi:10.1016/j.genhosppsych.2009.07.003.

[145] Halbert BT, Davis RB, Wee CC. Disproportionate longer-term opioid use among U.S. adults with mood disorders. Pain 2016;157:2452–7. doi:10.1097/j.pain.0000000000000650.

[146] Sullivan MD, Derbyshire SW. Is there a purely biological core to pain experience? Pain 2015;156:2119–20. doi:10.1097/j.pain.0000000000000357.

[147] Moles A, Kieffer BL, D'Amato FR. Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. Science 2004;304:1983–6. doi:10.1126/science.1095943.

[148] Eisenberger NI, Jarcho JM, Lieberman MD, Naliboff BD. An experimental study of shared sensitivity to physical pain and social rejection. Pain 2006;126:132–8. doi:10.1016/j.pain.2006.06.024.

[149] Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An FMRI study of social exclusion. Science 2003;302:290–2. doi:10.1126/science.1089134.

[150] Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med 2016;176:1286–93. doi:10.1001/jamainternmed.2016.3298.

[151] Goesling J, Henry M, Moser S, Rastogi M, Hassett A, J. Clauw D, et al. Symptoms of Depression Are Associated With Opioid Use Regardless of Pain Severity and Physical Functioning Among Treatment-Seeking Patients With Chronic Pain. vol. 16. 2015. doi:10.1016/j.jpain.2015.05.010.

[152] Scherrer JF, Salas J, Lustman PJ, Burge S, Schneider FD, Residency Research Network of Texas (RRNeT) Investigators. Change in opioid dose and change in depression in a longitudinal primary care patient cohort. Pain 2015;156:348–55. doi:10.1097/01.j.pain.0000460316.58110.a0.

[153] Smith JA, Fuino RL, Pesis-Katz I, Cai X, Powers B, Frazer M, et al. Differences in opioid prescribing in low back pain patients with and without depression: a cross-sectional study of a national sample from the United States. PAIN Reports 2017;2.

[154] Gressler. LE, Martin BC, Hudson TJ, Painter JT. The relationship between concomitant benzodiazepine-opioid use and adverse outcomes among U.S. veterans. Pain 2017;159:1. doi:10.1097/j.pain.0000000000001111.

[155] Hansen CA, Inacio MCS, Pratt NL, Roughead EE, Graves SE. Chronic Use of Opioids Before and After Total Knee Arthroplasty: A Retrospective Cohort Study. J Arthroplasty 2017;32:817.e1.

[156] Escobar A, Quintana JM, Bilbao A, Aróstegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthr Cartil 2007;15:273–80. doi:10.1016/j.joca.2006.09.001.

[157] Voepel-Lewis T, Caird MS, Tait AR, Malviya S, Farley FA, Li Y, et al. A High Preoperative Pain and Symptom Profile Predicts Worse Pain Outcomes for Children After Spine Fusion Surgery. Anesth Analg 2017;124:1594–602. doi:10.1213/ANE.0000000000001963.

[158] Pasternak GW, Pan Y-X. Mu Opioids and Their Receptors: Evolution of a Concept. Pharmacol Rev 2013;65:1257–317. doi:10.1124/pr.112.007138.

[159] Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin

Epidemiol 2010;63:737–45. doi:10.1016/j.jclinepi.2010.02.006.

[160] Snyder CF, Jensen RE, Segal JB, Wu AW. Patient-reported Outcomes (PROs). vol. 51. 2013. doi:10.1097/MLR.0b013e31829b1d84.

[161] Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

[162] Patten S. Health Measurement Scales: A Practical Guide to Their Development and Use, 4th Edition. Can J PSYCHIATRY-REVUE Can Psychiatr n.d.;56:187–8.

[163] Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika 1951;16:297–334. doi:10.1007/BF02310555.

[164] Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007;60:34–42. doi:10.1016/j.jclinepi.2006.03.012.

[165] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407–15.

[166] Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to Explain the Clinical Significance of Health Status Measures. Mayo Clin Proc 2002;77:371–83. doi:https://doi.org/10.4065/77.4.371.

[167] King MT. A point of minimal important difference (MID): a critique of terminology and methods. Expert Rev Pharmacoecon Outcomes Res 2011;11:171–84. doi:10.1586/erp.11.9.

[168] Beaton DE, Bombardier C, Katz JN, Wright JG, Wells G. Looking for Important Change / Differences in Studies of Responsiveness. J Rheumatol 2001;28:400–5.

[169] Davis AM, Perruccio A V., Lohmander LS. Minimally clinically important improvement: All non-responders are not really non-responders an illustration from total knee replacement. Osteoarthr Cartil 2012;20:364–7. doi:10.1016/j.joca.2012.02.005.

[170] Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association. n.d. http://www.e-therapeutics.ca (accessed November 20, 2017).

[171] Alberta Triplicate Prescription Program Guide. 2017.

[172] Tamper-Resistant Oxycodone: A Review of the Clinical Evidence and Cost-effectivenesse. Canadian Agency for Drugs and Technology in Health: 2015.

[173] Stanley TH. The Fentanyl Story. J Pain 2014;15:1215–26. doi:10.1016/j.jpain.2014.08.010.

[174] Stanley TH. The history and development of the fentanyl series. J Pain Symptom Manage 1992;7:S3-7.

[175] Bravo L, Mico JA, Berrocoso E. Discovery and development of tramadol for the treatment of pain. Expert Opin Drug Discov 2017;12:1281–91. doi:10.1080/17460441.2017.1377697.

[176] Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev 2006:CD005522. doi:10.1002/14651858.CD005522.pub2.

[177] Singh DR, Nag K, Shetti AN, Krishnaveni N. Tapentadol hydrochloride: A novel

analgesic. Saudi J Anaesth 2013;7:322–6. doi:10.4103/1658-354X.115319.

[178] CPSA. Meperidine(Demerol®): a relic misfit for chronic pain 2016.

[179] Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J 2004;80:654–9. doi:10.1136/pgmj.2004.022988.

[180] Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician 2012;58:37–41.

Appendices

Appendix 2.1: Properties of Patient-reported Outcome Measures

Reliability

Reliability describes the stability of the instrument and comprises the instruments repeatability and internal consistency [107]. Repeatability (test-retest reliability) reflects the variance of an instrument when used to measure outcomes under the same conditions [159]. If an instrument was completely reliable, a subject should produce the same score under the same circumstance [111]. The intraclass correlation coefficient (ICC) reflects an instruments reliability and higher values indicate increased reliability [160]. An instrument is considered to have acceptable repeatability if the ICC is greater than 0.70 for groups, or greater than 0.9 for individuals [160,161]. Finally, internal consistency determines the extent the instrument measures similar concepts within a specific domain and is inferred by Cronbach's alpha [162,163]. Cronbach's alpha can range from 0 - 1 and an instrument is considered acceptable if the Cronbach's alpha is between 0.7 and 0.95 [164].

Validity

Validity is defined as the ability of the instrument to measure the outcome of interest in a specific setting [106,159]. Different features of validity can be reported and include content validity, construct validity and criterion validity [159]. Content validity is "the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured" [159]. It describes whether domains contains sufficient items to properly assess the

target population [159]. Ceiling and floor effects are considered when assessing content validity [101]. This refers to the influence that low and high scores have on the ability to detect change. For example, a ceiling effect is the inability of the questionnaire to detect a change if the patient were to improve when a patient initially records a high score or when a patient reports a maximum outcome on the instrument [164]. Acceptable floor and ceiling effects have been defined as having less than 15% of individuals achieving the maximum or minimum level of scores [164].

Construct validity refers to the "degree to which an instrument measures a particular theoretical construct"[106]. This can be problematic in TKA as it requires comparison with other validated questionnaires that are often not available [101]. The lack of an adequate comparison is also challenging for determining criterion validity that determines how the instrument compares to the gold standard [160]. Finally, face validity falls under the umbrella of content validity and reflects "the degree to which a measurement instrument, indeed, looks as though it is an adequate reflection of the construct to be measured" [159].

Responsiveness

The responsiveness of instruments refers to its ability to detect change [156]. Physician's ability to interpret scores and differentiate clinical significance from statistical significance is crucial, but often challenging as the literature is filled with various terms and values [106,108,115,156]. Clinically significant scores are stated in the context of instrument's minimal clinical important difference (MCID). The MCID is defined as "the smallest difference in score in the domain of

interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects, and excessive cost, a change in the patient's management"[165].

The minimum important difference (MID) was later introduced and defined as "the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful and which would lead the clinician to consider a change in the patient's management"[166]. Despite the slight definitional differences, the terms are used interchangeably [167]. In contrast, the minimum detectable change (MDC) is related to the instrument's sensitivity and defines the smallest amount of detectable change that is beyond simple instrument measurement error [168].

Various methods are used to determine MCID's [106,112,115,156,169]. Two common approaches are anchor-based and distribution based methods [160]. Anchor based methods compare the change in PRO to an external criterion [156]. For example, Escobar *et al.* (2007) used an anchor based approach to determine the MCID for the WOMAC at 6 months and 2 years after TKA [156]. The patients answered questions at 6 months and 2 years regarding if they were "a great deal better", "somewhat better", "equal", "somewhat worse" or "a great deal worse". Based off these anchoring questions, they used "somewhat better" to establish the WOMAC's MCID [156].

In contrast, distribution based methods use variability to determine the MCID [160]. These include standardized response mean, standard deviation or standardized effect size [106,160]. For example, the standardized effect size is calculated by determining the change in score and dividing it by the baseline score. To simplify interpretations, MCID's scores can be reduced to a categorical (yes/no) variable that is based on the threshold at which a patient

considers themselves well [115]. One of these measures that transforms MCIDs to a categorical variable is termed the patient's acceptable symptom state, but is yet to be routinely reported in joint replacement studies [115].

Appendix 2.2: Common Opioid Formulations

Morphine

Morphine is a natural opioid and is considered the gold standard that all other opioids are compared to [35]. Available in multiple formulations including oral and parenteral, it has a wide range of clinical utility [170]. It is subject to first pass metabolisms and is converted to morphine-6-glucuronide that holds greater analgesic effect than the parent compound [170]. Due to its effects on mast cells, it can cause pruritus, skin urticarial, hypotension and bronchospasm [170]. The onset of action depends on dose and route of administration [170]. Oral immediate release takes approximate 30 minutes with a duration ranging from 3 - 24 hours depending on the formulation used [170].

Codeine

Codeine is a natural opioid with a low affinity for opioid receptors and is considered the classical weak opioid [42]. The analgesic effect of codeine is related to codeine's metabolism to morphine in the liver [170]. Approximately 10% of the population does not properly metabolize codeine, rendering it ineffective in managing pain [170]. In contrast, 2-4% of the population are considered rapid metabolizers which can cause life-threatening respiratory depression in the pediatric population [170]. Therefore, it is contraindicated in children less than 17 of age [170].Onset of action for 0.5 – 1 hour with peak effect between 1 – 1.5 hours for immediate release oral formulations with a duration ranging from 4 – 6 hours [170]**.** Codeine is often

combined with acetaminophen and caffeine (Tylenol No. 3) [170]. Unlike other opioids, codeine does not require a triplicate prescription but is still tracked using Alberta's TPP database [171].

Oxycodone

Oxycodone is a semi-synthetic opioid that selectively binds to the mu receptors [170]. Compared to morphine, oxycodone has 5 - 40 times lower binding affinity [170]. In addition, oxycodone has a faster onset of action, better oral bioavailability and fewer side effects compared to morphine [170]. It is available in a variety of oral formulations that vary from immediate-release to long-acting controlled release [170]. The onset of action for pain relief is approximately 10 - 15 minutes and duration can range from 3 – 12 hours [170]. In Canada, it is commonly prescribed as OxyNeo or Percocet, in which acetaminophen is combined with oxycodone [170]. OxyNeo has replaced OxyContin in Canada and is described as a crush, chew and dissolve-resistant formulation [172]. A recent Canadian review suggested taper resistant formations have the potential to decrease misuse and abuse [172].

Hydromorphone

Hydromorphone is a semisynthetic mu receptor agonist [170]. It is 8 times stronger than morphine and has a more rapid onset [170]. Oral immediate-release formulations have peak effect within 30 – 60 minutes with durations ranging from 3 – 13 hours depending on the formulation[170]. Unlike morphine, it has no active metabolites, which make it the preferred

drug in patients with renal failure [170]. It is thought that the recent rise in hydromorphone use in Canada is related to the new restrictions placed on OxyNeo [3].

Fentanyl

Fentanyl is a synthetic mu receptor agonist that was developed in 1959 and is available in parental, transdermal and transbuccal preparations [173]. It is 80 – 100 times stronger than morphine and has a quicker onset [174]. It takes less than 30 seconds for clinical effect and reaches maximal effect within minutes [170]. Due to its chemical properties, the termination of action is much more rapid than morphine as it redistributes quickly to peripheral tissues [170].

Tramadol

Tramadol was introduced into the USA in 1995 and classified as a weak opioid by the WHO [175]. It is structurally related to codeine with a weak affinity to mu receptors and is $1/5^{th}$ as strong when compared to morphine [175]. It is often considered an atypical opioid as it also has monoaminergic actions [175]. The drug, that is a racemic mixture of two enantiomers, also inhibits neuronal reuptake of norepinephrine and serotonin [175]. In a 2006 Cochrane review, tramadol was shown to decrease pain intensity, produce symptoms relief and improve function in patients with arthritis [176].

Tapentadol

Similar to Tramadol, Tapentadol is a centrally acting opioid analgesic with a dual mechanism of action [177]. Tapentadol acts as both a Mu opioid receptor agonist and a norepinephrine reuptake inhibitor and provides analgesia occurs within 30 minutes of oral administration [177]. Analgesic effects last up 4 to 6 hours and is indicated for moderate to severe acute pain, chronic pain and neuropathic pain [177]. Tapentadol is metabolized to inactive metabolites by the liver and an excreted (99%) via the kidneys [177].

Meperidine

Meperidine is an anticholinergic and serotonergic compound that was initially developed as an atropine analog that has significant side effects associated with its active metabolite normeperidine [178]. Normedperidine neurotoxic and renally cleared and poses significant risks such as seizures, agitation and delirium in patients with renal dysfunction such as the elderly [178]. Due to these serious risks, the Institute of Safe Medical Practices Canada has issued safety warnings advising against the use of meperidine and is not routinely prescribed for pain management [178].

Methadone

Methadone is a synthetic opioid that acts as an agonist at the Mu opioid receptors [179]. It can be used to manage pain and for opioid maintenance therapy in patients with opioid dependence [179]. Methadone is detected in plasma after 30 minutes of oral administration and due to its long duration of action allows once daily dosing in methadone maintenance therapy or opioid

detoxification [179]. Methadone limits the symptoms of opioid withdrawal, but does not provide euphoric effects in patients on maintenance therapy [179].

Buprenorphine

Buprenorphine is a partial Mu-opioid agonist and Kappa-opioid antagonist that can be used to treat opioid addiction or chronic noncancer pain [180]. Buprenorphine has been reported to result in modest reductions in pain in adults with chronic non-cancer pain, when compared to placebo [180]. Buprenorphine's partial agonist action can induce withdrawal in opioid-dependent patients who are using full agonists (methadone and heroin) by displacing opioids from the receptor [180]. Buprenorphine equivalent to methadone and is superior to clonidine for opioid detoxication [180]. For maintenance treatment, buprenorphine may be used as an alternative to methadone [180].

Appendix 3.1: Supplementary Tables

Supplementary Table 3.1 – Additional Data provided for Goesling *et at* (2016)

	Pre-op opioid users				Non-users			
Score	**n**	**Day of surgery**	**6 months**	**p value[1]**	**n**	**Day of surgery**	**6 months**	**p value[2]**
WOMAC Pain (SD)	111	12.1 (3.2)	3.6 (3.8)	<0.001	313	10.0 (3.3)	2.4 (2.6)	<0.001
WOMAC Stiffness (SD)	111	5.1 (1.7)	2.1 (1.7)	<0.001	315	4.4 (1.8)	1.9 (1.6)	<0.001
WOMAC Functioning (SD)	108	41.0 (10.3)	13.1 (11.9)	<0.001	308	34.2 (10.4)	9.9 (9.2)	<0.001
WOMAC Total (SD)	104	58.3 (14.1)	18.4 (16.6)	<0.001	306	48.6 (14.1)	13.9 (12.3)	<0.001

Abbreviations
WOMAC - The Western Ontario and McMaster Universities Osteoarthritis Index, n number of patients.

Notes
[1] Pairwise comparisons testing differences of scores at day of surgery and 6 months for pre-op opioid users
[2] Pairwise comparisons testing differences of scores at day of surgery and 6 months for non-opioid users

Supplementary Table 3.2 – Original Extracted Patient-Reported Outcome Scores

Study	Outcome Assessed	Statistic	Scoring	Preoperative Score			Post-operative Score			Change			
				OU	nOU	p	OU	nOU	p	OU	p	nOU	p
Zywiel *et al.*	KSS	mean (range) [95% CI]	0 to 100 point-scale (100 indicates the best possible score)	38 (11-63) [33, 42]	37(10-55) [33, 41]	0.513	79 (45 – 100) [76, 83]	92 (59 - 100) [89 - 95]	<0.001	41	-	55	-
Smith *et al.*	WOMAC Pain	mean [95% CI]	Transformed to a 0 to 100-point scale (100 indicating the worst possible score)	44.6 [40.3, 48.9]	43.7 [41.4, 46.0]	<0.05	17.1[12.8, 21.4]	10.5 [8.3,12.8]	<0.05	27.0 [22.7, 31.3]	<0.05	33.6 [31.4, 35.9]	<0.05
Franklin *et al.*	KSS	mean (SD)	0 to 100 point-scale (100 indicates the best possible score)	34.79 (15.17)	37.06 (15.57)	<0.001	81.3[1] (15.7)	86[1] (14.1)	-	46.51	-	48.94	-
Pivec *et al.*	HHS	mean (range)	0 to 100-point scale (100 indicates the best score)	43	45	0.26	84 (48 - 100)	91 (74-100)	0.002	41	0.01	49	0.01
Nguyen *et al.*	WOMAC	mean	0 to 100-point scale (100 indicates the best possible score)	47.5	44.1	-	65.3	83.1	<0.01	21.2	-	39	-
Goesling *et al.*	WOMAC Pain,	mean (SD)	0 - 20, higher indicates worse score	12.1 (3.2)	10.0 (3.3)	P<0.001	3.6 (3.8)	2.4 (2.6)	-	8.5	<0.001	7.6	<0.001
	WOMAC Function	mean (SD)	0 - 68, higher indicates worse score	41.0 (10.3)	34.2 (10.4)	P<0.001	13.1 (11.9)	9.9 (9.2)	-	27.9	<0.001	20.1	<0.001
	WOMAC Stiffness	mean (SD)	0 - 8, higher indicates wore score	5.1 (1.7)	4.4 (1.8)	P<0.001	2.1 (1.7)	1.9 (1.6)	-	3	<0.001	2.3	<0.001
	WOMAC Total	mean (SD)	0 - 96, higher indicates worse	58.3 (14.1)	48.6 (14.1)	P<0.001	18.4 (16.6)	13.9 (12.3)	-	39.9	<0.001	34.7	<0.001

Abbreviations
PRO –Joint or Disease Specific Patient-Reported Outcome Score. All scores Transformed to a 0 to 100-point scale (100 indicating the best possible score), WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index, KSS – Knee Society Score, HHS – Harris Hip Score, OU – Preoperative opioid use, nOU – preoperative opioid-naïve, n – number of patients, SD – Standard deviation, CI – Confidence Interval, '-' indicates note reported in study

Notes
[1]OU and NonOU postoperative score calculated based on pooled stratified data extracted from paper

Supplementary Table 3.3 – Comparison of Secondary Outcomes between Patient Prescribed Preoperative Opioids and Opioid-Naïve Patients

Study	Secondary Outcome	OU	nOU	p value
Zywiel *et al.*	Mean LOS (range)	4.3 (2-8)	3.4 [2-6]	0.013
	Mean morphine equivalence at discharge [95% CI]	85 mg [65, 106]	91 mg [67, 115]	0.946
	Number of arthroscopic evaluations for unexplained pain [95% CI]	5 [2, 11]	0 [0, 4]	0.066
	Number of referrals to chronic pain clinic [95% CI]	10 [6, 17]	1 [0, 6]	<0.001
	Number of revisions for recalcitrant pain and/or stiffness [95% CI]	8 [6, 17]	0 [0, 6]	<0.001
	Mean ROM at final follow up [95% CI]	107 [102, 113]	111 [107, 114]	0.223
Franklin *et al.*	Opioid use at 12 months follow up[1]	14.0	2.6	-
Pivec *et al.*	Mean LOS (range)	4 (2 - 10)	3 (2 - 8)	0.01
	Number of patients discharged to acute care rehabilitation facilities	30	24	0.37
	Mean morphine equivalences at 6 weeks follow up	63 mg	2mg	<0.001
	Percent of patients using opioids at final follow up	19%	4%	0.04
	Number of Revisions	2	2	-
Goesling *et al.*	Percent of TKA patients reporting opioids use at 1 months follow up	88.5	66.5	-
	Percent of TKA patients reporting opioids use at 2 months follow up	48.2	16.6	-
	Percent of TKA patients reporting opioids use at 6 months follow up	53.3	8.2	0.001
	Percent of THA patients reporting opioids use at 1 months follow up	63.9	22.5	-
	Percent of THA patients reporting opioids use at 2 months follow up	37.8	4.4	-
	Percent of THA patients reporting opioids use at 6 months follow up	34.7	4.3	<0.001

Abbreviations
CI – Confidence Interval, TKA – Total Knee Arthroplasty, THA – Total Hip Arthroplasty, OU – patients prescribed preoperative opioids, nOU – Preoperative opioid-naïve patients, '-' not reported in study

Notes
[1] 12% of preoperative opioid-naïve patients missing 12 months opioid data, 9% of preoperative opioid users missing 12 months opioid data

Appendix 3.2: Database Search Strategies

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

---

1 exp Arthroplasty, Replacement/ or exp Arthroplasty/ or (arthroplasty or ((joint or knee* or hip* or shoulder*) adj2 replacement)).mp.
2 exp narcotics/ or exp analgesics, opioid/
3 (opiate* or opioid* or narcotic* or morphin* or duramorph or ms contin or morphia or oramorph sr or sdz 202 250 or sdz202250 or sdz202 250 or alfenta or alfentanil or fanaxal or limifen or rapifen or r 39209 or r39209 or alphaprodine or Nisentil or prodine or buprenorphine or buprenex or buprex or prefin or subutex or temgesic or 6029 m or 6029m or rx6029m).mp.
4 (butorphanol or dolorex or moradol or stadol or torbugesic or bc 2627 or bc2627 or codeine or ardinex or idocodeine or n methylmorphine or Dextromoramide or d moramide or palfium or pyrrolamidol or Dextropropoxyphene or d propoxyphene or darvon or propoxyphene or Enkephalin or dago or dagol or damge or damgo or rx 783006 or dpdpe).mp.
5 (fentanyl or duragesic or durogesic or fentanest or fentora or phentanyl or r 4263 or r4263 or sublimaze or hydrocodon* or codinovo or dicodid or dihydrocodeinone or hycodan or hycon or hydrocodeinonebitartrate or robidone or hydromorphon* or dihydromorphinone or dilaudid or laudacon or palladone).mp.
6 (meperidine or demerol or dolantin or dolargan or dolcontral or dolin or dolosal or dolsin or isonipecain or lidol or lydol or operidine or pethidine or Meptazinol or meptid or wy 22811 or wy22811 or nalbuphine or nubain or en 2234a or en2234a or oxycodone or dihydrohydroxycodeinone or dihydrone or dinarkon or eucodal or oxiconum or oxycodeinon or oxycone or oxycontin or pancodine or theocodin or percocet).mp.
7 (oxymorphone or numorphan or opana or pentazocine or fortral or lexir or talwin or phenoperidine or fenoperidine or lealgin or operidine or r 1406 or r1406 or pirinitramid* or piritramid* or dipidolor or dipydolor or promedol or dimethylmeperidine or isopromedol or trimeperidine or sufentanil or sufentanilhameln or sulfentanil or sulfentanyl or r 30730 or r30730).mp.
8 (tramadol or adolonta or amadol or biodalgic or biokanol or contramal or jutadol or k 315 or k315 or mtwtramadol or nobligan or prontofort or ranitidin 1a pharma or takadol or theradol or tiral or topalgic or Tradol or tradolpuren or tradonal or tralgiol or trama or tramadorsch or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolor or tramadolratiopharm or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or xymel 50 or zamudol or zumalgic or zydol or zytram).mp.
9 (acetorophine or acetylcodeine or acetymethadol or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or brompton mixture or ciramadol or cocomadol or codydramol or conorfone or cyclazocine or dextrorphan or dezocine or diamorphine or diconal or dihydroetorphine or dihydromorphine or dimethylthiambutene or dipipanone or dynorphin or enadoline or eptazocine or ethylketazocine or ethylmorphine or etonitazene or etorphine or etoxeridine or faxeladol or furethidine or gelonida or isalmadol or isomethodone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or levorphanol or metazocine or methylsamidorphan or tilidine or nicodine or nicomorphine or noracymethadol or bufigen or nubain* or nalbufin* or nalcryn or nalpain or onfor or noracymethadol or norbuprenorphine or normorphine or norpethidine or norpropoxyphene or nortramadol or oliceridine or oripavine or pentamorphone or phenadoxone or phencyclidine or picenadol or piminodine or piritramide or profadol or propiram or sameridine or samidorphan or semorphone or tapentadol or thebaine or tifluadom or tilidine or tonazocine or vicodin).mp.
10 or/2-9
11 1 and 10
12 exp preoperative care/ or preoperative period/
13 (preoperativ* or pre-operativ* or pre-surg* or presurg*).mp. or ((prior or "before") adj3 (surg* or arthroplasty or replacement)).ti,ab,kf.

14 12 or 13
15 11 and 14

Embase <1974 to Current>

---

1 exp arthroplasty/ or (arthroplasty or ((joint or knee* or hip* or shoulder*) adj2 replacement)).ti,ab,kw.
2 exp narcotic agent/ or exp narcotic analgesic agent/
3 (opiate* or opioid* or narcotic* or morphin* or duramorph or ms contin or morphia or oramorph sr or sdz 202 250 or sdz202250 or sdz202 250 or alfenta or alfentanil or fanaxal or limifen or rapifen or r 39209 or r39209 or alphaprodine or Nisentil or prodine or buprenorphine or buprenex or buprex or prefin or subutex or temgesic or 6029 m or 6029m or rx6029m).ti,ab,kw.
4 (butorphanol or dolorex or moradol or stadol or torbugesic or bc 2627 or bc2627 or codeine or ardinex or idocodeine or n methylmorphine or Dextromoramide or d moramide or palfium or pyrrolamidol or Dextropropoxyphene or d propoxyphene or darvon or propoxyphene or Enkephalin or dago or dagol or damge or damgo or rx 783006 or dpdpe).ti,ab,kw.
5 (fentanyl or duragesic or durogesic or fentanest or fentora or phentanyl or r 4263 or r4263 or sublimaze or hydrocodon* or codinovo or dicodid or dihydrocodeinone or hycodan or hycon or hydrocodeinonebitartrate or robidone or hydromorphon* or dihydromorphinone or dilaudid or laudacon or palladone).ti,ab,kw.
6 (meperidine or demerol or dolantin or dolargan or dolcontral or dolin or dolosal or dolsin or isonipecain or lidol or lydol or operidine or pethidine or Meptazinol or meptid or wy 22811 or wy22811 or nalbuphine or nubain or en 2234a or en2234a or oxycodone or dihydrohydroxycodeinone or dihydrone or dinarkon or eucodal or oxiconum or oxycodeinon or oxycone or oxycontin or pancodine or theocodin or percocet).ti,ab,kw.
7 (oxymorphone or numorphan or opana or pentazocine or fortral or lexir or talwin or phenoperidine or fenoperidine or lealgin or operidine or r 1406 or r1406 or pirinitramid* or piritramid* or dipidolor or dipydolor or promedol or dimethylmeperidine or isopromedol or trimeperidine or sufentanil or sufentanilhameln or sulfentanil or sulfentanyl or r 30730 or r30730).ti,ab,kw.
8 (tramadol or adolonta or amadol or biodalgic or biokanol or contramal or jutadol or k 315 or k315 or mtwtramadol or nobligan or prontofort or ranitidin 1a pharma or takadol or theradol or tiral or topalgic or Tradol or tradolpuren or tradonal or tralgiol or trama or tramadorsch or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolor or tramadolratiopharm or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or xymel 50 or zamudol or zumalgic or zydol or zytram).ti,ab,kw.
9 (acetorophine or acetylcodeine or acetymethadol or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or brompton mixture or ciramadol or cocomadol or codydramol or conorfone or cyclazocine or dextrorphan or dezocine or diamorphine or diconal or dihydroetorphine or dihydromorphine or dimethylthiambutene or dipipanone or dynorphin or enadoline or eptazocine or ethylketazocine or ethylmorphine or etonitazene or etorphine or etoxeridine or faxeladol or furethidine or gelonida or isalmadol or isomethodone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or levorphanol or metazocine or methylsamidorphan or tilidine or nicodine or nicomorphine or noracymethadol or bufigen or nubain* or nalbufin* or nalcryn or nalpain or onfor or noracymethadol or norbuprenorphine or normorphine or norpethidine or norpropoxyphene or nortramadol or oliceridine or oripavine or pentamorphone or phenadoxone or phencyclidine or picenadol or piminodine or piritramide or profadol or propiram or sameridine or samidorphan or semorphone or tapentadol or thebaine or tifluadom or tilidine or tonazocine or vicodin).ti,ab,kw.
10 or/2-9
11 1 and 10
12 exp preoperative chemotherapy/ or exp preoperative care/ or exp preoperative period/ or exp preoperative treatment/
13 (preoperativ* or pre-operativ* or pre-surg* or presurg*).ti,ab,kw. or ((prior or "before") adj3 (surg* or arthroplasty or replacement)).ti,ab,kw.

14 12 or 13
15 11 and 14

Cochrane Library

#1 [mh "Arthroplasty, Replacement"] or [mh "Arthroplasty"] or (arthroplasty or ((joint or knee* or hip* or shoulder*) near/2 replacement)):ti,ab,kw
#2 [mh "narcotics"] or [mh "analgesics,opioid"]
#3 (opiate* or opioid* or narcotic* or morphin* or duramorph or "ms contin" or morphia or oramorph or "sdz 202 250" or sdz202250 or "sdz202 250" or alfenta or alfentanil or fanaxal or limifen or rapifen or "r 39209" or r39209 or alphaprodine or nisentil or prodine or buprenorphine or buprenex or buprex or prefin or subutex or temgesic or "6029 m" or 6029m or rx6029m):ti,ab,kw
#4 (butorphanol or dolorex or moradol or stadol or torbugesic or "bc 2627" or bc2627 or codeine or ardinex or idocodeine or methylmorphine or Dextromoramide or moramide or palfium or pyrrolamidol or dextropropoxyphene or propoxyphene or darvon or propoxyphene or enkephalin or dago or dagol or damge or damgo or "rx 783006" or rx783006 or dpdpe):ti,ab,kw
#5 (fentanyl or duragesic or durogesic or fentanest or fentora or phentanyl or "r 4263" or r4263 or sublimaze or hydrocodon* or codinovo or dicodid or dihydrocodeinone or hycodan or hycon or hydrocodeinonebitartrate or robidone or hydromorphon* or dihydromorphinone or dilaudid or laudacon or palladone):ti,ab,kw
#6 (meperidine or demerol or dolantin or dolargan or dolcontral or dolin or dolosal or dolsin or isonipecain or lidol or lydol or operidine or pethidine or meptazinol or meptid or "wy 22811" or wy22811 or nalbuphine or nubain or "en 2234a" or en2234a or oxycodone or dihydrohydroxycodeinone or dihydrone or dinarkon or eucodal or oxiconum or oxycodeinon or oxycone or oxycontin or pancodine or theocodin or percocet):ti,ab,kw
#7 (oxymorphone or numorphan or opana or pentazocine or fortral or lexir or talwin or phenoperidine or fenoperidine or lealgin or operidine or "r 1406" or r1406 or pirinitramid* or piritramid* or dipidolor or dipydolor or promedol or dimethylmeperidine or isopromedol or trimeperidine or sufentanil or sufentanilhameln or sulfentanil or sulfentanyl or "r 30730" or r30730):ti,ab,kw
#8 (tramadol or adolonta or amadol or biodalgic or biokanol or contramal or jutadol or "k 315" or k315 or mtwtramadol or nobligan or prontofort or ranitidin or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama or tramadorsch or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolor or tramadolratiopharm or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or xymel or zamudol or zumalgic or zydol or zytram):ti,ab,kw
#9 (acetorophine or acetylcodeine or acetymethadol or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "brompton mixture" or ciramadol or cocomadol or codydramol or conorfone or cyclazocine or dextrorphan or dezocine or diamorphine or diconal or dihydroetorphine or dihydromorphine or dimethylthiambutene or dipipanone or dynorphin or enadoline or eptazocine or ethylketazocine or ethylmorphine or etonitazene or etorphine or etoxeridine or faxeladol or furethidine or gelonida or isalmadol or isomethodone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or levorphanol or metazocine or methylsamidorphan or tilidine or nicodine or nicomorphine or noracymethadol or bufigen or nubain* or nalbufin* or nalcryn or nalpain or onfor or noracymethadol or norbuprenorphine or normorphine or norpethidine or norpropoxyphene or nortramadol or oliceridine or oripavine or pentamorphone or phenadoxone or phencyclidine or picenadol or piminodine or piritramide or profadol or propiram or sameridine or samidorphan or semorphone or tapentadol or thebaine or tifluadom or tilidine or tonazocine or vicodin):ti,ab,kw
#10 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 #1 and #10
#12 [mh "preoperative care"] or [mh "preoperative period"] or (preoperativ* or "pre-operativ*" or "pre-surg*" or presurg*):ti,ab,kw OR ((prior or "before") NEAR/3 (surg* or arthroplasty or replacement)):ti,ab,kw
#13 #11 and #12

Scopus

TITLE-ABS-KEY(arthroplasty or ((joint or knee* or hip* or shoulder*) w/2 replacement)) and TITLE-ABS-KEY(opiate* or opioid* or narcotic* or morphin* or duramorph or "ms contin" or morphia or oramorph or "sdz 202 250" or sdz202250 or "sdz202 250" or alfenta or alfentanil or fanaxal or limifen or rapifen or "r 39209" or r39209 or alphaprodine or nisentil or prodine or buprenorphine or buprenex or buprex or prefin or subutex or temgesic or "6029 m" or 6029m or rx6029m or butorphanol or dolorex or moradol or stadol or torbugesic or "bc 2627" or bc2627 or codeine or ardinex or idocodeine or methylmorphine or dextromoramide or moramide or palfium or pyrrolamidol or dextropropoxyphene or propoxyphene or darvon or propoxyphene or enkephalin or dago or dagol or damge or damgo or "rx 783006" or rx783006 or dpdpe or fentanyl or duragesic or durogesic or fentanest or fentora or phentanyl or "r 4263" or r4263 or sublimaze or hydrocodon* or codinovo or dicodid or dihydrocodeinone or hycodan or hycon or hydrocodeinonebitartrate or robidone or hydromorphon* or dihydromorphinone or dilaudid or laudacon or palladone or meperidine or demerol or dolantin or dolargan or dolcontral or dolin or dolosal or dolsin or isonipecain or lidol or lydol or operidine or pethidine or meptazinol or meptid or "wy 22811" or wy22811 or nalbuphine or nubain or "en 2234a" or en2234a or oxycodone or dihydrohydroxycodeinone or dihydrone or dinarkon or eucodal or oxiconum or oxycodeinon or oxycone or oxycontin or pancodine or theocodin or percocet or oxymorphone or numorphan or opana or pentazocine or fortral or lexir or talwin or phenoperidine or fenoperidine or lealgin or operidine or "r 1406" or r1406 or pirinitramid* or piritramid* or dipidolor or dipydolor or promedol or dimethylmeperidine or isopromedol or trimeperidine or sufentanil or sufentanilhameln or sulfentanil or sulfentanyl or "r 30730" or r30730 or tramadol or adolonta or amadol or biodalgic or biokanol or contramal or jutadol or "k 315" or k315 or mtwtramadol or nobligan or prontofort or ranitidin or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama or tramadorsch or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolor or tramadolratiopharm or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or xymel or zamudol or zumalgic or zydol or zytram or acetorophine or acetylcodeine or acetymethadol or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "brompton mixture" or ciramadol or cocomadol or codydramol or conorfone or cyclazocine or dextrorphan or dezocine or diamorphine or diconal or dihydroetorphine or dihydromorphine or dimethylthiambutene or dipipanone or dynorphin or enadoline or eptazocine or ethylketazocine or ethylmorphine or etonitazene or etorphine or etoxeridine or faxeladol or furethidine or gelonida or isalmadol or
isomethodone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or levorphanol or metazocine or methylsamidorphan
or tilidine or nicodine or nicomorphine or noracymethadol or bufigen or nubain* or nalbufin* or nalcryn or nalpain or onfor or noracymethadol or norbuprenorphine or normorphine or norpethidine or norpropoxyphene or nortramadol or oliceridine or oripavine or pentamorphone or phenadoxone or phencyclidine or picenadol or piminodine or piritramide or profadol or propiram or sameridine or samidorphan or semorphone or tapentadol or thebaine or tifluadom or tilidine or tonazocine or vicodin) and TITLE-ABS-KEY(preoperativ* or "pre-operativ*" or "pre-surg*" or presurg* or ((prior or "before") pre/3 (surg* or arthroplasty or replacement)))

Web of Science Core Collection

#1 TS=(arthroplasty or (joint or knee* or hip* or shoulder*) near/2 replacement)
#2 TS=(opiate* or opioid* or narcotic* or morphin* or duramorph or "ms contin" or morphia or oramorph or "sdz 202 250" or sdz202250 or "sdz202 250" or alfenta or alfentanil or fanaxal or limifen or rapifen or "r 39209" or r39209 or alphaprodine or nisentil or prodine or buprenorphine or buprenex or buprex or prefin or subutex or temgesic or "6029 m" or 6029m or rx6029m or butorphanol or dolorex or moradol or stadol or torbugesic or "bc 2627" or bc2627 or codeine or ardinex or idocodeine or methylmorphine or dextromoramide or moramide or palfium or pyrrolamidol or dextropropoxyphene or propoxyphene or darvon or propoxyphene or enkephalin or dago or dagol or damge or damgo or "rx 783006" or rx783006 or dpdpe or fentanyl or duragesic or durogesic or fentanest or fentora or phentanyl or "r 4263" or r4263 or sublimaze or hydrocodon* or codinovo or dicodid or dihydrocodeinone or hycodan or hycon or hydrocodeinonebitartrate or robidone or hydromorphon* or dihydromorphinone or dilaudid or laudacon or palladone or meperidine or demerol or dolantin or dolargan or dolcontral or dolin or dolosal or dolsin or isonipecain or lidol or lydol or operidine or

pethidine or meptazinol or meptid or "wy 22811" or wy22811 or nalbuphine or nubain or "en 2234a" or en2234a or oxycodone or dihydrohydroxycodeinone or dihydrone or dinarkon or eucodal or oxiconum or oxycodeinon or oxycone or oxycontin or pancodine or theocodin or percocet or oxymorphone or numorphan or opana or pentazocine or fortral or lexir or talwin or phenoperidine or fenoperidine or lealgin or operidine or "r 1406" or r1406 or pirinitramid* or piritramid* or dipidolor or dipydolor or promedol or dimethylmeperidine or isopromedol or trimeperidine or sufentanil or sufentanilhameln or sulfentanil or sulfentanyl or "r 30730" or r30730 or tramadol or adolonta or amadol or biodalgic or biokanol or contramal or jutadol or "k 315" or k315 or mtwtramadol or nobligan or prontofort or ranitidin or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama or tramadorsch or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolor or tramadolratiopharm or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or xymel or zamudol or zumalgic or zydol or zytram or acetorophine or acetylcodeine or acetymethadol or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "brompton mixture" or ciramadol or cocomadol or codydramol or conorfone or cyclazocine or dextrorphan or dezocine or diamorphine or diconal or dihydroetorphine or dihydromorphine or dimethylthiambutene or dipipanone or dynorphin or enadoline or eptazocine or ethylketazocine or ethylmorphine or etonitazene or etorphine or etoxeridine or faxeladol or furethidine or gelonida or isalmadol or
isomethodone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or levorphanol or metazocine or methylsamidorphan or tilidine or nicodine or nicomorphine or noracymethadol or bufigen or nubain* or nalbufin* or nalcryn or nalpain or onfor or noracymethadol or norbuprenorphine or normorphine or norpethidine or norpropoxyphene or nortramadol or oliceridine or oripavine or pentamorphone or phenadoxone or phencyclidine or picenadol or piminodine or piritramide or profadol or propiram or sameridine or samidorphan or semorphone or tapentadol or thebaine or tifluadom or tilidine or tonazocine or vicodin)
#3 #1 AND #2
#4 TS=(preoperativ* or "pre-operativ*" or "pre-surg*" or presurg* or ((prior or "before") near/3 (surg* or arthroplasty or replacement)))
#5 #3 AND #4

CINAHL Plus with Full-Text

(MH "Arthroplasty+") or arthroplasty or (joint or knee* or hip* or shoulder*) n2 replacement
AND
((MH "Analgesics, Opioid+") OR (MH "Narcotics+")) OR (opiate* or opioid* or narcotic* or morphin* or duramorph or "ms contin" or morphia or oramorph or "sdz 202 250" or sdz202250 or "sdz202 250" or alfenta or alfentanil or fanaxal or limifen or rapifen or "r 39209" or r39209 or alphaprodine or nisentil or prodine or buprenorphine or buprenex or buprex or prefin or subutex or temgesic or "6029 m" or 6029m or rx6029m or butorphanol or dolorex or moradol or stadol or torbugesic or "bc 2627" or bc2627 or codeine or ardinex or idocodeine or methylmorphine or dextromoramide or moramide or palfium or pyrrolamidol or dextropropoxyphene or propoxyphene or darvon or propoxyphene or enkephalin or dago or dagol or damge or damgo or "rx 783006" or rx783006 or dpdpe or fentanyl or duragesic or durogesic or fentanest or fentora or phentanyl or "r 4263" or r4263 or sublimaze or hydrocodon* or codinovo or dicodid or dihydrocodeinone or hycodan or hycon or hydrocodeinonebitartrate or robidone or hydromorphon* or dihydromorphinone or dilaudid or laudacon or palladone or meperidine or demerol or dolantin or dolargan or dolcontral or dolin or dolosal or dolsin or isonipecain or lidol or lydol or operidine or pethidine or meptazinol or meptid or "wy 22811" or wy22811 or nalbuphine or nubain or "en 2234a" or en2234a or oxycodone or dihydrohydroxycodeinone or dihydrone or dinarkon or eucodal or oxiconum or oxycodeinon or oxycone or oxycontin or pancodine or theocodin or percocet or oxymorphone or numorphan or opana or pentazocine or fortral or lexir or talwin or phenoperidine or fenoperidine or lealgin or operidine or "r 1406" or r1406 or pirinitramid* or piritramid* or dipidolor or dipydolor or promedol or dimethylmeperidine or isopromedol or trimeperidine or sufentanil or sufentanilhameln or sulfentanil or sulfentanyl or "r 30730" or r30730 or tramadol or adolonta or amadol or biodalgic or biokanol or contramal or jutadol or "k 315" or k315 or mtwtramadol or nobligan or prontofort or ranitidin or takadol or theradol or tiral or topalgic or tradol or tradolpuren or tradonal

or tralgiol or trama or tramadorsch or tramabeta or tramadin or tramadoc or tramadoldolgit or tramadolhameln or tramadolor or tramadolratiopharm or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or xymel or zamudol or zumalgic or zydol or zytram or acetorophine or acetylcodeine or acetymethadol or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "brompton mixture" or ciramadol or cocomadol or codydramol or conorfone or cyclazocine or dextrorphan or dezocine or diamorphine or diconal or dihydroetorphine or dihydromorphine or dimethylthiambutene or dipipanone or dynorphin or enadoline or eptazocine or ethylketazocine or ethylmorphine or etonitazene or etorphine or etoxeridine or faxeladol or furethidine or gelonida or isalmadol or isomethodone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or levorphanol or metazocine or methylsamidorphan or tilidine or nicodine or nicomorphine or noracymethadol or bufigen or nubain* or nalbufin* or nalcryn or nalpain or onfor or noracymethadol or norbuprenorphine or normorphine or norpethidine or norpropoxyphene or nortramadol or oliceridine or oripavine or pentamorphone or phenadoxone or phencyclidine or picenadol or piminodine or piritramide or profadol or propiram or sameridine or samidorphan or semorphone or tapentadol or thebaine or tifluadom or tilidine or tonazocine or vicodin)
AND
((MH "Preoperative Care") OR (MH "Preoperative Period")) OR (preoperativ* or "pre-operativ*" or "pre-surg*" or presurg*) or ((prior or "before") w3 (surg* or arthroplasty or replacement))

Appendix 3.3: JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____.

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

Appendix 4.1: Supplementary Tables

Supplementary Table 4.1 Calculated daily morphine equivalence dose (mg/day) for the classification episode based on different refill gaps

Mixed [c]		Long-term Opioid User [b]							
Fraction[c]	Fixed[c]	n	Mean	Median	IQR	Min	Max	95L	95U
0.04	1	635	151.9	75.1	125.6	4.5	3200.0	133.0	170.8
0.25	7	997	122.5	64.0	96.9	4.4	2827.6	110.4	134.6
0.5	14	1183	106.7	58.5	82.1	2.5	2620.1	96.7	116.7
0.75	21	1349	97.2	52.4	70.9	2.5	2620.1	88.4	106.0
1	28	1466	91.2	47.0	66.5	2.5	2620.1	83.0	99.3
1.5	42	1678	81.8	40.6	60.1	2.8	2458.1	74.8	88.9
2	56	1835	76.3	36.1	53.6	2.1	2458.1	69.7	82.9
2.5	70	1966	71.6	32.1	50.1	1.9	2458.1	65.5	77.8
3	84	2096	67.5	29.3	47.3	1.7	2458.1	61.7	73.3
3.2	90	2145	66.2	28.3	46.8	1.5	2458.1	60.5	71.9
Fraction[d]									
0.04		601	147.5	74.2	126.5	4.5	3200.0	129.2	165.9
0.25		955	124.5	64.7	99.4	4.4	2827.6	111.9	137.1
0.5		1130	109.5	59.2	86.2	2.5	2620.1	99.0	119.9
0.75		1257	101.6	54.8	77.1	2.5	2620.1	92.2	111.0
1		1358	95.5	50.1	72.9	2.5	2620.1	86.8	104.2
1.5		1521	88.1	44.0	65.9	2.8	2620.1	80.2	96.0
2		1653	83.1	40.8	60.7	2.1	2458.1	75.9	90.4
2.5		1746	79.5	38.1	56.3	1.9	2458.1	72.6	86.4
3		1842	75.6	35.2	53.2	1.7	2458.1	69.1	82.2
3.2		1879	74.5	34.5	52.1	1.7	2458.1	68.0	80.9
	Fixed								
	1	630	153.3	77.1	125.5	4.5	3200.0	134.1	172.4
	7	970	125.7	65.5	98.5	4.4	2827.6	113.2	138.2
	14	1115	112.6	60.3	87.8	4.4	2620.1	101.9	123.2
	21	1272	102.3	55.4	75.0	3.9	2620.1	93.0	111.7
	28	1395	95.3	50.5	68.4	3.9	2620.1	86.8	103.9
	42	1599	85.1	42.1	62.2	3.1	2458.1	77.7	92.5
	56	1757	78.9	37.5	55.9	2.9	2458.1	72.1	85.7
	70	1901	73.9	33.5	52.0	2.5	2458.1	67.6	80.2
	84	2028	69.9	30.5	49.3	2.3	2458.1	63.9	75.9
	90	2079	68.2	29.3	47.8	1.5	2458.1	62.4	74.1

n - number of patients, 95L - 95% confidence limited lower limit, 95U - 95% confidence limited upper limit, Min – minimum, Max – maximum, IQR – Interquartile range

Notes

[a] Intermittent OU defined as opioid prescriptions in 180-days prior to index TKA but does not meet criteria for a long-term OU

[b] Long-term OU defined as 90 days of consistent opioid use in 180-days prior to index TKA

[c] Mixed method selects whichever refill gap is greater (fixed or fraction)

[d] Fraction gap based on % length of previous opioid prescription

Supplementary Table 4.2: Duration opioid utilization (days) prior to index procedure based on different refill gaps

Mixed [c]		**Intermittent Opioid User [a]**							**Long-term Opioid User[b]**							
Fraction[c]	Fixed[c]	n	Mean	Min	Max	95L	95U	Utilization [e]	n	Mean	Min	Max	95L	95U	Utilization [e]	p-value
0.04	1	3758	50.3	1.0	178.0	48.8	51.9	28.0%	635	162.5	95.0	180.0	160.7	164.2	90.3%	<0.001
0.25	7	3396	39.5	1.0	164.0	38.3	40.8	22.0%	997	158.6	83.0	180.0	157.1	160.0	88.1%	<0.001
0.5	14	3210	34.9	1.0	162.0	33.7	36.0	19.4%	1183	152.6	67.0	180.0	151.0	154.1	84.8%	<0.001
0.75	21	3044	31.0	1.0	155.0	29.9	32.0	17.2%	1349	146.8	40.0	180.0	145.2	148.5	81.6%	<0.001
1	28	2927	28.5	1.0	147.0	27.5	29.4	15.8%	1466	142.5	32.0	180.0	140.8	144.3	79.2%	<0.001
1.5	42	2715	24.8	1.0	133.0	24.0	25.7	13.8%	1678	134.1	21.0	180.0	132.2	136.0	74.5%	<0.001
2	56	2558	22.5	1.0	119.0	21.7	23.3	12.5%	1835	128.0	13.0	180.0	126.0	129.9	71.1%	<0.001
2.5	70	2427	20.9	1.0	104.0	20.2	21.7	11.6%	1966	122.9	6.0	180.0	120.8	124.9	68.3%	<0.001
3	84	2297	19.7	1.0	93.0	19.0	20.5	11.0%	2096	117.9	1.0	180.0	115.7	120.0	65.5%	<0.001
3.2	90	2248	19.3	1.0	90.0	18.6	20.0	10.7%	2145	116.1	1.0	180.0	113.9	118.2	64.5%	<0.001
Fraction[d]																
0.04		3792	51.4	1.0	180.0	50.5	50.5	28.5%	601	162.3	95.0	180.0	160.5	164.1	90.2%	<0.001
0.25		3438	40.7	1.0	178.0	39.4	42.1	22.6%	955	159.4	83.0	180.0	158.0	160.9	88.6%	<0.001
0.5		3263	36.1	1.0	178.0	34.9	37.2	20.0%	1130	154.6	71.0	180.0	153.1	156.1	85.9%	<0.001
0.75		3136	32.9	1.0	178.0	31.9	34.0	18.3%	1257	150.4	50.0	180.0	148.9	152.0	83.6%	<0.001
1		3035	30.6	1.0	162.0	29.6	31.6	17.0%	1358	146.9	50.0	180.0	145.3	148.5	81.6%	<0.001
1.5		2872	27.3	1.0	154.0	26.4	28.2	15.2%	1521	140.7	40.0	180.0	139.0	142.4	78.2%	<0.001
2		2740	24.9	1.0	154.0	24.0	25.7	13.8%	1653	135.6	13.0	180.0	133.8	137.5	75.4%	<0.001
2.5		2647	23.5	1.0	154.0	22.7	24.3	13.0%	1746	131.9	6.0	180.0	130.0	133.8	73.3%	<0.001
3		2551	22.2	1.0	131.0	21.5	23.0	12.3%	1842	127.9	1.0	180.0	126.0	129.9	71.1%	<0.001
3.2		2514	21.8	1.0	131.0	21.0	22.5	12.1%	1879	126.5	1.0	180.0	124.5	128.4	70.3%	<0.001
	Fixed															
	1	3763	50.5	1.0	178.0	48.9	52.1	28.1%	630	162.4	95.0	180.0	160.7	164.2	90.2%	<0.001
	7	3423	40.3	1.0	166.0	39.0	41.6	22.4%	970	159.3	87.0	180.0	157.9	160.7	88.5%	<0.001
	14	3278	36.6	1.0	166.0	35.4	37.8	20.3%	1115	154.6	67.0	180.0	153.1	156.2	85.9%	<0.001
	21	3121	33.0	1.0	158.0	31.9	34.1	18.4%	1272	148.8	40.0	180.0	147.1	150.4	82.7%	<0.001
	28	2998	30.4	1.0	147.0	29.3	31.4	16.9%	1395	144.3	32.0	180.0	142.6	146.0	80.2%	<0.001
	42	2794	26.7	1.0	135.0	25.8	27.7	14.8%	1599	136.2	21.0	180.0	134.2	138.1	75.6%	<0.001
	56	2636	24.2	1.0	124.0	23.3	25.1	13.4%	1757	130.1	13.0	180.0	128.1	132.1	72.3%	<0.001
	70	2492	22.1	1.0	110.0	21.3	22.9	12.3%	1901	124.8	9.0	180.0	122.7	126.8	69.3%	<0.001
	84	2365	20.8	1.0	96.0	20.0	122.1	11.5%	2028	119.9	7.0	180.0	117.8	122.1	66.6%	<0.001
	90	2314	20.1	1.0	90.0	19.4	20.9	11.2%	2079	118.2	6.0	180.0	116.1	120.3	65.7%	<0.001

n - number of patients, 95L - 95% confidence limited lower limit, 95U - 95% confidence limited upper limit, Min – minimum, Max – maximum, IQR – Interquartile range

Notes

[a] Intermittent OU defined as opioid prescriptions in 180-days prior to index TKA but does not meet criteria for a long-term OU

[b] Long-term OU defined as 90 days of consistent opioid use in 180-days prior to index TKA

[c] Mixed method selects whichever refill gap is greater (fixed or fraction)

[d] Fraction gap based on % length of previous opioid prescription

P value calculated with two-sample Students t-test comparing median dose between two gro

Appendix 5.1: Supplementary Tables

Supplementary Table 5.1: ABJHI selection algorithm to identify elective knee arthroplasty in Alberta, Canada

Cohort Name	Elective Knee Arthroplasty		
Short/Other Name	Knee		
Description	All adult elective knee arthroplasty performed in Alberta		
	Description	**Technical Criteria**	**Technical Detail**
Include	Elective admissions	ADMITCAT=L	L=elective
	Knee arthroplasty performed	PROCCODE1-20 = 1VG53*, 1VA53*, 1VP53* **AND** PROCSTAT <> (A,R)	**ICD-10-CA Codes** 1VG53=implantation, knee 1VP53=implantation, patella **PROCSTAT** A = abandoned R = revision
	Age at admission 18 years or older	AGE_ADMIT >= 18	
Exclude	Cement spacer	1VA53LASLN 1VA53LLSLN 1VG53LASLN **OR** PROCEXT=0	**PROCEXT** 0=cement spacer
	Cases performed at Alberta Children's Hospital	INST=80015	
	Partial hip arthroplasty	1VA53***M*	

Note

Table created and provided by ABJHI

Supplementary Table 5.2: Anatomic therapeutic codes (ATC) used to extract opioid from PIN database

ATC Code	Drug Class
N02AA	Natural opium alkaloids
N02AA01	Morphine
N02AA02	Opium
N02AA03	Hydromorphone
N02AA04	Nicomorphine
N02AA05	Oxycodone
N02AA08	Dihydrocodeine
N02AA10	Papaveretum
N02AA51	Morphine, combinations
N02AA55	Oxycodone, combinations
N02AA58	Dihydrocodeine, combinations
N02AA59	Codeine, combinations excluding pyscholeptics
N02AA79	Codeine, combinations with pyscholeptics
N02AB	Phenylpiperidine derivatives
N02AB01	Ketobemidone
N02AB02	Pethidine
N02AB03	Fentanyl
N02AB52	Pethidine, combinations excluding psycholeptics
N02AB72	Pethidine, combinations with psycholeptics
N02AC	Diphenylpropylamine derivatives
N02AC01	Dextromoramide
N02AC03	Piritramide
N02AC04	Dextropropoxyphene
N02AC05	Bzitraamide
N02AC52	Methadone, combinations exlcuding pyscholeptics
N02AC54	Dextropropoxyphene, combinations excluding psycholeptics
N02AC74	Dextropropoxyphene, combinations with psycholeptics
N02AD	Benzomorphan derivatives
N02AD01	Pentazocine
N02AD02	Phenazocine
N02AE	Oripavine derivatives
N02AE01	Buprenorphine
N02AF	Morphinan derivatives
N02AF01	Butorphanol
N02AF02	Nalbuphine
N02AG	Opioids in combination with antispasmodics
N02AG01	Morphine and antispasmodics
N02AG02	Ketobemidone and antispasmodics
N02AG03	Pethidine and antispasmodics
N02AG04	Hydromorphone and antispasmodics
N02AX	Other opioids
N02AX01	Tilidine
N02AX02	Tramadol
N02AX03	Dezocine
N02AX05	Meptazinol
N02AX06	Tapentadol
N02AX52	Tramadol, combinations
N02AJ01	dihydrocodeine and paracetamol

N02AJ02	dihydrocodeine and acetylsalicylic acid
N02AJ03	dihydrocodeine and other non-opioid analgesics
N02AJ06	codeine and paracetamol
N02AJ07	codeine and acetylsalicylic acid
N02AJ08	codeine and ibuprofen
N02AJ09	codeine and other non-opioid analgesics
N02AJ13	tramadol and paracetamol
N02AJ14	tramadol and dexketoprofen
N02AJ17	oxycodone and paracetamol
N02AJ18	oxycodone and acetylsalicylic acid
N02AJ19	oxycodone and ibuprofen

Supplementary Table 5.3: Comparison of baseline patient characteristics for those included in final study cohort and those with missing data

Variable	Study Cohort (n = 1907)	Missing data (n = 9985)
Age (SD)	66.6 (8.7)	67.1 (9.5)
Sex, n (%)		
Female	1234 (64.7)	5965 (59.7)
Male	673 (35.3)	4020 (40.3)
Comorbidities, n (%)		
Depression	301 (15.8)	1671 (16.7)
Stroke	28 (1.5)	156 (1.6)
Pulmonary disease	168 (8.8)	1123 (11.3)
Cardiac disease	456 (23.9)	2750 (27.5)
Diabetes	388 (20.4)	2215 (22.2)
Renal disease	48 (2.5)	325 (3.3)
Obesity disease	549 (28.8)	2702 (27.1)
Hepatic disease	22 (1.2)	145 (1.5)

Supplementary Table 5.4: Comparison of WOMAC pain and function scores for those included in final study cohort and those with missing data

		Study Cohort (n = 1907)		Missing WOMAC data	
WOMAC Score	Time Point	n	Mean [95% CI]	n	Mean [95% CI]
Pain	Preoperative	1907	45.85 [45.04, 46.65]	5760	44.87 [44.40, 45.34]
	12-months postoperatively	1907	78.02 [77.02, 79.02]	1109	77.77 [76.42, 79.11]
Function	Preoperative	1907	45.54 [44.76, 46.31]	7114	44.87 [44.40, 45.34]
	12-months postoperatively	1907	76.78 [75.81, 77.75]	1106	76.51 [75.25, 77.78]

Notes

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; n number of patients

Supplementary Table 5.5: Interaction model with adjusted parameter estimates for 12-months postoperative WOMAC function scores

Variable	Estimate	Standard Error	p-value
Age	0.007	0.055	0.905
Sex	0.638	0.983	0.517
Preoperative Pain Score	0.358	0.027	<.001
Opioid Naive	*1 [Reference]*		
Intermittent Opioid User	-3.522	1.193	0.003
Long-term Opioid User	-5.706	2.261	0.012
Diabetes	1.126	1.643	0.493
Depression	-2.442	1.153	0.034
Pulmonary disease	-3.117	1.644	0.058
Cardiac disease	-2.037	1.124	0.070
Depression*Intermittent Opioid User	-10.398	2.892	<.001
Depression*Long-term Opioid User	-9.183	4.243	0.031

Notes

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; n number of patients

Supplementary Table 5.6: Interaction model with adjusted parameter estimates for 12-months postoperative WOMAC pain scores

Variable	Estimate	Standard Error	p-value
Age	0.096	0.058	0.096
Sex	0.044	1.032	0.966
Preoperative Pain Score	0.316	0.028	<.001
Opioid Naive	*1 [Reference]*		
Intermittent Opioid User	-2.869	1.253	0.022
Long-term Opioid User	-5.972	2.368	0.012
Diabetes	-3.632	1.207	0.003
Depression	0.695	1.721	0.686
Pulmonary disease	-3.467	1.722	0.044
Cardiac disease	-2.246	1.178	0.057
Liver Disease	-7.485	4.539	0.099
Depression*Intermittent Opioid User	-8.842	3.030	0.004
Depression*Long-term Opioid User	-7.324	4.439	0.099

Notes

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; n number of patients

Appendix 6.1: Analysis of regression models

Overview of Variable Selection

- Several variable selection methods were performed
    - Forward, Backward, and Stepwise using conventional method
    - Forward, Backward, and Stepwise using adjusted R-square, AIC, BIC, SBC, Mallows's Cc(p), CV as criteria
    - Bootstrap stepwise method where No. of bootstrap sample N=1,000.
- Table 1 below shows the result of variable selection using bootstrap stepwise selection method (N=1,000)
    - For instance, across all models "Pre WOMAC Pain and Function Score" variable was selected from every bootstrap sample (Selected %=100) and significant (Significance %=100).
    - From main effect model with WOMAC Pain at 12 months as outcome, "opioid_1" variable was selected 996 times (selected %=98.7) out of N=1,000 bootstrap samples and 96.9% of those were significant.
- For main and interaction effect model,
    - Diagnostic plots and influential plot (based on Cook's Distance) to explore influential case were examined.

Supplementary Table 6.1: Result of variable selection using bootstrap stepwise

Outcome	Covariates	Main effect model		Covariates	Interaction effect model	
		Selected (%)	Sig. (%)		Selected (%)	Sig. (%)
WOMAC Pain	**Pre WOMAC Pain**	**100.0**	**100.0**	**Pre WOMAC Pain**	**100.0**	**100.0**
	Intermittent OU	**98.7**	**96.9**	**Depress_Op1**	**93.6**	**93.1**
	Long-term OU	**98.7**	**96.3**	**cihidiabetes**	**92.9**	**89.7**
	Diabetes	**92.2**	**89.7**	**Long-term OU**	**86.7**	**87.2**
	Depression	**71.0**	**73.9**	**Intermittent OU**	**81.2**	**78.8**
	Cardiac History	**70.5**	**70.8**	**Pulmonary Disease**	**68.1**	**72.7**
	Pulmonary Disease	**66.7**	**69.6**	**Cardiac History**	**66.1**	**69.7**
	Liver Disease	**62.5**	**67.3**	**Depress_Op2**	**60.4**	**68.7**
	Age	**61.8**	**64.9**	**Liver Disease**	**60.3**	**68.4**
	Renal Disease	34.2	45.9	**Age**	**58.5**	**65.0**
	Obesity	18.4	39.7	Renal Disease	31.5	43.8
	Stroke	15.4	31.8	Depression	19.2	43.8
	Sex	14.2	28.9	Obesity	18.7	40.6
				Stroke	15.7	31.2
				Sex	15.2	30.9
WOMAC Function	**Intermittent OU**	**100.0**	**100.0**	**WOMAC function**	**100.0**	**100.0**
	WOMAC Function	**100.0**	**99.6**	**Depress_Op_1**	**97.6**	**96.4**
	Long-term OU	**99.2**	**97.7**	**Intermittent OU**	**93.5**	**88.5**
	Depression	**74.5**	**74.5**	**Long-term OU**	**84.9**	**85.4**
	Diabetes	**71.6**	**73.9**	**Depress_Op_2**	**73.6**	**77.3**
	Pulmonary Disease	**65.4**	**67.5**	**Diabetes**	**71.4**	**75.4**
	Cardiac History	**64.3**	**65.6**	**Pulmonary**	**67.7**	**70.5**
	Liver Disease	44.3	55.3	**Cardiac Disease**	**60.0**	**69.0**
	Obesity	35.6	48.6	Liver Disease	44.3	53.3
	Renal Disease	26.0	36.5	Obesity	37.5	50.4
	Sex	22.2	36.5	Depression	23.0	44.5
	Age	18.8	31.9	Sex	22.9	39.1
	Stroke	12.4	25.8	Renal Disease	22.0	36.2
				Age	18.5	30.9
				Stroke	14.5	26.9

Abbreviations

OU – Opioid User, Depress_Op_1- Interaction effect term between Depression and Long-term OU, Depress_Op_2 - Interaction effect term between Depression and Intermittent OU

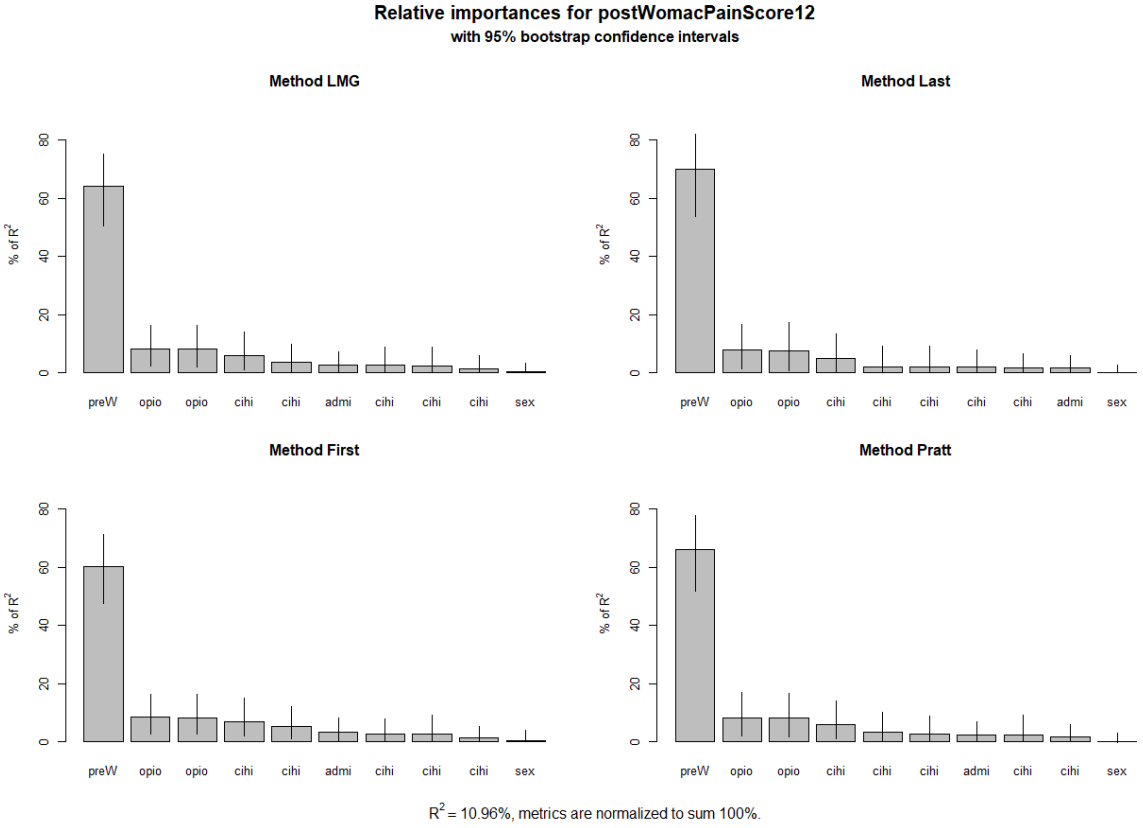
Results of linear regression model (Outcome: WOMAC Pain Score at 12 months)

Supplementary Table 6.2: Final model for WOMAC Pain

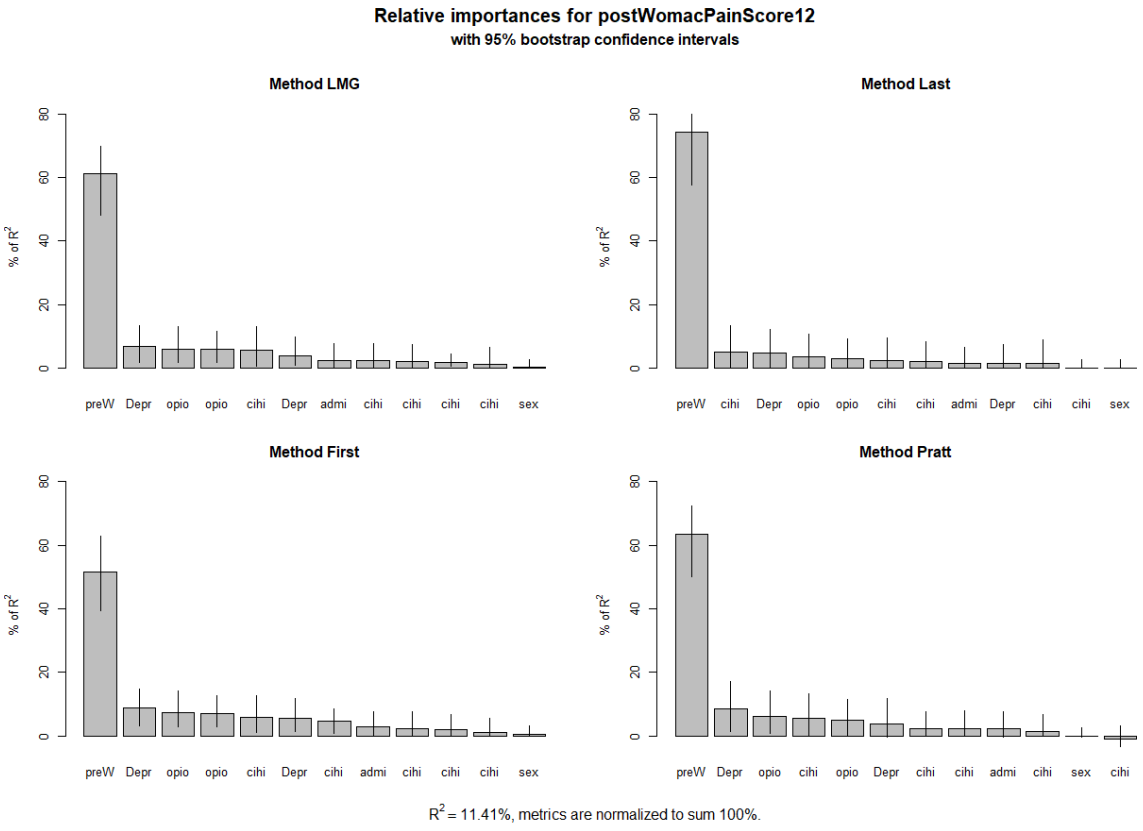
Model	Variable	Estimate	SE	t Value	Pr > |t|
Main effect (R^2=10.96, Adjusted R^2=10.50)	Intercept	60.582	3.942	15.370	<.001
	Age	0.100	0.058	1.730	0.085
	Sex	-0.016	1.034	-0.020	0.988
	Pre WOMAC Pain	0.316	0.028	11.390	<.001
	Intermittent OU	-4.337	1.145	-3.790	0.000
	Long-term OU	-7.646	2.016	-3.790	0.000
	Diabetes	-3.671	1.209	-3.040	0.002
	Depression	-2.591	1.354	-1.910	0.056
	Cardiac History	-2.338	1.180	-1.980	0.048
	Pulmonary Disease	-3.325	1.724	-1.930	0.054
	Liver Disease	-7.983	4.542	-1.760	0.079
Interaction effect (R^2=11.41, Adjusted R^2=10.85)	Intercept	60.309	3.936	15.320	<.001
	Age	0.096	0.058	1.670	0.096
	Sex	0.044	1.032	0.040	0.966
	Pre WOMAC Pain	0.316	0.028	11.430	<.001
	Intermittent OU	-2.869	1.253	-2.290	0.022
	Long-term OU	-5.972	2.368	-2.520	0.012
	Diabetes	-3.632	1.207	-3.010	0.003
	Depression	0.695	1.721	0.400	0.686
	Pulmonary Disease	-3.467	1.722	-2.010	0.044
	Cardiac History	-2.246	1.178	-1.910	0.057
	Liver Disease	-7.485	4.539	-1.650	0.099
	Depress_Op1[1]	-8.842	3.030	-2.920	0.004
	Depress_Op2[2]	-7.324	4.439	-1.650	0.099

Notes
[1] Interaction effect term between "cihidepression" and "opioid_1"
[1] Interaction effect term between "cihidepression" and "opioid_2

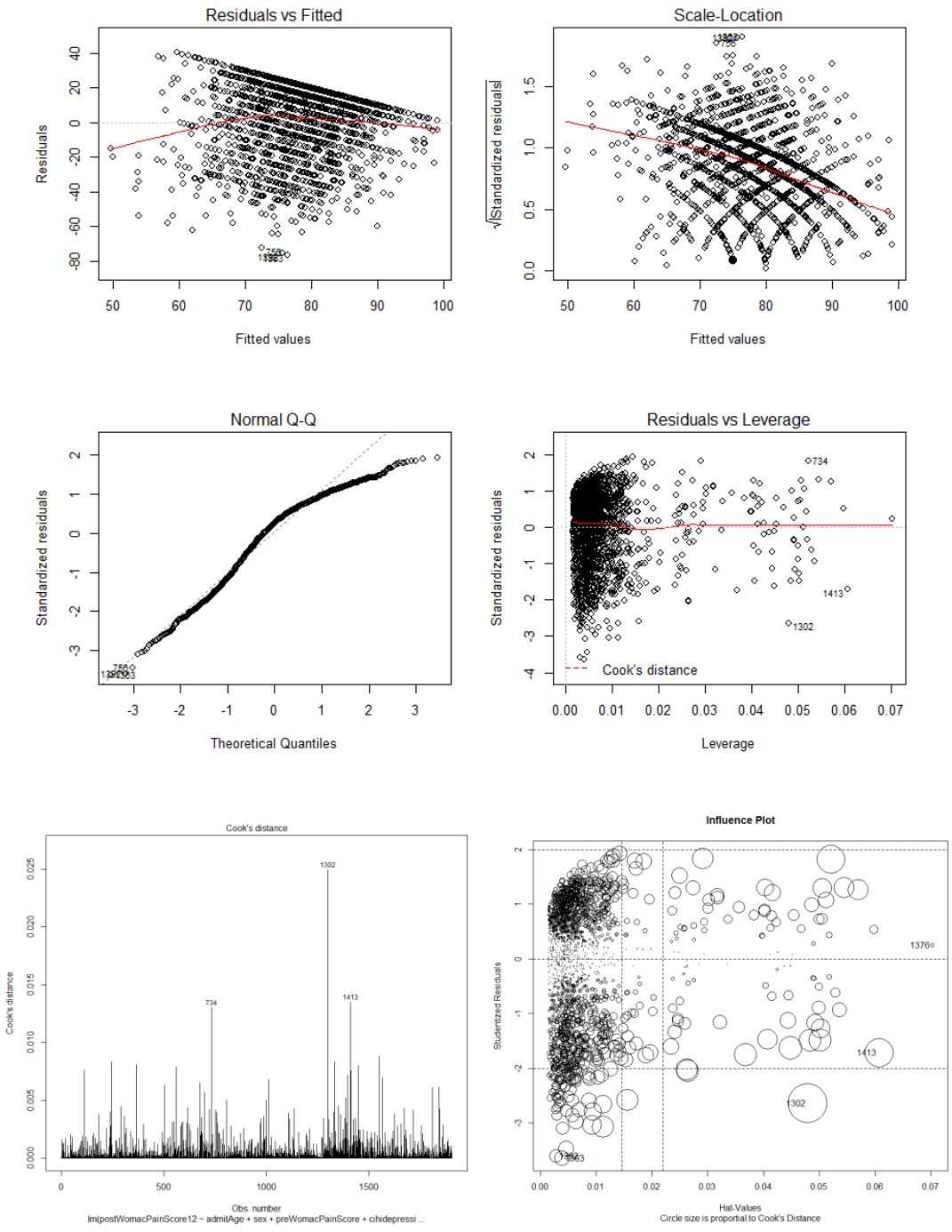
After considering results of variable selection outputs and further model implementation, final main and interaction effect model were generated as shown in Table 2 above for WOMAC Pain score at 12 months



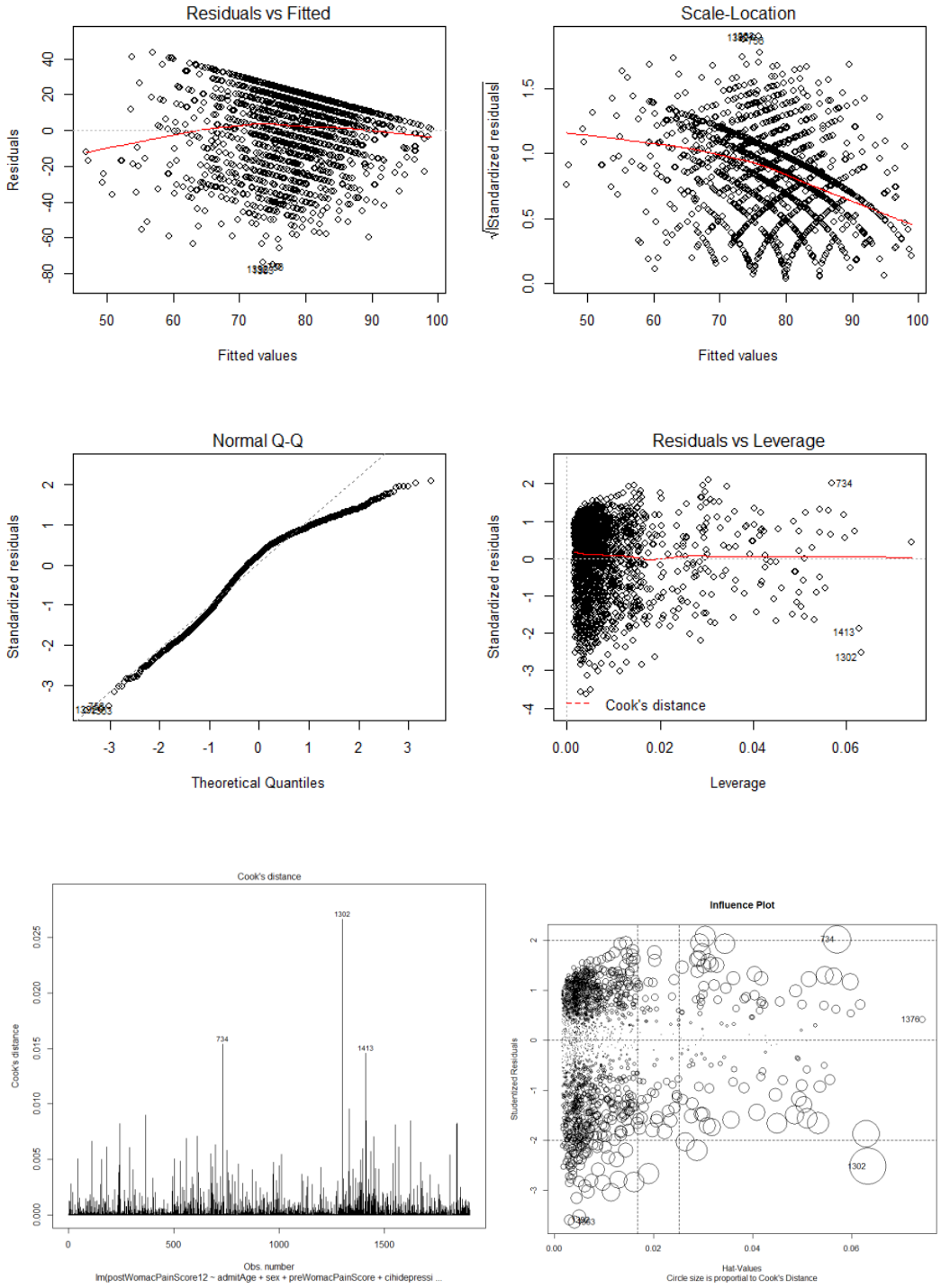
Supplementary Figure 6.1: Relative importance plot for main effect model (Womac Pain)



Supplementary Figure 6.2: Relative importance plot for interaction effect model (WOMAC Pain)



Supplementary Figure 6.3: Diagnostic plots main effect model (WOMAC Pain)



Supplementary Figure 6.4: Diagnostic plots interaction effect model (WOMAC Pain)

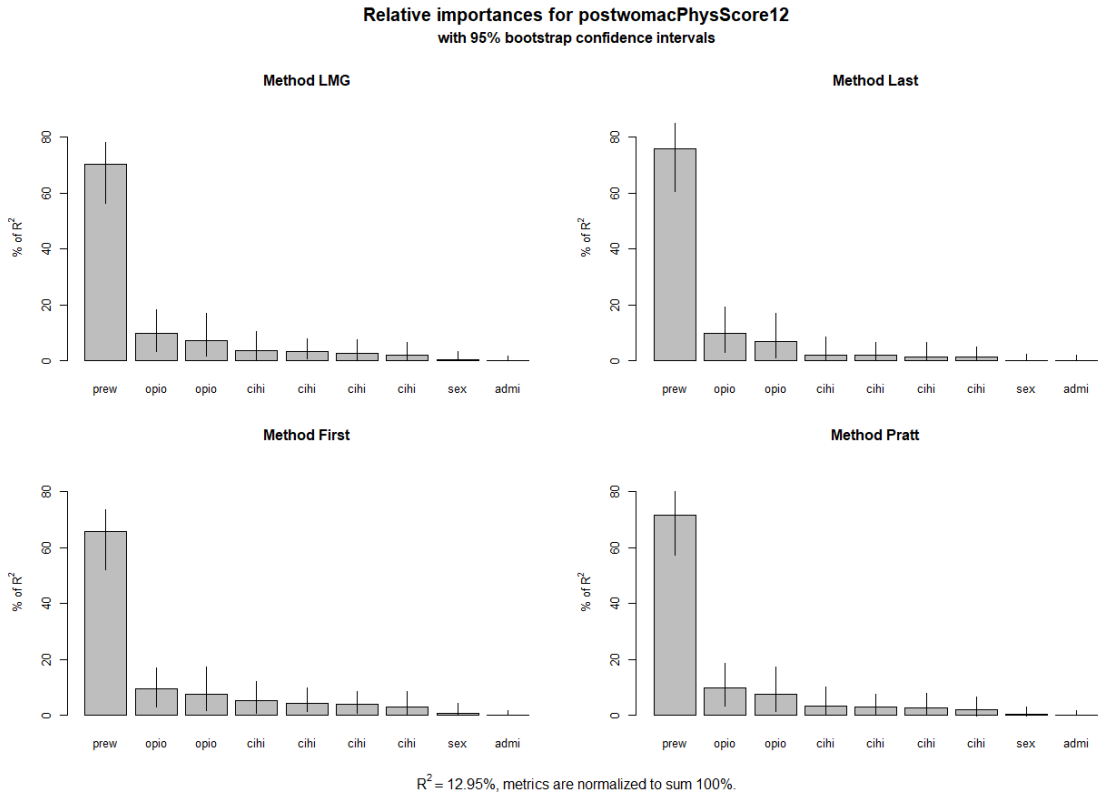
Supplementary Table 6.3: Results of linear regression model (Outcome: WOMAC Function Score at 12 months)

Model	Variable	Estimate	SE	t Value	Pr > |t|
Main effect (R^2=12.95, Adjusted R^2=12.53)	Intercept	62.943	3.885	16.200	<.001
	Age	0.011	0.055	0.200	0.845
	Sex	0.554	0.986	0.560	0.574
	Pre WOMAC Function	0.361	0.027	13.260	<.001
	Intermittent OU	-5.236	1.093	-4.790	<.001
	Long-term OU	-7.818	1.928	-4.050	<.001
	Depression	-2.798	1.295	-2.160	0.031
	Diabetes	-2.480	1.156	-2.150	0.032
	Pulmonary Disease	-2.937	1.649	-1.780	0.075
	Cardiac History	-2.148	1.127	-1.910	0.057
Interaction effect (R^2=13.63, Adjusted R^2=13.12)	Intercept	62.778	3.873	16.210	<.001
	Age	0.007	0.055	0.120	0.905
	Sex	0.638	0.983	0.650	0.517
	Pre WOMAC Function	0.358	0.027	13.200	<.001
	Intermittent OU	-3.522	1.193	-2.950	0.003
	Long-term OU	-5.706	2.261	-2.520	0.012
	Depression	1.126	1.643	0.690	0.493
	Diabetes	-2.442	1.153	-2.120	0.034
	Pulmonary Disease	-3.117	1.644	-1.900	0.058
	Cardiac History	-2.037	1.124	-1.810	0.070
	Depress_Op1	-10.398	2.892	-3.600	0.000
	Depress_Op2	-9.183	4.243	-2.160	0.031

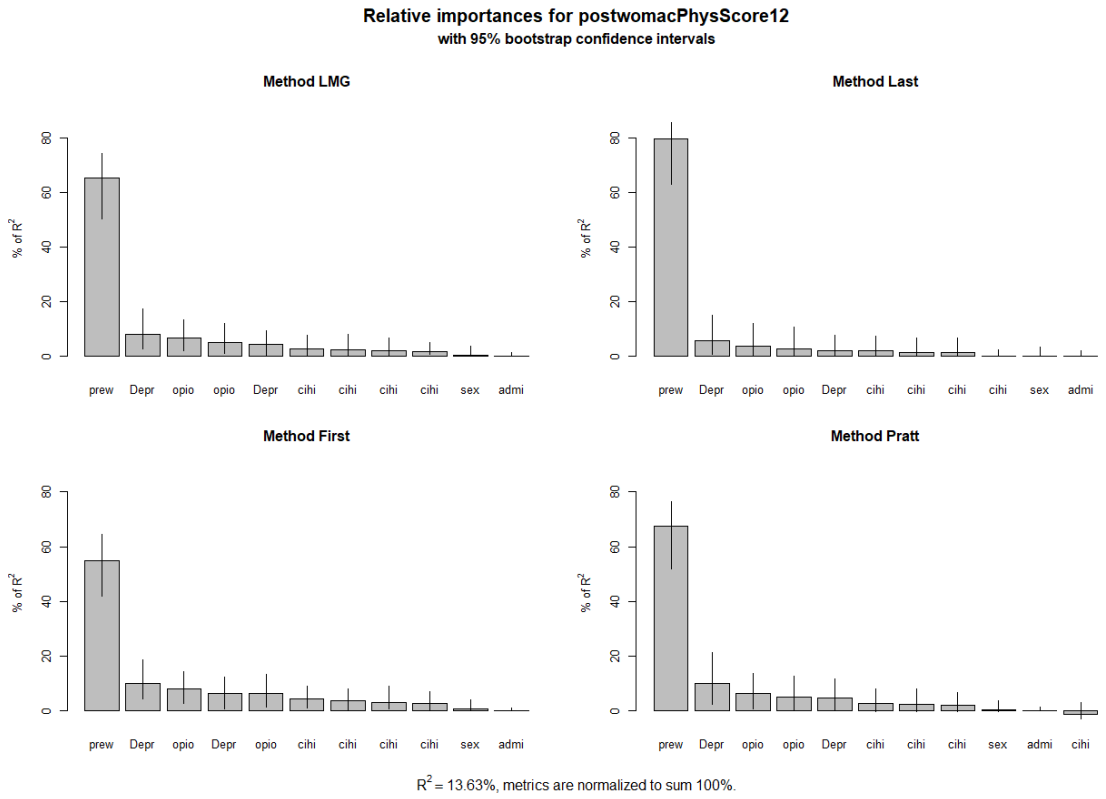
Abbreviations

OU – Opioid User, Depress_Op_1- Interaction effect term between Depression and Long-term OU, Depress_Op_2 - Interaction effect term between Depression and Intermittent OU

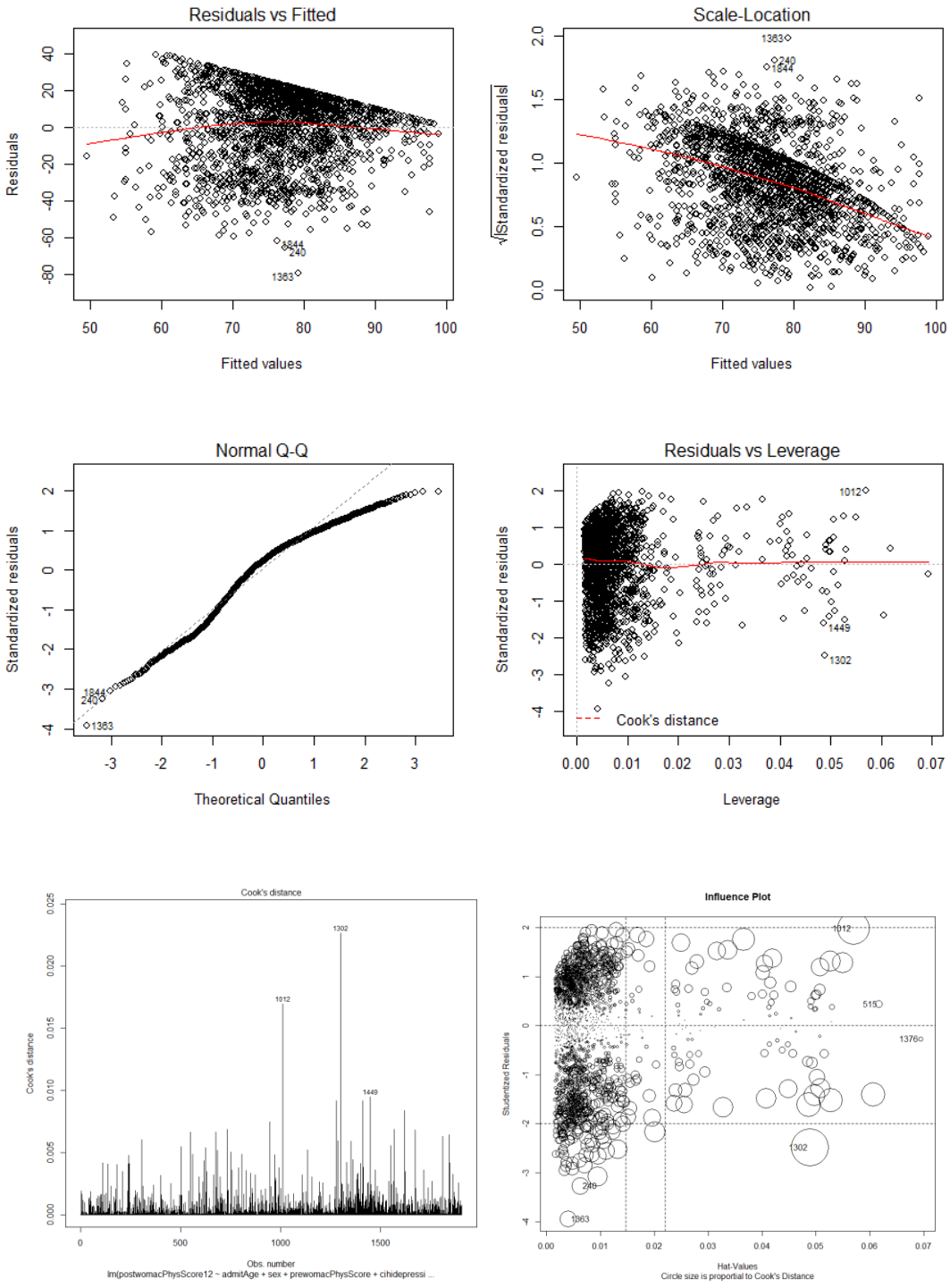
After considering results of variable selection and further model implementation, final main and interaction effect model were generated as shown in Table 3 above for WOMAC Function score at 12 months as outcome



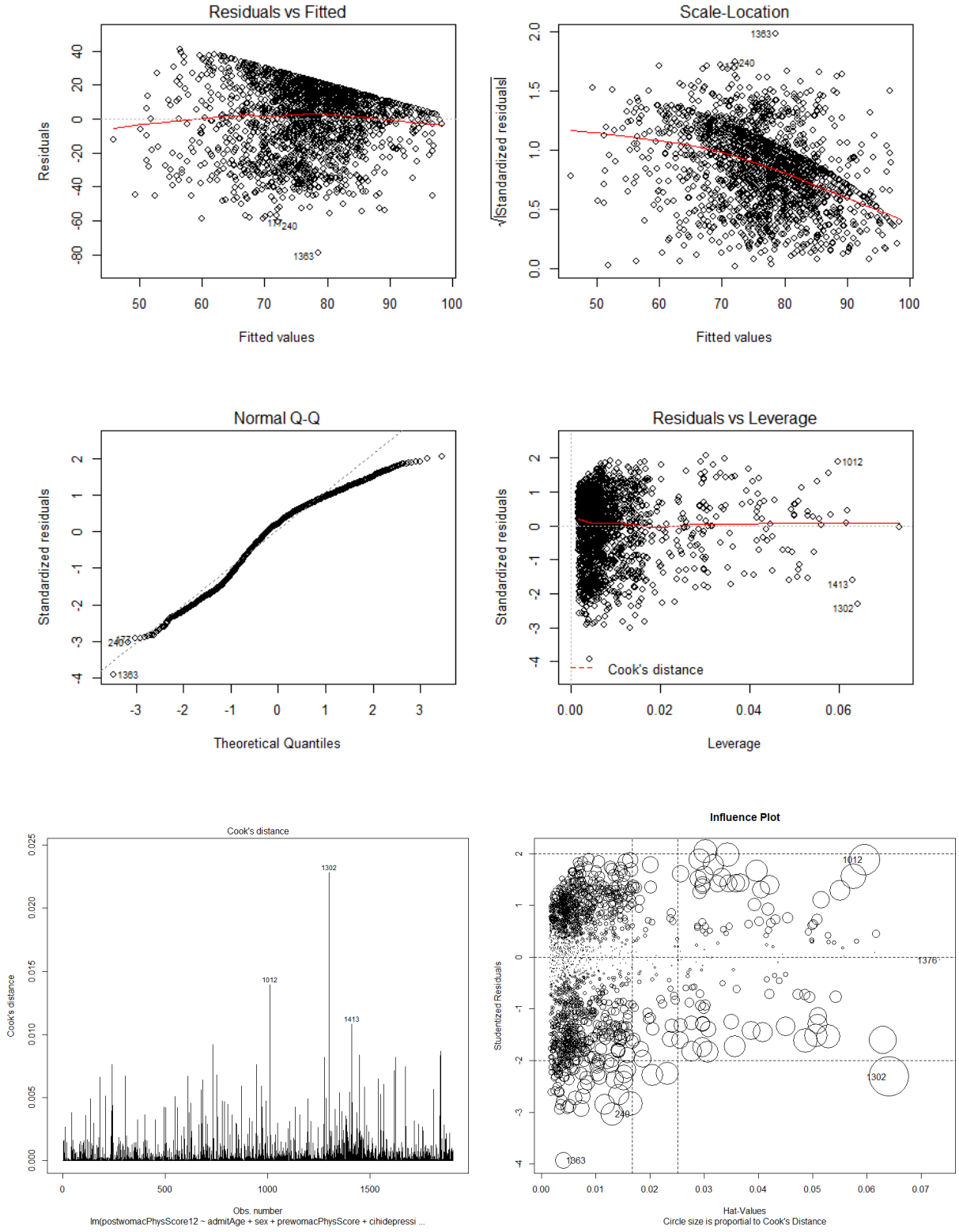
Supplementary Figure 6.4: Relative importance plot main effect model (WOMAC Function)



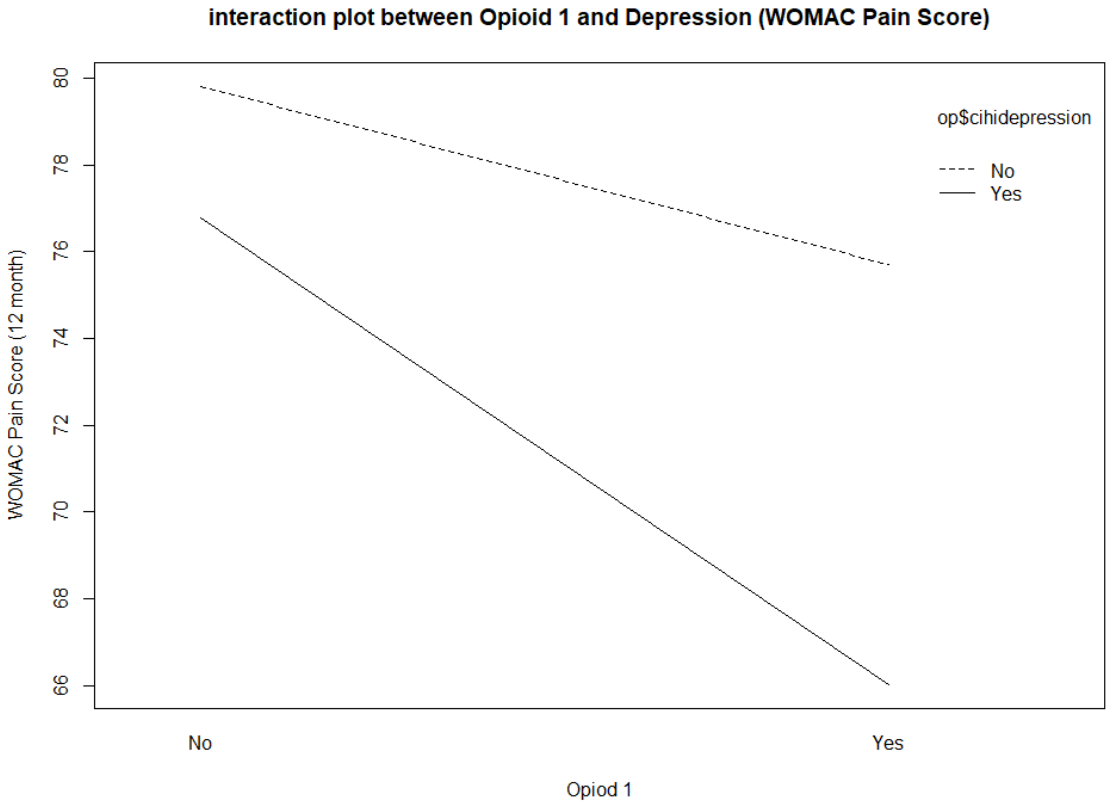
Supplementary Figure 6.5: Relative importance plot interaction effect model (WOMAC Function)



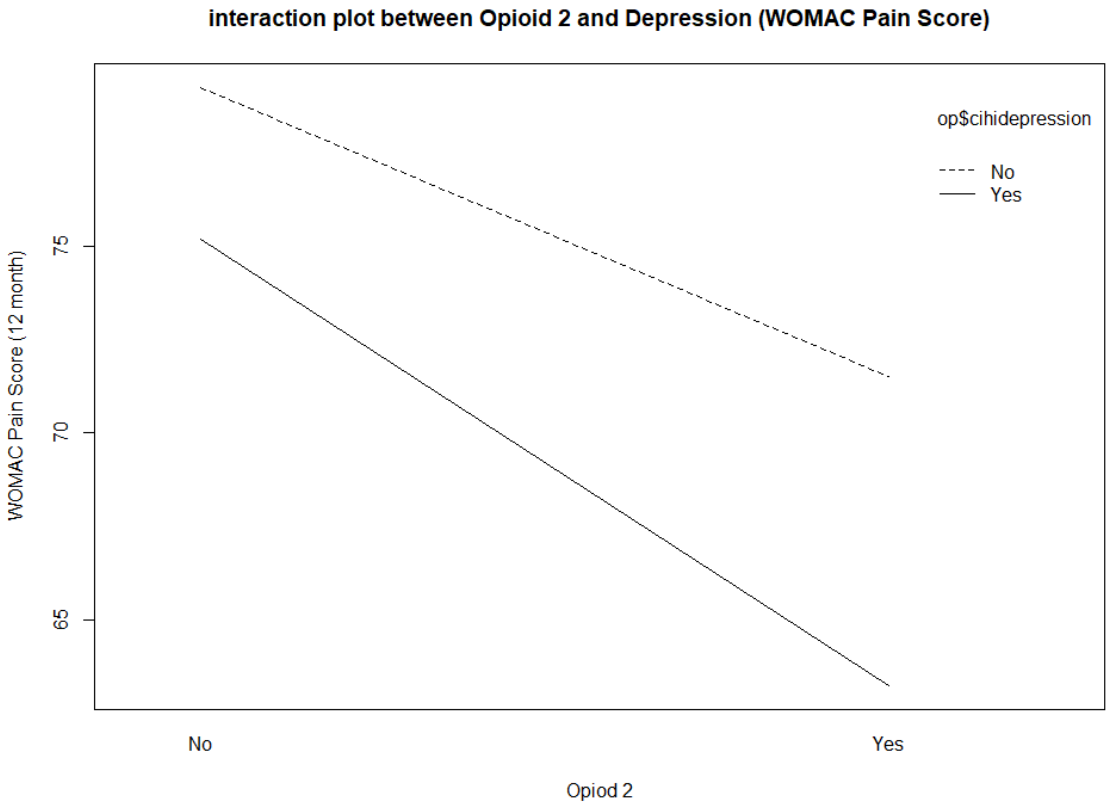
Supplementary Figure 6.6: Diagnostic plots main effect model (WOMAC Function)



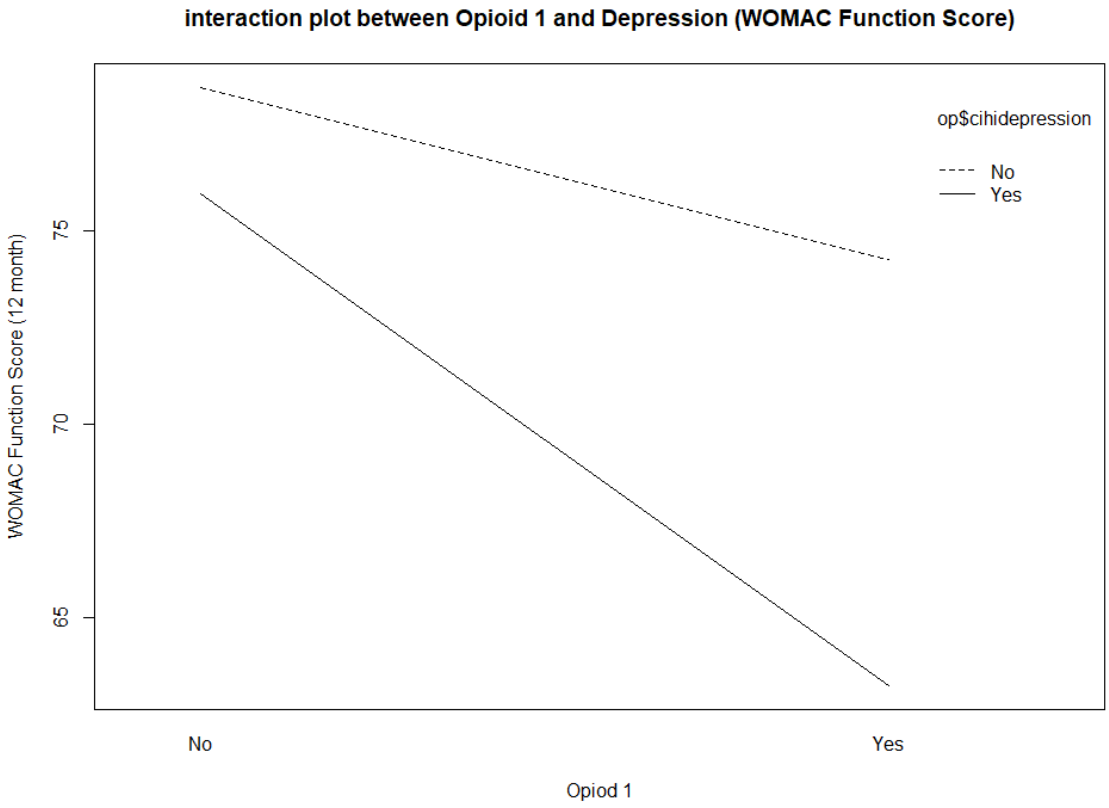
Supplementary Figure 6.7: Diagnostic plots interaction effect model (WOMAC Function)



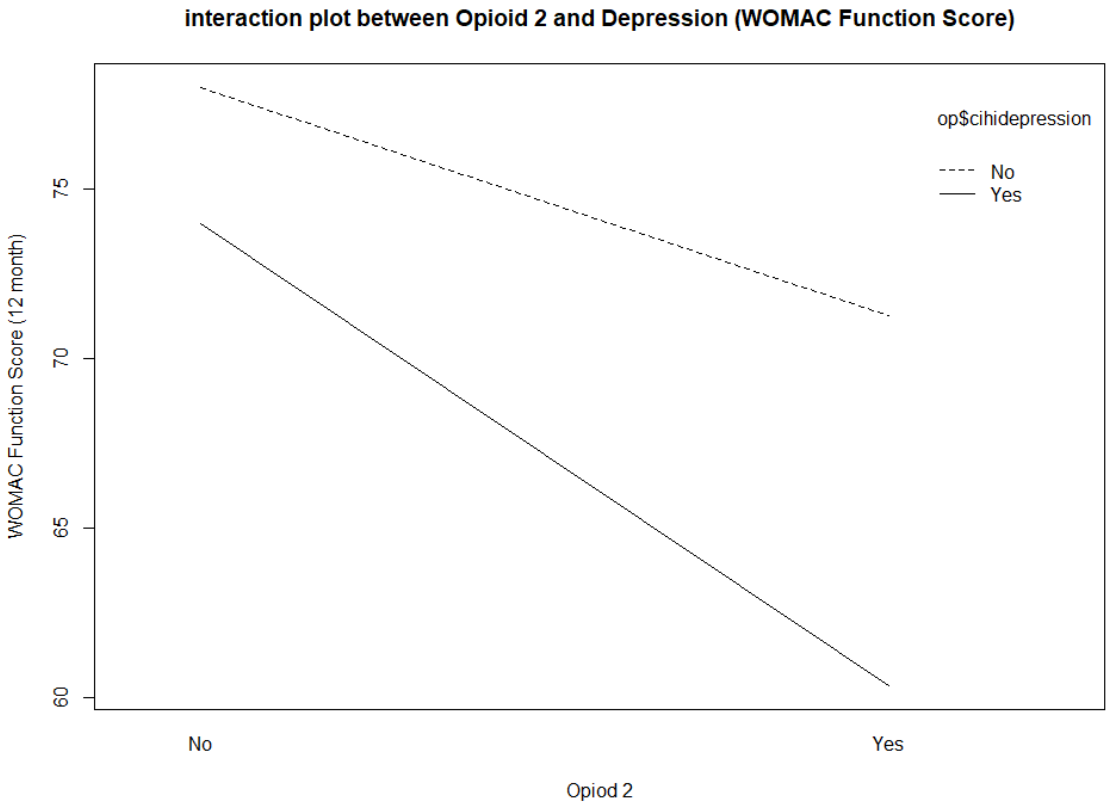
Supplementary Figure 6.8: Interaction plot between intermittent opioid users (Opioid_1) and Depression (Outcome WOMAC Pain score)



Supplementary Figure 6.9: Interaction plot between long-term opioid users (Opioid_2) and Depression (Outcome WOMAC Pain score)



Supplementary Figure 6.10: Interaction plot between intermittent opioid users (Opioid_1) and Depression (Outcome WOMAC Function score)



Supplementary Figure 6.11: Interaction plot between long-term opioid users (Opioid_2) and Depression (Outcome WOMAC Function score)