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Original Article

Factors associated with persistent opioid use 6–12 months after primary total knee arthroplasty

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Summary

Persistent pain following knee arthroplasty occurs in up to 20% of patients and may require ongoing analgesia, including extended opioid administration. A comprehensive secondary analysis was performed from results of a study that considered persistent postoperative pain in 242 patients who underwent unilateral knee arthroplasty using a standardised enhanced recovery programme. Opioid prescribing for 12 months before and 12 months after surgery was evaluated and converted to oral morphine equivalents. Demographic, functional, psychological and pain questionnaires were completed along with quantitative sensory testing and genetic analysis. Forty-nine percent of patients had at least one opioid prescription in the 12 months before surgery. Opioid prescriptions were filled in 93% of patients from discharge to 3 months and in 27% of patients ≥6 months after surgery. Persistent opioid use ≥6 months after surgery was strongly associated with pre-operative opioid use (RR 3.2, $p < 0.001$ (95%CI 1.9–5.4)). The median (IQR [range]) oral morphine equivalent daily dose was 3.6 (0.9–10.5 [0–100.0]) mg pre-operatively, 35.0 (22.5–52.5 [4.6–180.0]) mg in hospital, 12.8 (5.1–24.8 [0–57.9]) mg from discharge to 3 months and 5.9 (4.5–12.0 [0–44.5]) mg at ≥6 months following surgery. Predictors of increased daily oral morphine equivalent ≥6 months after surgery included increased average daily oral morphine equivalent dose compared with previous values (lag), increased body mass index and three or more comorbid pain sites. Persistent opioid use was not associated with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (RR 1.003, $p = 0.655$, 95%CI 0.65–1.002) or WOMAC function (RR 1.001, $p = 0.99$, 95%CI 0.99–1.03) outcomes 6 months after surgery. There was no association between persistent opioid use and pre-operative quantitative sensory testing results or psychological distress. Pre-operatively, patients with a higher body mass index, more comorbid pain sites and those who had filled an opioid prescription in the last 12 months, were at increased risk of persistent opioid use and a higher oral morphine equivalent daily dose ≥ 6 months after surgery. Strategies need to be developed to limit dose and duration of persistent opioid use in patients following knee arthroplasty surgery.

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Introduction

Total knee joint arthroplasty is a common procedure undertaken for symptomatic and functional improvement of knee osteoarthritis. Given an increasingly overweight and elderly population, the number of people presenting for arthroplasty is projected to increase significantly over the next 20 years [1].

While multimodal analgesia has been proposed to manage acute postoperative pain, oral opioids are almost always a central component of this treatment [2]. There is evidence that despite surgery, knee pain can persist postoperatively and, in some cases, be worse than pre-operative levels. In addition, persistent opioid use may continue far past that expected from a normal postoperative trajectory [3], potentially leading to long-term opioid harm, including a predisposition to chronic postsurgical pain [4]. Recent international guidelines recommend a combination of non-pharmacological and pharmacological management of osteoarthritis pain [5, 6]. Opioids are either not recommended [7] or have limited support as a second- or third-line treatment option [8]. Despite this clinical guidance, many patients with osteoarthritis are prescribed opioids before their surgery and this may be exacerbated by delays in surgery, currently further aggravated by the COVID-19 pandemic [9]. The majority of previous studies looking at persistent postoperative opioid use after total knee arthroplasty originate from the USA using large institutional or insurance databases [10]. Most studies focus on associations between opioid prescribing patterns and demographic factors, with few undertaking a comprehensive analysis of other potential risk factors that may influence prescribing patterns (e.g. psychological, genetic and neurophysiological factors) in the same standardised population.

The aims of this study were to: determine the proportion of patients undergoing primary total knee arthroplasty who become persistent opioid users in a New Zealand population (i.e. filling an opioid prescription 6–12 months after surgery); examine the relationships between pre-operative opioid use and persistent postoperative opioid use and examine specific opioid prescribing patterns; examine differences in pain and function outcomes in persistent opioid users vs non-users at 6 months following surgery; and explore pre-operative and peri-operative predictors of persistent opioid use, specifically the role of genetics, quantitative sensory testing and psychological factors.

Methods

This study was a secondary analysis of data from a prospective cohort study of patients undergoing primary total knee arthroplasty [11]. Data collection and secondary analysis were approved by the New Zealand Northern Regional Y Ethics Committee. All patients from the original cohort study (n = 300) were approached to provide additional written, informed consent to access their medical records, including all prescriptions filled in the 12 months before and 12 months after their total knee arthroplasty surgery. Inclusion criteria for the original cohort were planned primary unilateral total knee arthroplasty and being fluent in English. Exclusion criteria were age < 18 y; diagnosed learning disability; Raynaud's syndrome; unsuitable for neuraxial anaesthesia; a diagnosed neurological condition that may affect quantitative sensory testing; or revision surgery within the follow-up period. Patients were recruited between November 2012 and September 2015 from the Waitematā District Health Board, Auckland, New Zealand. Consenting patients attended a pre-operative assessment session in the 2 weeks before surgery. Clinical information was collected, questionnaires completed, quantitative sensory testing procedures undertaken, and a 6 ml blood sample collected for subsequent genetic analysis. Acute postoperative pain was measured on days 1, 2, 3, 7 and 14 after surgery. Follow-up questionnaires were sent to patients 6 months after surgery. The predictors of persistent pain outcomes have previously been published along with the full methodology [11].

All patients underwent unilateral, cemented total knee arthroplasty and followed a standardised enhanced recovery after surgery protocol. All patients had multimodal postoperative analgesia including regular oral paracetamol, non-steroidal anti-inflammatory drugs and oral opioids (oxycodone) as required. Gabapentin was available as `rescue´ medication only.

A record of all prescriptions filled in the 12 months before and the 12 months after the index primary total knee arthroplasty was obtained for each participant from the New Zealand National Prescription Database. All filled opioid

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prescriptions were extracted, including paracetamol plus codeine; ibuprofen plus codeine; codeine phosphate; dihydrocodeine tartrate; tramadol; morphine (rapid and controlled release); oxycodone (rapid and controlled release); and fentanyl patches. Oral morphine equivalents were calculated using a standard conversion table [12]. An oral morphine equivalent daily dose was then calculated by summing the total dose based on the quantity of supply and dividing by the number of days in each period of interest. The number of prescriptions filled and oral morphine equivalent daily dose were calculated for the 12 months before surgery, from hospital discharge to 3 months, 3–6 months, and ≥6 months after surgery. In-hospital opioid use was collected separately from the medical record and converted into an oral morphine equivalent daily dose using the same conversion table and the recorded length of in-hospital stay as the divisor. Any opioid prescription occurring ≤3 months after another hospital admission or surgical procedure in the 12 months after the index total knee arthroplasty were discarded and not included in the final analysis.

Age, sex and pre-operative BMI were collected. The Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain scale was completed to obtain a measure of pre-operative knee pain intensity. The WOMAC pain (0–100) and function scale (0–100) was used to assess pain and disability 6 months after total knee arthroplasty. A pre-operative comorbid pain score was calculated by counting the number of additional pain sites where pain was present for 1 month or longer and rated ≥3/10. The Leeds Assessment of Neuropathic Signs and Symptoms Pain Questionnaire (LANSS) was completed pre-operatively and was utilised both to identify participants with `likely neuropathic pain´ before surgery (cut point of ≥12), and as a predictor (continuous score) of persistent postoperative pain.

The Pain Catastrophising Scale, Beck Depression Inventory-2 and State Trait Anxiety Inventory were completed pre-operatively. Both State Anxiety and Trait Anxiety scores were calculated from the State Trait Anxiety Inventory. The total Pain Catastrophising Scale score, as well as the magnification, rumination and helplessness sub-scores were calculated. Expected pain was also measured using a single question, ``*Please indicate the level of pain you think you will experience in your operated knee 6 months after your surgery?*´´, scored on a 0–10 numerical rating scale (0 = no pain; 10 = extreme pain).

Quantitative sensory testing involved measuring temporal summation and pressure pain thresholds. Temporal summation was calculated as the difference in pain intensity (0 = no pain; 100 = worst pain imaginable) between the 10th stimulus of a 1 Hz train of stimuli and a single stimulus to a 1 cm^2 area of the skin over the medial joint line using a #6.45 (180 g) monofilament. Pressure pain threshold was measured over the contralateral shoulder (midway between the C7 spinous process and acromion) and the affected knee (medial joint line). A handheld pressure algometer (Sbmedic, Solna, Sweden) with a 1 cm^2 probe and ramping rate of 30 $kPa.s^{-1}$ was used (range 0–2000 kPa). Patients were instructed to push a button when the sensation `first becomes painful´. The pressure pain threshold was taken as the average of three measures at each site, with a 30 s rest given between measures. Conditioned pain modulation was assessed by immersing the contralateral hand in cold water (8 ± 2 °C) until a cold pain of ≥3/10 was reported. At this time, the pressure pain threshold was repeated at the knee. Conditioned pain modulation is presented as absolute change (in kPa) and percentage change in knee pressure pain threshold during cold water immersion (the conditioned stimulus) compared with knee pressure pain threshold alone (the test stimulus) and multiplied by −1, so that negative values indicated inhibition.

Deoxyribonucleic acid was extracted from EDTA-treated whole blood and genotyped for the opioid receptor mu-1 (OPRM1, rs1799971) and catechol-o-methyltransferase (COMT, rs4680) single nucleotide polymorphisms as described previously [11]. Peri-operative factors including the total surgical time (min), patella resurfacing (yes/no) and anaesthetic type (combined spinal epidural; spinal plus local infiltration analgesia or other) were collected from medical records.

The primary outcome was persistent opioid use ≥6 months after primary total knee arthroplasty.

Secondary outcomes included the WOMAC pain (0–100) and function scale (0–100) 6 months after total knee arthroplasty.

Descriptive, between-group comparisons were carried out using the Mann–Whitney U-test as most data were skewed. Univariate, RR models were applied to assess the risk of persistent opioid use (yes/no) ≥6 months after surgery. The predictors applied to each of these models were naïve pre-operative opiate use (naïve vs. not naïve), the WOMAC pain at 6 months and WOMAC function measures 6 months postoperatively. The WOMAC models were controlled for baseline values. Models were also run for sensory variables (LANSS, temporal summation and conditioned pain modulation), as well as COMT and OPRM1 biomarkers.

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Repeated measures logit models were applied, evaluating covariates associated with naïve, pre-operative opiate use (naïve vs. not naïve). These models were stratified to account for confounding.

Multivariate repeated measures generalised least squares model with AR (1) autocorrelation were carried out to evaluate predictors of increased average daily oral morphine equivalent. These models were carried out with average daily oral morphine equivalent treated as a lag variable. Models were evaluated for confounding and differential treatment effects, using inverse probability treatment weights. These did not alter overall results, so models presented are reported without using inverse probability treatment weights. Statistical analyses were carried out using Stata version 16 (StataCorp, College Station, TX, USA).

Results

Of 300 patients approached from the original cohort, 242 provided informed consent for this study. Participant characteristics are provided in Table 1. WOMAC pain and function outcomes were obtained from 238 patients (98%) 6 months after surgery.

The number (proportion) of OPRM1 (rs1799971) alleles were, A/A 190 (79%), A/G 51 (21%), G/G 1 (< 1%). The number (proportion) of COMT (rs4680) alleles were, A/A 47 (19%), A/G 113 (47%), G/G 82 (34%). No genotype frequencies deviated from Hardy Weinberg Equilibrium ($p > 0.26$).

The number of participants taking opioids across different pre-operative and postoperative time periods is provided in Table 2. Forty-nine percent of participants filled ≥1 opioid prescription in the 12 months before surgery, while 51% were opioid naïve during this period. All participants had opioids during their hospital stay and the vast majority (93%) filled ≥1 opioid prescription after discharge, with 35% filling at least one opioid prescription ≥3 months after surgery. Twenty-seven percent of all participants (n = 65) were considered persistent opioid users, filling at least one opioid prescription ≥6/12 after surgery (Table 2). The median (IQR [range]) daily oral morphine equivalent was 3.6 (0.9–10.9 [0–100.0]) mg pre-operatively, 35.0 (22.5–52.5 [4.6–180.0]) mg in hospital, 12.8 (5.1–24.8 mg [0–57.9]) mg from discharge to 3 months after surgery, 11.1 (4.4–20.4 [0–78.4]) mg from 3–6 months after surgery and 5.9 (4.5–12.0 [0–44.5]) mg from 6–12 months after surgery.

Overall, 42% (49) of participants who filled ≥1 opioid prescription in the 12 months before surgery were persistent opioid users 6 months after surgery, compared with 13% (16) of opioid naïve participants, a RR (95%CI) of 3.2 (1.9–5.3) (Table 3). There was no association between persistent postoperative opioid use and WOMAC pain and function outcomes, quantitative sensory testing values and genetic polymorphisms (Table 3). The oral morphine equivalent values for the pre-operative, in-hospital and discharge to 6-month periods are shown in Table 4. The number and type of opioid prescriptions in the pre- and postoperative periods are shown in Table 5.

We further evaluated factors that could be predictive for persistent opioid use ≥6 months after surgery. As indicated in Table 6, any opioid use in the 12 months before surgery was predictive of increased odds of persistent opioid use ≥6 months after total knee arthroplasty (model 1). Patients who were opioid naïve in the 12 months before surgery, but used opioids postoperatively, were not at increased odds of persistent opioid use ≥6 months after

Table 1 Participant characteristics (n = 242), WOMAC pain and function outcomes (n = 238 after 6 months). Values are mean (SD), number (proportion) or median (IQR [range]).

Age; y	70 (9)
Female	132 (54%)
BMI; kg.m^2	31 (6)
WOMAC pain; 0–100	46 (21)
WOMAC function; 0–100	47 (20)
Expected pain; 0–10	1.20 (1.44)
Pain catastrophising; 0–52	13.5 (11.2)
Beck Depression II; 0–63	7.6 (6.0)
State Anxiety; 20–80	29.0 (9.3)
LANSS; 0–24	4.2 (3.4)
Knee PPT; kPa	318.4 (157.5)
Scapular PPT; kPa	302.85 (233.3–404 [86.3–924.3])
CPM; absolute change	−65.5 (−121.3 to −26.7 [−463.3–353.3])
CPM; percentage change	−23.45 (−44.29 to −9.17 [−260.79–53.64])
Temporal summation; 0–100	8.33 (2.33–23.33 [−10–78.33])
COMT (rs4680)	
A/A allele 0	47 (19%)
A/G allele 1	113 (47%)
G/G allele 2	82 (34%)
OPRM1 (rs1799971)	
A/A allele 0	190 (79%)
A/G allele 1	51 (21%)
G/G allele 2	1 (<1%)

WOMAC, Western Ontario and McMaster Osteoarthritis Index; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; PPT, pressure pain threshold; CPM, conditioned pain modulation; COMT, catechol-o-methyltransferase; OPRM1, opioid receptor mu-1.

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Table 2 Participants taking opioids in the 12 months before and 12 months after primary total knee arthroplasty. Values are number (proportion).

	Taking an opioid prescription	
Time-point	**Yes**	**No**
12 months pre-operatively	118 (49%)	124 (51%)
In-hospital	242 (100%)	0
Discharge to 3 months postoperatively	225 (93%)	17 (7%)
≥ 6 months postoperatively	65 (27%)	177 (73%)

total knee arthroplasty (model 2). No other pre-operative factors, including psychological factors, quantitative sensory testing or genetic polymorphisms were predictive of persistent opioid use.

In addition, we evaluated factors that could result in increased average daily oral morphine equivalent ≥6 months after total knee arthroplasty. Average daily oral morphine equivalent lag (a lag variable being a variable whose value at the current time-point is dependent on its value at the previous time-point), increased BMI and three or more comorbid pain sites were statistically significant predictors of increased average daily oral morphine equivalent ≥6 months after total knee arthroplasty. While not statistically significant, the pre-operative Pain Catastrophising Scale helplessness sub-score exhibited a consistent dose–response relationship with higher average daily oral morphine equivalent ≥6 months after total knee arthroplasty, representing a potentially clinically important finding which should be examined in future studies (Table 6, model 3).

Discussion

To date, this prospective cohort study is the most in-depth evaluation of risk factors for persistent opioid use at 12 months following total knee arthroplasty. Important genetic (COMT, OPRM1) or neurophysiological (quantitative sensory testing) predictors of persistent opioid use were not identified. However, pre-operative opioid use in the 12 months before surgery, increased BMI and multiple comorbid pain sites were associated with persistent opioid use and increased average daily oral morphine equivalent ≥6 months after total knee arthroplasty.

Due to the historically high rates of opioid prescribing, most prevalence studies looking at persistent opioid use following total knee arthroplasty have originated from the USA [10]. Lack of standardisation across prescribing patterns, definition of opioids and usage, and variability in recording periods makes direct comparisons between studies difficult. Rates of persistent opioid use range from 17% at 6 weeks [13] to 7.6% at 12 months [3] and up to 21% at 2 years postoperatively [14]. A recent systematic review from Europe covering eight countries demonstrated opioid use after 3–6 months between 7.9% and 41% after lower limb arthroplasty [15]. In an Australian review of 15,000 primary total knee arthroplasty cases, 29% of patients received `some opioid´ at 12 months post-surgery, while 5% were described as chronic persistent users [16]. Epidemiological data from New Zealand demonstrated persistent opioid use of between 11% and 12%

Table 3 Univariate relative risk of persistent opioid use 6 months after primary total knee arthroplasty.

Model		RR	SE	Z	p	95%CI
1	Opioid naïve					
	Opioid not naïve	3.218	0.831	4.528	< 0.001	1.940–5.338
2	WOMAC function at 6 months	1.101	0.006	0.23	0.817	0.990–1.013
3	WOMAC pain at 6 months	1.003	0.006	0.45	0.655	0.655–1.002
4	OPRM1 A/A	-	-	-	-	-
	OPRM1A/G	0.759	0.221	−0.95	0.344	0.429–1.343
5	COMT A/A	-	-	-	-	-
	COMT A/G	1.373	0.435	1.000	0.318	0.737–2.556
	COMT G/G	1.261	0.423	0.690	0.489	0.654–2.433
6	LANSS	1.00	0.038	0.117	0.907	0.933–0.081
7	Temporal summation	1.006	0.005	1.213	0.225	0.996–1.017
8	CPM	1.001	0.003	0.047	0.963	0.994–1.005

WOMAC, Western Ontario and McMaster Osteoarthritis Index; OPRM1, opioid receptor mu-1; COMT, catechol-o-methyltransferase; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; CPM, conditioned pain modulation.

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6–12 months after total knee arthroplasty surgery [1]. This is lower than the present study, which identified 27% as persistent users 6–12 months after surgery. This may reflect differences in the reporting period, our single centre cohort and the exclusion of patients who had a second hip or knee replacement within 6 years of the primary total knee arthroplasty.

The median oral morphine equivalent at 6 months (5.2 mg) was relatively low in our cohort of patients compared with other studies. In an Australian study, 29% of patients had some opioid use after 90 days with an oral morphine equivalent of 37 mg per day, while 5.2% of the cohort had ongoing chronic use with an oral morphine equivalent of 55 mg per day [16]. Similarly, in a study from the USA of 676 total knee arthroplasty patients, 60% of patients required a second opioid prescription, 13.7% needed more than 5 prescriptions and 12% required opioids for longer than 6 months. The oral morphine equivalent again was high, 85 mg and 57 mg per day for the first and second prescriptions respectively [17]. In a study looking at patterns of opioid prescribing from 2014–2017 in 150,000 total knee arthroplasties in the USA, the proportion of patients receiving an opioid prescription rose from 82% to 92% over the 4 years, with an average oral morphine equivalent of 20 mg per day [18]. While direct comparisons of opioid prescribing between countries are difficult to evaluate [15], there is some evidence that there are important geographical variations. In a comparison of opioid prescribing following four surgical procedures, USA and Canadian prescribing rates were seven-fold greater than that of Sweden [19]. The prescribing pattern in this study may be affected by local study and prescribing practices. The protocol for the original study [11] used oxycodone as the default postoperative opioid, to allow prescribing in patients with normal and impaired renal function. The pharmacogenetic issues associated with codeine prescribing have been highlighted locally and access has also been limited to controlled drug status. Tramadol can be associated with significant side effects, while tapentadol is not yet available in New Zealand. In many cases, non-steroidal anti-inflammatory drugs are contraindicated due to their associated renal and/or cardiac comorbidities.

Persistent opioid use was not associated with any improvements in WOMAC pain or function scale compared with non-users at 6 months after total knee arthroplasty surgery. The lack of effect of opioid use and functionality and patient reported outcomes were also reported in a low-performance trajectory group following total knee arthroplasty. Similar to the current study, risk factors for ongoing opioid use and impaired functionality included pre-operative opioid use as well as pain catastrophising [20].

Genetic factors may be important determinants of opioid use and pain severity in the immediate postoperative period [21], including after total knee arthroplasty [22]. Furthermore, there is evidence from twin studies that between 30% and 50% of the risk for opioid dependence is heritable, with polymorphisms in dopaminergic and opioid pathways frequently associated with increased risk [23]. While variations in gene expression of COMT have been associated with persistent pain following cardiac [24] and breast cancer surgery [25, 26], this association was not identified in the present study. Neither pain nor persistent opioid use was associated with COMT or OPRM1 genotypes.

Similarly, we could not identify any important relationship between pre-operative quantitative sensory testing measures and persistent opioid use. Opioid use may impair descending pain inhibitory pathways [27] and, in some cases, exacerbate hyperalgesia. Increased thermal pain sensitivity and/or higher temporal summation of pain have previously been shown to be correlated with greater opioid consumption in the acute peri-operative period after total knee arthroplasty [28]. However, as far as we are aware, this is the first study to explore the association between pre-operative quantitative sensory testing and persistent opioid use after total knee arthroplasty. Future studies may wish to explore the relationships between persistent opioid use and pre-operative measures of thermal pain sensitivity and pain tolerance, as these appear to have stronger relationships to both opioid-induced hyperalgesia [29] and risk of opioid misuse [30].

Pre-operative use of opioids before arthroplasty is associated with an increased risk of wound infection, length of stay, revision surgery, and readmission, as well as increased medical costs [31]. The specific duration, frequency and dose risk thresholds are unknown. Some studies have shown that doses as low as an oral morphine equivalent of 10 mg per day may be associated with increased emergency department visits and readmission [32]. Factors associated with chronic pre-operative use are challenging to identify due to complex biopsychosocial interactions [31]. Anxiety, depression, catastrophising, younger age, female gender, pain elsewhere and lower socio-economic status have all been associated with pre-operative opioid use [33]. In contrast, the present study did not identify age, gender and psychological variables as specific risk factors. Instead, the strongest predictors in this study for persistent opioid use and higher daily oral

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Table 4 Daily opioid morphine equivalents (mg) in the pre-, peri- and postoperative time periods for those who did and did not become persistent opioid users at 6 months, with respect to pre-operative opioid use (naïve vs. not naïve). Values are median (IQR [range]).

	Naïve n = 124		Not naïve n = 118	
	Not persistent opioid use n = 108	Persistent opioid use n = 16	Not persistent opioid use n = 69	Persistent opioid use n = 49
12 months pre-operatively	-	-	3.2 (0.38–5.8 [0–54.6])	3.6 (2.1–13.1 [0–100])
In-hospital	31.3 (21.3–46.9 [0–180])	40.4 (22.5–64.5 [13.9–107.5])	35.0 (23.1–52.8 [0–124])	43.3 (27.5–58.8 [5–155])
Discharge to 6 months	8.3 (3.4–15.6 [0–57.9])	13.4 (6.6–24.1 [0–57.9])	14.0 (6.7–22.5 [0–57.9])	26.9 (9.9–37.6 [0–78.4])

Table 5 Prescription frequency by medication.

	Pre-operative		Postoperative	
	Total prescriptions	Total number of subjects	Total prescriptions	Total number of subjects
Paracetamol plus codeine	154	55	65	47
Ibuprofen plus codeine	1	1	-	-
Codeine phosphate	112	41	91	59
Dihydrocodeine tartrate	35	7	14	6
Tramadol	181	46	226	137
Morphine	8	6	44	22
Oxycodone	76	12	300	91
Fentanyl patch	1	1	3	1

morphine equivalent ≥6 months after total knee arthroplasty were pre-operative opioid use, increasing BMI and more than three comorbid pain sites. In a meta-analysis of 458,993 patients who underwent a variety of orthopaedic procedures, BMI ≥ 40 increased the risk of postoperative opioid use by 2.32 from baseline [34]. In addition, it is recognised that increasing BMI is associated with persistent postoperative pain [35]. There is evidence that obese patients may have a greater degree of central sensitisation [36] and, in turn, this may result in increased requirement for opioid analgesia. Similarly, co-existing pain has been shown in multiple studies to be associated with persistent postoperative pain and prolonged opioid use [10]. While other risk factors for persistent opioid use other than pre-operative opioid use have been identified (e.g. peri-operative opioid use, increased comorbidity, substance abuse, younger age and female gender), potentially protective factors such as educational level and pre-operative non-steroidal anti-inflammatory use have also been suggested, which are potentially modifiable [37].

Conclusions drawn from this study are limited by some important methodological limitations. Consistent with other previous studies, we measured the number of opioid prescriptions filled, which may not reflect the actual medication taken by patients. Prediction of postoperative opioid requirement can be challenging. Some discharge prescribing patterns may be based on pre-discharge opioid use, while others may be arbitrary or even exceed in-hospital requirements [38]. Studies have shown that high proportions of prescriptions are not used or unfilled. In a prospective study of five common orthopaedic procedures, including total knee arthroplasty, 61% of prescribed opioids were not used and of these only 41% were disposed of safely [39]. Some patients with known risk factors for high or escalating use may be subject to overview by a transition pain service or supervised tapering plan. The Oregon Minimising Opioids after Joint Operation (MOJO) project utilised a time-limited multimodal approach to opioid prescribing, which led to a decrease in total dose of opioids with improvements in function, length of stay and resting pain [40]. This reflects more closely the model currently used in New Zealand and may explain the relatively low absolute opioid oral morphine equivalent prescribed in the present study. The indication for opioid prescribing was not

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Table 6 Predictors of persistent opioid use at 6 months and increased average daily opioid morphine equivalents.

		OR	Robust SE	z	p	Lower CI	Upper CI
Model 1	Pre-operative opioid use (not naïve)						
	Prescription (lag*)	2.124	0.366	4.37	<=0.001	1.515	2.989
Model 2	No pre-operative opioid use (naïve)	1.312	0.363	0.98	0.325	0.763	2.256
		β	SE	z	p	Lower CI	Upper CI
Model 3	Average daily OME (lag)	0.098	0.029	3.43	<=0.001	0.042	0.154
	BMI	0.306	0.114	2.68	0.007	0.082	0.530
	Opioid naïve	−3.854	1.230	−3.13	0.002	−6.365	−1.444
	Comorbid pain sites	-	-	-	-	-	-
	1	1.051	1.824	0.58	0.565	−2.524	4.625
	2	1.054	1.813	0.58	0.561	−2.500	4.608
	3	3.314	1.668	1.99	0.047	0.045	6.583
	PCS helplessness						
	Quartile 1 (0–2)	-	-	-	-	-	-
	Quartile 2 (3–4)	1.179	1.843	0.64	0.523	−2.434	4.791
	Quartile 3 (5–9)	1.328	1.504	0.88	0.377	−1.620	4.276
	Quartile 4 (10–23)	3.039	1.700	1.79	0.074	−0.293	6.371

All models repeated measures. Models 1 and 2 repeated measures logit with opioid use categorised yes/no, as a lag variable. Model 3, repeated measures generalised least squares model, OME as a lag variable, AR (1) autocorrelation. Zero comorbid pain sites and quartile 1 of PCS helplessness scores were used as the reference values for model 3. OME, oral morphine equivalent; PCS, pain catastrophising scale.

available, so opioid use may have been clinically justified in a portion of our participants. To account for this, any opioid prescriptions filled ≤3 months after another hospital admission or surgical procedure in the 12 months after the index total knee arthroplasty were discarded and not included in the final analysis. Finally, as our sample size was relatively small, we were likely underpowered to detect some potentially important relationships between persistent opioid use and the included variables where the effect sizes may be lower.

This study, however, does have some important strengths. The study population was well defined, with a prospective design and implemented a highly controlled peri-operative management programme. Most importantly, few studies, if any, have evaluated such a comprehensive range of demographic, psychological, neurophysiological and genetic risk factors for persistent opioid use in a total knee arthroplasty population.

This study shows that in a New Zealand population undergoing primary total knee arthroplasty, persistent use of some opioids ≥6 months after surgery is common but the absolute oral morphine equivalent appears be less than in other countries. Opioid use in the 12 months before surgery, increased BMI and three or more comorbid pain sites were predictors of persistent opioid use and greater oral morphine equivalent ≥6 months after total knee arthroplasty while costly and labour-intensive predictors (e.g. quantitative sensory testing and genetic analysis) appeared to confer no added benefit. As these predictors are easily identified and potentially modifiable, use of screening tools which action targeted interventions may be of use to further limit the impact of persistent opioid use after total knee arthroplasty. Active interventions utilising integrated transitional pain service models should be considered to reduce patient and societal consequences of extended opioid use postoperatively.

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