

## BRIEF REPORT

# Prescription Opioids Higher Among Knee Arthroplasty Recipients Randomized to Inpatient Rehabilitation

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**Objective.** To determine whether the purchase of prescription opioids was lower among people randomized to inpatient rehabilitation (IR) compared with those discharged directly home following total knee arthroplasty (TKA).

**Method.** A secondary analysis of a previous clinical trial in which participants were randomized 3 to 5 days after surgery to 10 days of IR and a home program or to a home program alone. The primary outcome for this secondary analysis was the purchase of opioid-based pain relief up to 10-weeks after surgery, which was captured via patient diaries. Between-group differences were analyzed using a  $\chi^2$  test and relative risk (RR) (95% confidence interval [CI]). We report this outcome alongside the main outcomes observed at 10 weeks for the original study (6-minute walk test, index joint pain, and function) for context.

**Results.** At 10 weeks, 158 participants were available for follow-up; 120 (76%) provided diaries, with 113 providing generic or brand names for the pain relief purchased. In the IR group, 60% (33/55) reported the purchase of opioid-based medications after discharge compared with 34% (20/58) in the home group ( $\chi^2 = 7.4$ ;  $P = 0.007$ ); thus, the risk of purchasing opioids for those in the IR group was almost double (RR, 1.7 [95% CI, 1.1–2.6]). No significant or meaningful between-group differences in index joint pain, function, or mobility were observed.

**Conclusion.** Contrary to what was hypothesized, IR is a strong driver of opioid purchase after discharge from the hospital following TKA.

## INTRODUCTION

Chronic opioid use and dependency are not only problematic within the general community, but there is evidence within the knee arthroplasty literature—entirely from observational studies—of an association between chronic opioid use before surgery and poorer outcomes after surgery (1,2). Similarly problematic, many patients continue to consume opioids many months after surgery (3), which is likely contributing to the poorer outcomes observed. Much of the extant data are based on administrative datasets (2,3), and granular detail is lacking such that we do not know why some preoperative opioid users remain on opioids many months

after total knee arthroplasty (TKA) and why some preoperatively opioid-naïve patients become chronic users after surgery. Understanding the drivers of persistent use after surgery would help inform future strategies intended to reduce inappropriate opioid use among surgical patients at a time when joint pain should be resolving.

This study aimed to determine whether opioid purchase after discharge from a hospital following TKA differed on the basis of rehabilitation pathways. Specifically, we hypothesized that the “purchase” (a proxy for use) would be lower among patients randomized to inpatient rehabilitation (IR) given that pain management, which is designed to minimize both pain

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and distress, is a core treatment focus of rehabilitation medicine physicians (4,5).

## PATIENTS AND METHODS

For this analysis, data from a previous randomized trial comparing 10 days of IR following TKA with a clinician-monitored home program were used (6). The study was approved by the St. Vincent's Hospital Human Research Ethics Committee and was prospectively registered (clinicaltrials.gov identifier NCT01583153). All participants provided informed written consent.

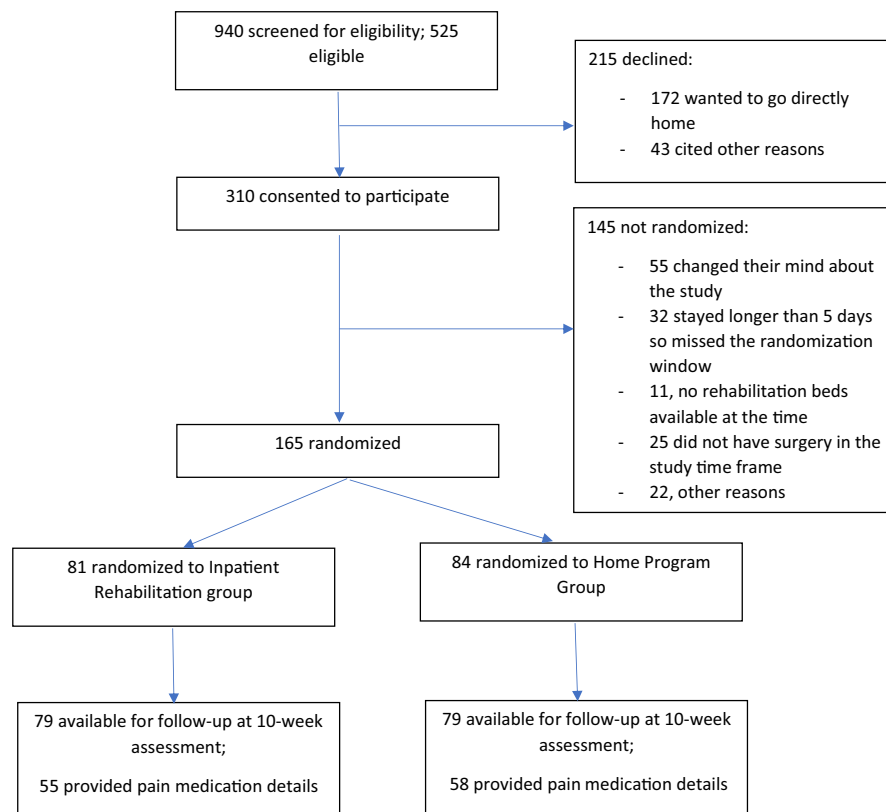
Detailed descriptions of the methods and results are provided elsewhere (6,7); thus, only brief descriptions are provided here.

In the original study, eligible people were randomized 3 to 5 days after surgery to either 10 days of IR and a home program or to a home program alone. The eligibility criteria included primary unilateral TKA for osteoarthritis, age of 40 years or more, the ability to speak English, and the ability to perform a home exercise program without supervision. People who consented prior to surgery but experienced a major complication during the acute-care phase (such as repeat surgery) were not randomized and subsequently excluded.

For the IR component, after discharge from the acute hospital, participants received daily intensive therapy comprising 1 to

1.5 hours of one-on-one physiotherapy and another 1- to 1.5-hour class-based session later in the day in an IR facility. For the home-based group, after discharge from the acute hospital, the participants attended three group-based outpatient physiotherapy sessions between 2 weeks and 10 weeks after surgery. Participants were expected to perform daily exercises at home and were also permitted to contact therapists if any rehabilitation-related issues arose. The IR group also participated in the same home-based program after discharge from the rehabilitation facility.

For this secondary analysis, the primary outcome of interest was any opioid purchase after discharge from the acute (home group) or rehabilitation hospital (IR group) up to Week 10 after surgery. We collected opioid purchase information as part of health resource utilization, which itself was to be incorporated in a cost-effectiveness analysis if the IR program was shown to be superior. Data pertaining to opioid purchases were retrieved from patient diaries detailing their medication purchases over the early subacute period. During the time of the study, combination products that had 8 mg or 15 mg of codeine (with ibuprofen or acetaminophen) were available for purchase without a prescription from pharmacies only. Opioids available on prescription included buprenorphine, codeine, hydromorphone, fentanyl, oxycodone, tramadol, tapentadol, morphine, and methadone. Opioids indicated for opioid substitution (eg, methadone liquid), coughs (eg,



**Figure 1.** Cohort ascertainment and retention to 10 weeks. This flow chart has been adapted from the original flowchart for the original study and is shortened from its original form (6). [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**Table 1.** Participant characteristics at baseline (before surgery) by treatment group

Characteristic	Inpatient Rehabilitation Group (n = 55)	Home Group (n = 58)	Mean Difference or Relative Risk <sup>a</sup> (95% CI)
Age, mean (SD), years	67.8 (7.7)	66.4 (8.3)	1.4 (-1.6 to 4.4)
Female, sex, %	67	67	1.0 (0.8 to 1.3)
Body mass index, mean (SD, kg/m <sup>2</sup> )	34.8 (6.6)	34.3 (7.0)	0.56 (-2.0 to 3.1)
KOOS pain, <sup>b</sup> mean (SD)	36.9 (13.7)	32.2 (16.2)	4.7 (-0.9 to 10.4)
Oxford Knee Score, <sup>c</sup> mean (SD)	18.1 (7.4)	16.4 (7.8)	1.7 (-1.1 to 4.5)
6MWT, mean (SD), m	308.0 (106.7)	321.6 (107.5)	-13.4 (-53.2 to 26.3)

Abbreviation: 6MWT, 6-minute walk test; CI, confidence interval; KOOS, Knee Injury and Osteoarthritis Outcome Score.

<sup>a</sup> Inpatient Rehabilitation Group compared to Home Group.

<sup>b</sup> The KOOS ranges from 0% to 100% (higher scores are better).

<sup>c</sup> The Oxford Knee Score ranges from 0 to 48 (higher scores are better).

pholcodine, dextromethorphan, and dihydrocodeine), and diarrhea (eg, loperamide) were excluded a priori. Along with opioid purchase, other outcomes for the trial included distance walked (in meters) in the 6-minute walk test (6MWT) at 26 weeks (original primary outcome), the 6MWT at 10 weeks and 52 weeks after surgery, and patient-reported outcomes, including the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale and the Oxford Knee Score at 10, 26, and 52 weeks. As opioid purchase information was only obtained over the first 10-week period, we also only report these outcomes to 10 weeks.

Analyses involved  $\chi^2$  tests to determine relative risk (RR) (95% confidence interval [CI]) and unpaired t-tests using SPSS version 26.

## RESULTS

In the original study, 310 people consented to the study, and 165 were randomized (Figure 1). A total of 158 participants (96%) were available for follow-up at 10 weeks; 120 (76.4%) provided diaries, 113 (IR group: 55/81 [68%]; home group: 58/84 [69%]) of whom provided generic or brand names for the pain relief they purchased. Table 1 summarizes the cohort characteristics by each treatment group who provided data about the

pain medication purchased, and Table 2 compares the cohort who provided diaries with those who did not; no between-group differences were observed across a range of characteristics (Table 2).

In the IR group, 60% (33/55) reported the purchase of opioid-based medications after discharge ("type" defined in Table 3) compared with 34% (20/58) in the home group ( $\chi^2 = 7.4$ ;  $P = 0.007$ ); thus, the risk of purchasing opioids for those in the IR group was almost double (RR, 1.7 [95% CI, 1.1-2.7]). Consistent with the findings at 10, 26, and 52 weeks after surgery in the original study, no significant or meaningful between-group differences in index joint pain, function, or mobility were observed (Table 3).

## DISCUSSION

Opioid-based medications are a key component of multimodal analgesia in the early postsurgical period. However, the utility and safety of opioid-based analgesia in the subacute period is questionable. Opioids have been demonstrated to increase pain and have been implicated in the development of persistent pain (8). Contrary to our hypothesis, the ongoing purchase was greater after exposure to IR, and this was in the absence of any differences in pain or functional recovery. Our novel finding suggests

**Table 2.** Presurgical characteristics and 10-week outcomes: returning diary versus no diary

Characteristic	Diary (n = 120)	No Diary (n = 38)	Mean Difference or Relative Risk <sup>a</sup> (95% CI)
Age, mean (SD), years	67.0 (8.0)	66.5 (9.2)	-0.5 (-3.6 to 2.6)
Female sex, n (%)	82 (68.3)	26 (70.3)	-1.0 (0.8 to 1.3) <sup>a</sup>
Body mass index, mean (SD, kg/m <sup>2</sup> )	34.5 (6.8)	34.2 (7.2)	-0.3 (-2.8 to 2.3)
Baseline KOOS pain, <sup>b</sup> mean (SD)	34.3 (15.4)	36.6 (13.7)	2.4 (-3.3 to 8.0)
10-week KOOS pain, <sup>b</sup> mean (SD)	70.2 (19.4)	70.5 (21.5)	0.3 (-7.4 to 8.1)
Baseline Oxford Knee Score, <sup>c</sup> mean (SD)	17.0 (7.6)	18.2 (5.5)	1.3 (-1.4 to 4.0)
10-week Oxford Knee Score, <sup>c</sup> mean (SD)	32.5 (7.8)	33.6 (8.8)	1.1 (-1.9 to 4.1)
Baseline 6MWT, mean (SD), m	314.0 (106.8)	344.2 (108.3)	30.1 (-9.7 to 70.0)
10-week 6MWT, mean (SD), m	372.6 (98.2)	399.8 (120.7)	27.2 (-11.4 to 65.8)

Abbreviation: 6MWT, 6-minute walk test; CI, confidence interval; KOOS, Knee Injury and Osteoarthritis Outcome Score.

Baseline measures are preoperative measures.

<sup>a</sup> Relative risk for diary compared with no diary.

<sup>b</sup> The KOOS ranges from 0% to 100% (higher scores are better).

<sup>c</sup> The Oxford Knee Score ranges from 0 to 48 (higher scores are better).

**Table 3.** Ten-week outcomes based on rehabilitation pathway: inpatient rehabilitation group versus home group

Outcome	Inpatient Rehabilitation Group (n = 55)	Home Group (n = 58)	Mean Difference (95% CI)	Relative Risk <sup>a</sup> (95% CI)
Opioid-based medication, n (%) <sup>b</sup>	33 (60.0)	19 (32.8)	N/A	1.7 (1.1 to 2.6)
NSAIDs, n (%)	11 (20.0)	14 (24.1)	N/A	0.8 (0.4 to 1.7)
Nonopioid analgesia, n (%)	25 (45.5)	31 (53.4)	N/A	0.9 (0.6 to 1.2)
KOOS pain, mean (SD)	70.5 (19.2)	69.8 (19.5)	0.7 (−6.6 to 7.9)	N/A
Oxford Knee Score, mean (SD)	33.2 (7.1)	31.9 (7.9)	1.4 (−1.4 to 4.2)	N/A
6MWT, mean (SD), m	361.1 (93.2)	386.6 (100.5)	−25.6 (−61.8 to 10.6)	N/A

Abbreviation: 6MWT, 6-minute walk test; CI, confidence interval; KOOS, Knee Injury and Osteoarthritis Outcome Score; N/A, not appropriate; NSAID, nonsteroidal anti-inflammatory drug.

<sup>a</sup> Relative risk for inpatient rehabilitation group.

<sup>b</sup> Includes buprenorphine, codeine, hydromorphone, fentanyl, oxycodone, tramadol, tapentadol, morphine or methadone.

<sup>c</sup> The KOOS ranges from 0% to 100% (higher scores are better)

<sup>d</sup> The Oxford Knee Score ranges from 0 to 48 (higher scores are better).

that the rehabilitation pathway is a causal determinant of opioid purchase after discharge from the hospital. The greater risk in the IR group may be because rehabilitation specialists provide repeat scripts at discharge (~14 days after surgery) (as was the current practice at the time the study was undertaken) and/or because IR patients had more prolonged exposure to opioids compared with those discharged directly home owing to daily opioid prescription prior to therapy for those in the IR program, leading to greater medication reliance. Thus, such patients seek more prescriptions once home.

Although numerous studies exist exploring the predictors of persistent use of opioids following arthroplasty (9–11), few have included rehabilitation pathways in their modeling. We are aware of only one earlier study conducted in the United States using claims data that found that discharge to an IR facility was a predictor of persistent use among people who were not chronic users prior to surgery (12). We did not collect a history of opioid use prior to surgery from the cohort, but balance in all measured characteristics between the IR and home groups at baseline (both in the complete cohort [6] and the subset included here [Tables 1 and 2]) indicates successful randomization, which, in turn, strongly suggests that there is likely to be no systematic bias in any unmeasured baseline characteristics, including opioid use prior to surgery. We contend, therefore, that it is the rehabilitation pathway and not differences in presurgical use of opioids that explains the between-group difference in opioid purchase following discharge home in this current study.

Another point of interest is that a recent meta-analysis of predominantly retrospectively collected administrative data concluded that discharge to IR is associated with almost five and three times the odds for readmission and periprosthetic complications, respectively, compared with discharge home (13). Our study points to a possible cause of a greater rate of adverse events amongst people referred to IR after TKA—greater opioid use.

Our study has limitations. We used patient-reported purchase of prescription opioids; thus, deficits in patient recall may have undermined the reporting. That said, we would expect such

a deficit to be similar in both groups. We also acknowledge that “purchase” may not equate to “use.” The use of purchase as a proxy for use is not unique to our study and is similarly problematic for all prior studies relying on prescription-based administrative records as the signal for “use” (9–12). We note, however, that patient report allows the capture of nonprescription (though lower-dose) opioids, which prescription-based administrative records cannot do. Future studies should include a measure of actual consumption when possible.

In conclusion, this study indicates that the rehabilitation pathway may be contributing to persistent or even increased opioid use after TKA surgery. Pain management strategies during and following IR may be contributing to the inappropriate persistent use of opioids following TKA and, thus, should undergo scrutiny by all stakeholders, including rehabilitation specialists, orthopedic surgeons, and consumer groups.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. A/Professor Naylor and Dr. Buhagiar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design.** Naylor, Buhagiar, Harris, Xuan.

**Acquisition of data.** Naylor, Buhagiar.

**Analysis and interpretation of data.** Naylor, Buhagiar, Johns, Penn, Adie, Harris, Xuan.

## REFERENCES

- 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.
- Kim SC, Jin Y, Lee YC, Lii J, Franklin PD, Solomon DH, et al. Association of preoperative opioid use with mortality and short-term safety outcomes after total knee replacement. *JAMA Netw Open* 2019;2:e198061.
- Shah R, Kuo YF, Westra J, Lin YW, Raji MA. Opioid use and pain control after total hip and knee arthroplasty in the US, 2014 to 2017. *JAMA Netw Open* 2020;3:e2011972.

4. The Royal Australasian College of Physicians Australasian Faculty of Rehabilitation Medicine. Rehabilitation medicine physician scope of practice: adult rehabilitation medicine 2018. 2018. URL: [https://www.racp.edu.au/docs/default-source/about/afm/afm-scope-of-practice-statement-adult-rehabilitation-medicine.pdf?sfvrsn=94d6021a\\_16](https://www.racp.edu.au/docs/default-source/about/afm/afm-scope-of-practice-statement-adult-rehabilitation-medicine.pdf?sfvrsn=94d6021a_16).
5. Wade DT. What is rehabilitation? An empirical investigation leading to an evidence-based description. *Clin Rehabil* 2020;34:571–83.
6. Buhagiar M, Naylor JM, Harris IA, Xuan W, Kohler F, Wright R, et al. Effect of inpatient rehabilitation vs a monitored home-based program on mobility in patients with total knee arthroplasty: the HIHO randomized clinical trial. *JAMA* 2017;317:1037–46.
7. Buhagiar MA, Naylor JM, Harris IA, Xuan W, Kohler F, Wright RJ, et al. Hospital inpatient versus home-based rehabilitation after knee arthroplasty (the HIHO study): study protocol for a randomized controlled trial. *Trials* 2013;14:432.
8. Rivat C, Ballantyne J. The dark side of opioids in pain management: basic science explains clinical observation. *Pain Rep* 2016;1:e570.
9. Brock JL, Jain N, Phillips FM, Malik AT, Khan SN. Postoperative opioid cessation rates based on preoperative opioid use: analysis of common orthopaedic procedures. *Bone Joint J* 2019;101:1570–7.
10. Namba RS, Singh A, Paxton EW, Inacio MC. Patient factors associated with prolonged postoperative opioid use after total knee arthroplasty. *J Arthroplasty* 2018;33:2449–54.
11. Politzer CS, Kildow BJ, Goltz DE, Green CL, Bolognesi MP, Seyler TM. Trends in opioid utilization before and after total knee arthroplasty. *J Arthroplasty* 2018;33:S147–53.
12. 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. *Osteoarthritis Cartilage* 2017;25:1399–406.
13. Onggo JR, Onggo JD, de Steiger R, Hau R. The efficacy and safety of inpatient rehabilitation compared with home discharge after hip or knee arthroplasty: a meta-analysis and systematic review. *J Arthroplasty* 2019;34:1823–30.