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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

Erin E. Krebs, MD, MPH; Amy Gravely, MA; Sean Nugent, BA; Agnes C. Jensen, MPH; Beth DeRonne, PharmD; Elizabeth S. Goldsmith, MD, MS; Kurt Kroenke, MD; Matthew J. Bair; Siamak Noorbaloochi, PhD

IMPORTANCE Limited evidence is available regarding long-term outcomes of opioids compared with nonopioid medications for chronic pain.

OBJECTIVE To compare opioid vs nonopioid medications over 12 months on pain-related function, pain intensity, and adverse effects.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, 12-month, randomized trial with masked outcome assessment. Patients were recruited from Veterans Affairs primary care clinics from June 2013 through December 2015; follow-up was completed December 2016. Eligible patients had moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use. Of 265 patients enrolled, 25 withdrew prior to randomization and 240 were randomized.

INTERVENTIONS Both interventions (opioid and nonopioid medication therapy) followed a treat-to-target strategy aiming for improved pain and function. Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen (paracetamol) or a nonsteroidal anti-inflammatory drug. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.

MAIN OUTCOMES AND MEASURES The primary outcome was pain-related function (Brief Pain Inventory [BPI] interference scale) over 12 months and the main secondary outcome was pain intensity (BPI severity scale). For both BPI scales (range, 0-10; higher scores = worse function or pain intensity), a 1-point improvement was clinically important. The primary adverse outcome was medication-related symptoms (patient-reported checklist; range, 0-19).

RESULTS Among 240 randomized patients (mean age, 58.3 years; women, 32 [13.0%]), 234 (97.5%) completed the trial. Groups did not significantly differ on pain-related function over 12 months (overall $P = .58$); mean 12-month BPI interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference, 0.1 [95% CI, −0.5 to 0.7]). Pain intensity was significantly better in the nonopioid group over 12 months (overall $P = .03$); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5 [95% CI, 0.0 to 1.0]). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (overall $P = .03$); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9 [95% CI, 0.3 to 1.5]).

CONCLUSIONS AND RELEVANCE Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

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Supplemental content

Author Affiliations: Center for Chronic Disease Outcomes Research, Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota (Krebs, Gravely, Nugent, Jensen, DeRonne, Goldsmith, Noorbaloochi); Department of Medicine, University of Minnesota Medical School, Minneapolis (Krebs, Noorbaloochi); Division of Epidemiology, University of Minnesota School of Public Health, Minneapolis, Minneapolis, Minnesota (Goldsmith); Center for Health Information and Communication, Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana (Kroenke, Bair); Department of Medicine, Indiana University School of Medicine, Indianapolis (Kroenke, Bair); Regenstrief Institute, Indianapolis, Indiana (Kroenke, Bair).

Corresponding Author: Erin E. Krebs, MD, MPH, Minneapolis Veterans Affairs Health Care System (152), 1 Veterans Dr, Minneapolis, MN 55417 (erin.krebs@va.gov).

Long-term opioid therapy became a standard approach to managing chronic musculoskeletal pain despite a lack of high-quality data on benefits and harms.[1]

Rising rates of opioid overdose deaths have raised questions about prescribing opioids for chronic pain management. Because of the risk for serious harms without sufficient evidence for benefits, current guidelines discourage opioid prescribing for chronic pain.[2-4] Systematic reviews cited by guidelines identified no randomized trials of opioid therapy that reported long-term pain, function, or quality-of-life outcomes.[4,5]

The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial was a pragmatic randomized trial that compared opioid therapy vs nonopioid medication therapy over 12 months for primary care patients with chronic back pain or hip or knee osteoarthritis pain of at least moderate severity despite analgesic use. Hypotheses were that opioids compared with nonopioid medications would lead to better pain-related function and pain intensity and more adverse effects.

Key Points

Question For patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use, does opioid medication compared with nonopioid medication result in better pain-related function?

Findings In this randomized clinical trial that included 240 patients, the use of opioid vs nonopioid medication therapy did not result in significantly better pain-related function over 12 months (3.4 vs 3.3 points on an 11-point scale at 12 months, respectively).

Meaning This study does not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Methods

The Minneapolis Veterans Affairs (VA) institutional review board approved the trial protocol and patients provided written informed consent. Recruitment details and the trial protocol have been published.[6] The trial protocol and statistical analysis plan are in Supplement 1.

Pragmatic Trial Design

To maximize applicability to primary care, the trial was designed to be pragmatic.[6,7] Eligibility criteria facilitated enrollment of diverse patients from primary care. Interventions were delivered with flexibility in medication selection and dosage. Patients were allowed to participate in nonpharmacological pain therapies outside of the study and were encouraged to complete outcome assessments regardless of their participation in the active interventions.

Participants

Eligible patients had chronic back pain or hip or knee osteoarthritis pain that was moderate to severe despite analgesic use. Chronic pain was defined as pain nearly every day for 6 months or more. Moderate or greater severity was defined by a score of 5 or more on the 3-item pain intensity, interference with enjoyment of life, and interference with general activity (PEG) scale (range, 0-10).[8]

Patients on long-term opioid therapy were excluded. Other reasons for exclusion included contraindications to all drug classes in either group, including class-level opioid contraindications (eg, active substance use disorder), and conditions that could interfere with outcome assessment (eg, life expectancy <12 months).[6] Patients with severe depression or posttraumatic stress disorder symptoms were not excluded because these patients often receive opioids in practice.

Patients were recruited from 62 Minneapolis VA primary care clinicians from June 2013 to December 2015 (**Figure**). Primary care clinicians were located at multiple clinics affiliated with the Minneapolis VA Health Care System, including clinics in the main medical center building and 4 outpatient clinics in the greater Minneapolis-Saint Paul metropolitan area. Potentially eligible patients were identified by searching the electronic health record (EHR) for back, hip, or knee pain diagnoses at a primary care visit in the prior month. Study personnel screened patients by telephone and then conducted a focused chart review.

Randomization and Blinding

To ensure balanced numbers of patients with back and osteoarthritis pain in each group, randomization was stratified by primary pain diagnosis. The SAS (SAS Institute), version 9.4, uniform random number generator was used to produce a computerized randomization table. Approximately 1 week after the enrollment visit, patients met with the study clinical pharmacist, who initiated random group assignment using a programmed study application that automatically assigned the next unused position in the randomization table. This process simultaneously informed the pharmacist and patient of group assignment. EHR documentation informed patients' primary care clinicians of study participation and group assignment. Study medications were visible in the EHR. Outcome assessors were blinded to group assignment.

Intervention Delivery

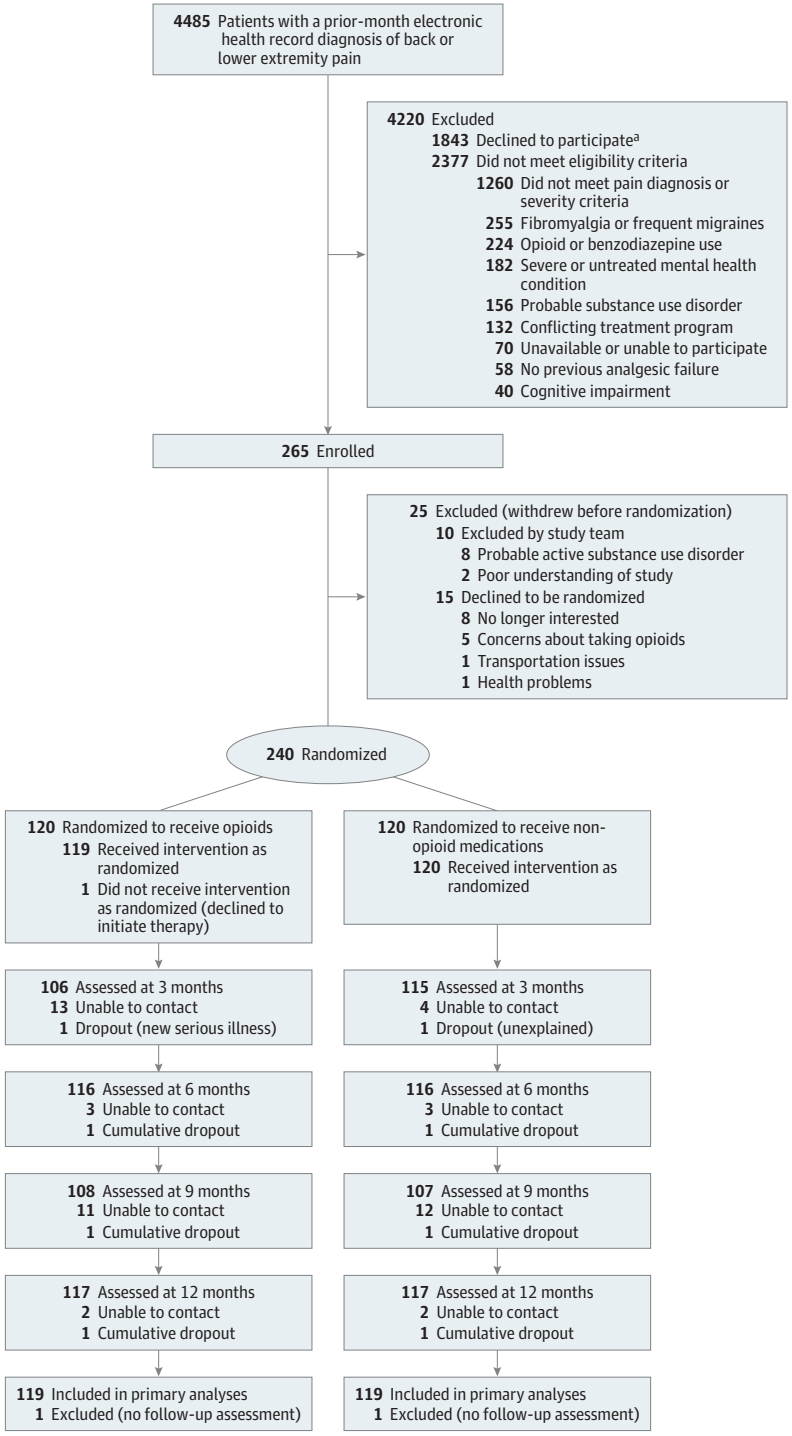
Medication was delivered using a collaborative pain care model with demonstrated effectiveness.[9,10] In both groups, patients received structured symptom monitoring and a treat-to-target approach to medication management delivered primarily by a single pharmacist. After randomization, the pharmacist reviewed past medications and identified individual functional goals. The initial medication regimen was determined by the assigned group and considerations such as patient preference and comorbidities. Follow-up visits were monthly until a stable regimen was established, then visits occurred every 1 to 3 months. Visits were in-person at 6 and 12 months when possible and otherwise mostly by telephone.

Both interventions used 3 medication steps. Medications were adjusted within the assigned group to achieve targets of improved PEG scores and progress toward individual goals. Study medications were dispensed from the VA pharmacy.

Opioid Prescribing Strategy

Per protocol, patients in the opioid group started taking immediate-release (IR) opioids. Step 1 was morphine IR,

Figure. Flow of Participants Through the Study



[a] Patients could decline to participate at any point in the screening process, including before the telephone eligibility interview; therefore, patients who declined to participate were not necessarily eligible.

hydrocodone/acetaminophen, and oxycodone IR. Step 2 was morphine sustained-action (SA) and oxycodone SA. Step 3 was transdermal fentanyl. Single-opioid therapy was preferred, but dual therapy with a scheduled SA opioid and as-needed IR opioid was considered based on patient needs and preferences. Opioids were titrated to a maximum daily dosage of 100 morphine-equivalent (ME) mg. If dosages were titrated to 60 ME mg/d without a response, rotation to another opioid was considered before dosage escalation.[11]

Nonopioid Prescribing Strategy

In the nonopioid medication group, step 1 was acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs). Step 2 included adjuvant oral medications

(ie, nortriptyline, amitriptyline, gabapentin) and topical analgesics (ie, capsaicin, lidocaine). Step 3 included drugs requiring prior authorization from the VA clinic (ie, pregabalin, duloxetine) and tramadol. Patients were initially prescribed a step 1 medication, unless all were clinically inappropriate. Subsequent changes included titrating, replacing, or adding medications.

Intervention Adherence

Patients were instructed to receive medications for back, hip, or knee pain only from the study. Nonpharmacological therapies were allowed outside of the study. If patients desired discontinuation of all study medications, they were transitioned back to preenrollment pain medications. Medication adherence was monitored by discussion with patients and checking the state prescription monitoring program website.

Descriptive Measures

Before randomization, patients were asked to state their preferred treatment group, perceptions of effectiveness and safety of opioid and nonopioid medications, and expectations for improvement on 0 to 10 scales (higher scores = more favorable).[12,13] To characterize the study population and provide data required by federal funders, self-identified race/ethnicity was assessed by asking patients to select from 6 categories.

Main Outcomes

The primary outcome was pain-related function, assessed with the 7-item Brief Pain Inventory (BPI) interference scale.[14] Pain intensity, the main secondary outcome, was assessed with the 4-item BPI severity scale. Both BPI scales yield 0 to 10 scores (higher score = worse function or intensity). A prior study of chronic pain in primary care estimated a minimal clinically important difference (MCID) of 0.7 points for both BPI interference and BPI severity.[15] Following consensus guidelines, this trial used a 1-point difference as the MCID for BPI interference and BPI severity, and used a 30% reduction from baseline as MCID for moderate improvement.[16] The primary adverse outcome was a patient-reported checklist of 19 medication-related symptoms,[17] modified from the original version by adding common analgesic adverse effects (eg, memory problems, sweating).[18]

Secondary Health Outcomes

Secondary outcomes were as follows: the Veterans RAND 12-item Health Survey (VR-12) quality-of-life measure (range, 0-100; higher score = better quality of life, standardized to mean of 50),[19] the 11-item Roland-Morris Disability Questionnaire (RMDQ) measure of pain-related physical function (range, 0-11; higher score = worse function, MCID = 2.0),[20] the 8-Item Patient Health Questionnaire (PHQ-8) depression measure (range, 0-24; higher score = worse depression, MCID = 5), the 7-Item Generalized Anxiety Disorder measure (GAD-7; range, 0-21; higher score = worse anxiety, MCID = 5)[21]; the Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance short form (range, 8-32; higher score = worse sleep disturbance)[22]; the Migraine Disability Assessment (MIDAS) questionnaire (range, 0-270; higher score = worse headache disability),[23] the Arizona Sexual Experience Scale (ASEX; range 5-30; higher score = worse sexual function)[24]; and the Multidimensional Fatigue Inventory (MFI) general fatigue, mental fatigue, physical fatigue, reduced activity, and reduced motivation scales (for each scale: range, 4-20; higher score = worse, MCID = 2).[25] Additional secondary outcomes not reported here were the global impression of pain change, the Fullerton Advanced Balance scale, 6-m gait speed, chair stand, grip strength tests, cold pain tolerance, free testosterone, and the Indiana University Telephone-Based Assessment of Neuropsychological Status.

Assessment for Adverse Events and Potential Opioid Misuse

At each assessment, patients reported new hospitalizations, emergency department (ED) visits, and falls. VA hospitalizations and ED events were identified by searching EHR databases from enrollment to 13 months after randomization. Two independent raters determined whether events were analgesic-related.[26] Discrepancies were resolved by discussion.

Opioid misuse describes use of prescription opioids in a manner other than as prescribed. This study used multiple approaches to evaluate for potential misuse, including medical record surveillance for evidence of "doctor-shopping" (seeking medication from multiple physicians), diversion, substance use disorder, or death; checking the state prescription monitoring program website at each visit and as needed; and completing the Addiction Behavior Checklist[27] at each intervention visit. The Addiction Behavior Checklist measures aberrant medication-related behaviors that may indicate misuse (range, 0-20; higher score = more aberrant behavior; 3 = threshold for opioid misuse). At 6-month and 12-month assessments, patients completed self-report measures and had urine drug testing. Substance use was assessed with the Alcohol Use Disorders Identification Test (AUDIT) and drug use questions from a National Institute on Drug Abuse screening tool.[28,29]

Assessment of Study Treatment Received and Nonstudy Co-Interventions

Pain medication dispensing data were obtained from EHR databases. Total study visit duration was calculated for each patient as the sum of minutes from clinician-entered *Current Procedural Terminology* (*CPT*) codes for all intervention encounters; for *CPT* codes that include a range of minutes (ie, 5-10, 11-20, 21-30), the highest value was used. Nonstudy co-interventions were obtained from patient report and EHR data.

Statistical Analysis

Assuming a 2-sided α level of .05 and a standard deviation of 2.7,[30] 115 patients completing the study per group were required for 80% power to detect a 1-point between-group difference in mean BPI interference at 12 months.[16] The initial target was 276 randomized patients, but enrollment was stopped at 265 due to difficulty recruiting and better-than-anticipated retention.

Analyses were intention-to-treat, with all patients included in their assigned treatment group. Scales were not scored if less than 70% of items were completed. When less than 30% of items were missing, the average of nonmissing

Table 1. Baseline Characteristics of Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

Characteristic	Opioid Group, No. (%) (n = 120)	Nonopioid Group, No. (%) (n = 120)
Age, y		
Mean (SD)	56.8 (13.3)	59.7 (14.0)
Median (IQR)	59.5 (46.5-67.0)	64.0 (53.0-69.0)
Women	36 (13)	36 (13)
Race/ethnicity		
White	105 (88)	102 (86)
Black	7 (6)	11 (9)
Other or multiple	7 (6)	6 (5)
Education ≥4-y degree	29 (24)	31 (26)
Employment		
Employed for wages	50 (42)	31 (26)
Self-employed	7 (6)	7 (6)
Retired	43 (36)	56 (47)
Other	19 (16)	24 (20)
Primary pain diagnosis[a]		
Back pain	78 (65)	78 (65)
Hip or knee osteoarthritis pain	42 (35)	42 (35)
Substance use assessment		
Current smoker	25 (21)	13 (11)
Hazardous alcohol use (AUDIT score ≥8)	3 (3)	2 (2)
Past-year illicit drug use	8 (7)	15 (13)
Mental health measures		
Moderate depression (PHQ-9 score ≥10)	28 (23)	25 (21)
Moderate anxiety (GAD-7 score ≥10)	11 (9)	11 (9)
Positive PTSD screen (PC-PTSD score ≥3)	25 (21)	25 (21)
Prerandomization treatment group preference[b]		
Unsure or no preference	72 (60)	51 (43)
Opioid medication group	25 (21)	44 (37)
Nonopioid medication group	23 (19)	25 (21)
Prerandomization perceptions of treatment groups, mean (SD)[c]		
Opioid effectiveness	7.8 (2.1)	7.8 (2.0)
Opioid safety	5.8 (2.5)	5.8 (2.8)
Nonopioid effectiveness	5.7 (2.7)	5.6 (2.8)
Nonopioid safety	6.6 (2.7)	6.5 (2.8)
Expectations for improvement[d]	7.6 (1.8)	7.4 (2.0)

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; GAD-7, 7-Item Generalized Anxiety Disorder Questionnaire; IQR, interquartile range; PHQ-9, 9-Item Patient Health Questionnaire; PC-PTSD, primary care posttraumatic stress disorder screener.

[a] Patients self-identified 1 condition as their most bothersome pain problem.

[b] Patients were asked, "Now, imagine if you were given a choice between groups. Considering what you know so far, which treatment group would you choose?"

[c] Patients were asked, "In general, how (effective or safe) do you consider (opioid medications or nonopioid medications) for long-term treatment of pain?" (range, 0-10; 0 = not at all [effective or safe], 10 = most [effective or safe] possible).

[d] Patients were asked, "In terms of your pain, how much improvement do you think is likely for you personally during this study?" (range, 0-10; 0 = no improvement to 10 = a great deal of improvement).

items was used for measures scored as an average, and missing "count" data were scored as 0.

Two-sided *t* tests and χ^2 tests were used for unadjusted between-group comparisons of primary and secondary outcomes at each assessment time point. Main analyses included data from all time points in mixed models (logistic, Poisson, Gaussian) for repeated measures to compare mean scores between treatment groups over 12 months, adjusting for baseline values, with time as fixed effects and intercept as random effects. For medication-related symptoms, groups were compared using a statistical test for treatment × time interaction. Individual patient-level functional response and pain intensity response were defined as 30% or more reduction from baseline to 12-month follow-up in BPI interference and severity, respectively.[16] χ^2 Tests were used to compare response rates as a secondary measure of effectiveness. The threshold for statistical significance was a *P* value less than .05. Analyses of secondary outcomes were exploratory and not adjusted for multiple testing. Post hoc treatment group by primary pain diagnosis interaction tests were used to explore possible differential treatment effects. Post hoc sensitivity analyses adjusting for smoking status were conducted to examine potential effects of the baseline group imbalance in current smoking. SAS (SAS Institute), version 9.2, was used for statistical analysis.

Results

Of 265 enrolled patients, 25 withdrew prior to randomization and 240 were randomized (Figure). Follow-up rates were 92% at 3 months (106 in the opioid group and 115 in the nonopioid group), 97% at 6 months (116 in each group), 90% at 9 months (108 in the opioid group and 107 in the nonopioid group), and 98% at 12 months (117 in each group). Two patients dropped out before completing follow-up assessments and were excluded; 1 patient randomized to opioids declined to initiate opioid therapy; all others received assigned therapy (Figure).

Mean age was 58.3 years (range, 21-80) and 32 patients (13.0%) were women (**Table 1**). For primary pain diagnosis, 156 patients (65%) had back pain and 84 patients (35%) had hip or knee osteoarthritis pain. The opioid group had 25 current smokers (21%) and the nonopioid group had 13 current smokers (11%). Regarding treatment group preference, in the opioid group, 72 patients (60%) had no preference and 25 patients (21%) preferred opioids. In the nonopioid group, 51 patients (43%) had no preference and 44 patients (37%) preferred opioids.

Pain and Health Outcomes

There was no significant difference in pain-related function between the 2 groups over 12 months (overall *P* = .58). At 12 months, mean BPI interference was 3.4 in the opioid group (SD, 2.5) vs 3.3 in the nonopioid group (SD, 2.6); difference, 0.1 (95% CI, −0.5 to 0.7). Pain intensity was significantly better in the nonopioid group over 12 months (overall *P* = .03). At 12 months, mean BPI severity was 4.0 in the opioid group (SD, 2.0) vs 3.5 in the nonopioid group (SD, 1.9); difference, 0.5 (95% CI, 0.0 to 1.0).

Table 2. Patient-Reported Primary and Secondary Outcomes Among Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

Outcome	Opioid Group, Mean (SD) (n = 119)	Nonopioid Group, Mean (SD) (n = 119)	Between-Group Difference (95% CI)[a]	Overall *P* Value[b]
Pain-Related Function (Primary Outcome)				
BPI interference scale (range, 0-10; higher score = worse)[c]				.58
Baseline	5.4 (1.8)	5.5 (2.0)	−0.1 (−0.6 to 0.4)	
3 mo	3.7 (2.1)	3.7 (2.2)	0.0 (−0.6 to 0.6)	
6 mo	3.4 (2.1)	3.6 (2.4)	−0.2 (−0.8 to 0.4)	
9 mo	3.6 (2.2)	3.3 (2.4)	0.4 (−0.2 to 1.0)	
12 mo	3.4 (2.5)	3.3 (2.6)	0.1 (−0.5 to 0.7)	
Pain Intensity (Secondary Outcome)				
BPI severity scale (range, 0-10; higher score = worse)[d]				.03
Baseline	5.4 (1.5)	5.4 (1.2)	0.0 (−0.4 to 0.3)	
3 mo	4.3 (1.8)	4.0 (1.7)	0.3 (−0.2 to 0.7)	
6 mo	4.1 (1.8)	4.1 (1.9)	0.0 (−0.5 to 0.5)	
9 mo	4.2 (1.7)	3.6 (1.7)	0.7 (0.2 to 1.2)	
12 mo	4.0 (2.0)	3.5 (1.9)	0.5 (0.0 to 1.0)	
Additional Secondary Health Outcomes				
VR-12 physical health (range, 0-100; lower score = worse)				.23
Baseline	27.2 (9.0)	27.0 (7.2)	0.2 (−1.9 to 2.2)	
3 mo	32.5 (9.8)	33.5 (9.9)	−1.0 (−3.6 to 1.6)	
6 mo	33.3 (9.7)	33.6 (10.0)	−0.3 (−2.8 to 2.2)	
9 mo	32.0 (10.5)	34.8 (10.9)	−2.9 (−5.8 to 0.0)	
12 mo	32.7 (10.1)	33.9 (9.9)	−1.3 (−3.8 to 1.3)	
VR-12 mental health (range, 0-100; lower score = worse)				.40
Baseline	47.3 (11.2)	47.8 (13.0)	−0.3 (−3.4 to 2.8)	
3 mo	51.8 (10.1)	50.5 (12.0)	1.3 (−1.6 to 4.3)	
6 mo	51.6 (9.8)	50.3 (12.5)	1.4 (−1.5 to 4.3)	
9 mo	51.8 (10.7)	52.6 (11.5)	−0.8 (−3.8 to 2.2)	
12 mo	51.2 (11.6)	50.4 (12.6)	0.7 (−2.4 to 3.8)	
RMDQ-11 pain-related physical function (range, 0-11; higher score = worse)[e]				.47
Baseline	8.0 (2.5)	8.6 (1.9)	−0.5 (−1.1 to 0.0)	
6 mo	6.3 (3.3)	7.1 (3.1)	−0.8 (−1.7 to 0.0)	
12 mo	5.8 (3.4)	5.9 (3.5)	−0.1 (−1.0 to 0.8)	
PHQ-8 depression symptoms (range, 0-24; higher score = worse)[f]				.13
Baseline	6.3 (4.5)	5.8 (5.0)	0.5 (−0.7 to 1.7)	
6 mo	4.4 (3.9)	4.8 (5.2)	−0.4 (−1.6 to 0.8)	
12 mo	4.3 (4.0)	4.5 (5.3)	−0.2 (−1.5 to 1.1)	
GAD-7 anxiety symptoms (range, 0-21; higher score = worse)[g]				.02
Baseline	4.0 (3.6)	3.5 (4.0)	0.5 (−0.5 to 1.4)	
6 mo	3.0 (3.5)	3.2 (4.5)	−0.2 (−1.3 to 0.8)	
12 mo	2.5 (3.3)	2.8 (4.2)	−0.4 (−1.4 to 0.7)	
PROMIS sleep disturbance (range, 8-32; higher score = worse)[g]				.33
Baseline	25.5 (7.8)	24.2 (8.4)	1.2 (−0.8 to 3.3)	
6 mo	22.2 (8.8)	22.0 (9.0)	0.2 (−2.2 to 2.5)	
12 mo	23.4 (8.2)	21.0 (8.3)	2.3 (0.1 to 4.6)	

(continued)

Functional response (≥30% improvement in BPI interference) occurred in 69 patients (59.0%) in the opioid group vs 71 patients (60.7%) in the nonopioid group; difference, −1.7% (95% CI, −14.4 to 11.0); *P* = .79. Pain intensity response (≥30% improvement in BPI severity) occurred in 48 patients (41.0%) in the opioid group vs 63 patients

Table 2. Patient-Reported Primary and Secondary Outcomes Among Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication (continued)

Outcome	Opioid Group, Mean (SD) (n = 119)	Nonopioid Group, Mean (SD) (n = 119)	Between-Group Difference (95% CI)[a]	Overall *P* Value[b]
MIDAS headache disability (range, 0-270; higher score = worse)[h]				
Baseline	6.1 (16.5)	6.1 (16.2)	−0.1 (−4.2 to 4.1)	.82
6 mo	3.8 (12.6)	5.5 (18.8)	−1.7 (−6.0 to 2.5)	
12 mo	3.7 (11.6)	3.2 (11.6)	−0.5 (−2.7 to 3.6)	
ASEX sexual function (range, 5-30; higher score = worse)[i]				
Baseline	17.4 (5.6)	17.7 (6.0)	−0.3 (−1.8 to 1.3)	.49
12 mo	17.9 (6.0)	19.0 (6.5)	−1.1 (−2.8 to 0.7)	
MFI general fatigue (range, 4-20; higher score = worse)[j]				
Baseline	13.8 (3.8)	12.8 (4.1)	1.0 (−0.0 to 2.0)	.68
6 mo	12.7 (3.9)	12.5 (4.3)	0.2 (−0.9 to 1.3)	
12 mo	12.5 (3.9)	12.0 (4.4)	0.6 (−0.6 to 1.7)	
MFI mental fatigue (range, 4-20; higher score = worse)[j]				
Baseline	10.0 (4.2)	9.6 (4.7)	0.4 (−0.7 to 1.6)	.39
6 mo	9.0 (4.2)	9.3 (4.4)	−0.3 (−1.4 to 0.9)	
12 mo	9.2 (3.9)	9.3 (4.3)	0.1 (−1.3 to 1.0)	
MFI physical fatigue (range, 4-20; higher score = worse)[j]				
Baseline	13.6 (4.1)	12.9 (4.1)	0.7 (−0.3 to 1.8)	.73
6 mo	12.9 (4.4)	12.5 (4.5)	0.4 (−0.8 to 1.5)	
12 mo	12.4 (4.3)	11.8 (4.3)	0.7 (−0.5 to 1.9)	
MFI reduced activity (range, 4-20; higher score = worse)[j]				
Baseline	11.4 (4.1)	10.9 (4.6)	0.5 (−0.7 to 1.6)	.74
6 mo	10.6 (4.6)	10.5 (4.5)	0.2 (−1.0 to 1.4)	
12 mo	10.6 (4.2)	10.3 (4.5)	0.3 (−1.0 to 1.5)	
MFI reduced motivation (range, 4-20; higher score = worse)[j]				
Baseline	9.8 (3.6)	8.8 (3.8)	1.0 (0.0 to 2.0)	.09
6 mo	9.1 (3.6)	8.9 (4.0)	0.2 (−0.8 to 1.2)	
12 mo	8.6 (3.2)	8.8 (3.7)	−0.2 (−0.7 to 1.6)	

Abbreviations: ASEX, Arizona Sexual Experience Scale; BPI, Brief Pain Inventory; GAD-7, 7-Item Generalized Anxiety Disorder Questionnaire; MFI, Multidimensional Fatigue Inventory; MIDAS, Migraine Disability Assessment Scale; PHQ-8, 8-Item Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RMDQ-11, 11-Item Roland-Morris Disability Questionnaire; VR-12, Veterans RAND 12-item Health Survey.

[a] Unadjusted time-specific between-group comparisons.

[b] *P* values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points.

[c] Missing data for 1 patient in the opioid group at 9 mo.

[d] Missing data for 1 patient in the opioid group at 3 mo.

[e] Missing data for 2 patients in the nonopioid group at 12 mo.

[f] Missing data for patients: at 6 mo, 3 in the opioid group and 9 in the nonopioid group; at 12 mo, 12 in the opioid group and 15 in the nonopioid group.

[g] Missing data for patients: at 6 mo, 2 in the opioid group and 8 in the nonopioid group; at 12 mo, 11 in the opioid group and 12 in the nonopioid group.

[h] Missing data for patients: at 6 mo, 3 in the opioid group and 8 in the nonopioid group ; at 12 mo, 13 in the opioid group and 14 in the nonopioid group.

[i] Missing data for patients: at baseline, 11 in the opioid group and 9 in the nonopioid group; at 12 mo, 19 in the opioid group and 17 in the nonopioid group.

[j] Missing data for patients: at baseline, 2 in the opioid group and 3 in the nonopioid group; at 6 mo, 2 in the opioid group and 9 in the nonopioid group; at 12 mo, 14 in the opioid group and 18 in the nonopioid group.

(53.9%) in the nonopioid group; difference, −12.8% (95% CI, −25.6 to 0.0); *P* = .05.

Health-related quality of life did not significantly differ between the 2 groups (physical health overall: *P* = .23; difference at 12 months, −1.3 [95% CI, −3.8 to 1.3]; mental health overall: *P* = .40; difference at 12 months, 0.7 [95% CI, −2.4 to 3.8]). Of the remaining secondary outcomes, only anxiety significantly differed between groups (**Table 2**; eTables 1-2 in Supplement 2).

Adverse Outcomes and Potential Misuse

The opioid group had significantly more medication-related symptoms over 12 months than the nonopioid group (overall: *P* = .03; difference at 12 months, 0.9 [95% CI, 0.3 to 1.5]) (**Table 3**).

There were no significant differences in adverse outcomes or potential misuse measures (Table 3). Two hospitalization or ED visit events were determined analgesic-related: 1 hospitalization in the nonopioid group and 1 ED visit in the

Table 3. Adverse Outcomes and Measures of Potential Misuse Among Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

Outcome	Opioid Group	Nonopioid Group	Between-Group Difference (95% CI)[a]	*P* Value
Primary Adverse Outcome				
Medication-related symptom checklist (0-19; higher score = worse), mean (SD)[b]				
Baseline	1.2 (1.9)	1.2 (1.9)	0.0 (−0.5 to 0.5)	.03[c]
3 mo	2.3 (2.5)	1.3 (1.8)	1.0 (0.5 to 1.6)	
6 mo	2.1 (2.7)	1.3 (2.3)	0.7 (0.1 to 1.4)	
9 mo	1.9 (2.8)	0.9 (1.9)	1.0 (0.4 to 1.6)	
12 mo	1.8 (2.6)	0.9 (1.8)	0.9 (0.3 to 1.5)	
Secondary Adverse Outcomes				
All-cause hospitalization, No.(%)[d]				
0	99 (83)	99 (83)	0 (−10 to 10)	.94[e]
1	15 (13)	16 (13)	1 (−9 to 8)	
≥2	6 (5)	5 (4)	1 (−5 to 6)	
All-cause ED visit, No.(%)[d]				
0	60 (50)	73 (61)	−11 (−24 to 2)	.18[e]
1	34 (28)	30 (25)	3 (−8 to 15)	
≥2	26 (22)	17 (14)	8 (−2 to 17)	
Number of falls in 12 mo after enrollment, No.(%)[f]				
0	63 (53)	63 (53)	0 (−13 to 13)	.19[e]
1	26 (22)	17 (14)	8 (−2 to 17)	
≥2	29 (25)	39 (33)	−8 (−20 to 3)	
Potential Misuse Measures				
Patients with ≥1 positive urine drug tests for an illicit drug or unexplained prescription drug, No. (%)[g]				
Illicit drug positive	6 (5)	12 (11)	−5 (−12 to 2)	.13[e]
Unexplained prescription drug positive	11 (10)	9 (8)	3 (−5 to 10)	.67[e]
Clinician-assessed behaviors, No.(%)				
Significant PMP finding at any visit[h]	6 (5)	4 (3)	2 (−3 to 7)	.75[i]
Misuse behavior at any visit[j]	11 (9)	8 (7)	3 (−4 to 9)	.47[e]
Patient-reported substance use at 12 mo, No.(%)				
Hazardous alcohol use[k]	2 (2)	4 (4)	−2 (−6 to 3)	.44[i]
Past-year drug use[l]	17 (16)	13 (13)	3 (−6 to 13)	.56[e]

Abbreviations: ED, emergency department; PMP, Prescription Monitoring Program.

[a] Unadjusted time-specific between-group comparison of means or percentages.

[b] Missing data for patients: at 3 mo, 1 in the nonopioid group; at 6 mo, 1 in the opioid group and 1 in the nonopioid group; at 12 mo, 3 in the opioid group and 3 in the nonopioid group (n = 119 in each group).

[c] *P* value for treatment by time interaction.

[d] Hospitalization and ED visit events were counted until 13 mo after randomization for all randomized patients (n = 120 in each group). Events that started in the ED and resulted in hospitalization were counted as hospitalizations and do not contribute to the ED visit count.

[e] *P* value from χ^2 test.

[f] The sum of falls reported at each follow-up interview. Missing data for 1 patient in the opioid group.

[g] Illicit drugs are illegal substances, including cannabis. Unexplained prescription drugs are potentially prescribed substances for which there was no known prescription. Missing data for patients: 4 in the opioid group and 6 in the nonopioid group.

[h] Significant PMP finding is any prescription that was not disclosed and for which there was no clear acute pain-related indication (n = 119 in each group).

[i] *P* value for Fisher exact test.

[j] Misuse behavior was an Addiction Behavior Checklist score of 3 or more at any visit (n = 119 in each group).

[k] Hazardous alcohol use is Alcohol Use Disorders Identification Test score of 8 or more. Missing data for patients: 4 in the opioid group and 6 in the nonopioid group.

[l] Positive result was defined as a patient report of any past-year use of cannabis, cocaine, methamphetamine, inhalants, hallucinogens, street opioids, or prescription medications (opioids, sedatives, or stimulants) for nonmedical purposes. Missing data for 13 opioid patients and 17 nonopioid patients.

opioid group. No deaths, "doctor-shopping," diversion, or opioid use disorder diagnoses were detected.

Intervention Adherence and Retention

Number and duration of study visits were similar in the 2 groups (**Table 4**). Twenty-three patients (19%) in the opioid group and 10 patients (8%) in the nonopioid group discontinued study medication (eTable 6 in Supplement 2). Most patients in the opioid group received low or moderate dosage therapy (eTables 7-8 in Supplement 2). In each 90-day follow-up period, fewer than 15% of patients in the opioid group had a mean dispensed dosage of 50 ME mg/d or more. In the

Table 4. Medications and Visits Over 12 Months From the Electronic Health Records of Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

	Opioid Group (n = 119)		Nonopioid Group (n = 119)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Study drugs, No.[a]	1.7 (0.8)	2.0 (1.0-2.0)	3.8 (1.7)	4.0 (3.0-5.0)
Study prescribed analgesic, months, No.[b]				
Acetaminophen	0.1 (0.5)	0.0 (0.0-0.0)	2.6 (3.2)	1.0 (0.0-4.0)
Oral NSAID	0.4 (2.0)	0.0 (0.0-0.0)	5.9 (4.9)	5.0 (0.5-10.0)
Analgesic adjunct	0.2 (1.4)	0.0 (0.0-0.0)	3.3 (4.3)	1.0 (0.0-6.2)
Topical	0.0 (0.6)	0.0 (0.0-0.0)	3.5 (3.5)	3.0 (1.0-6.0)
Tramadol	0.1 (0.6)	0.0 (0.0-0.0)	0.4 (1.3)	0.0 (0.0-0.0)
Opioid[c]	8.1 (4.1)	8.4 (5.6-11.2)	0.0 (0.0)	0.0 (0.0-0.0)
Study visits, No.				
In-person visits	2.8 (2.0)	2.0 (2.0-3.0)	2.8 (2.2)	2.0 (2.0-3.0)
Telephone visits	6.2 (2.9)	7.0 (5.0-8.0)	6.2 (2.5)	7.0 (5.0-8.0)
Total study visit duration, min[d]	231 (95)	230 (159-289)	217 (82)	197 (155-267)
Nonstudy outpatient visits, No.[e]				
Primary care	6.8 (6.5)	5.0 (2.0-8.0)	7.1 (7.1)	4.0 (2.0-9.0)
Specialty	6.7 (12.0)	3.0 (1.0-8.0)	6.3 (6.4)	4.0 (1.0-9.0)
Mental health	4.8 (10.3)	0.0 (0.0-6.0)	7.5 (22.1)	0.0 (0.0-5.0)
Rehabilitation	4.5 (15.8)	1.0 (0.0-3.0)	3.1 (6.1)	1.0 (0.0-4.0)

Abbreviations: IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Number of unique study-prescribed medication formulations during the intervention, regardless of duration of use.

[b] Analgesic months is the sum of the number of months of medication dispensed from Veterans Affairs outpatient pharmacies for each discrete medication within a category during the 12-mo intervention period. For example, a patient dispensed analgesic A for 6 mo and analgesic B for 12 mo would have 18 analgesic months. Crossover (ie, nonopioid medications in the opioid group and vice versa) is accounted for by patients who desired discontinuation of all medications in their assigned study group. Study clinicians restarted preenrollment medications if requested by these patients, but did not manage or adjust these off-protocol medications.

[c] Opioid months do not include tramadol.

[d] The sum of minutes extracted from clinician-entered *Current Procedural Terminology* codes for all study encounters.

[e] Outpatient visits include both in-person and telephone encounters with any type of clinician, including physicians, mental health providers, physical therapists, and nurses. Encounters for diagnostic testing (eg, radiology examinations, endoscopy) and nonmedical ancillary services (eg, social work, nutrition, education) are not included.

nonopioid group, tramadol was dispensed to 4 patients (3%), 6 patients (5%), 8 patients (7%), and 13 patients (11%) in the first, second, third, and fourth 90-day follow-up windows, respectively. eTables 9 to 10 in Supplement 2 show nonstudy pain treatments.

Subgroup and Sensitivity Analyses

Post hoc tests for interaction of primary pain diagnosis (ie, back pain, osteoarthritis pain) by treatment group on pain outcomes were not statistically significant (P = .25 for BPI interference, P = .34 for BPI severity). For the back pain subgroup at 12 months, BPI interference was 2.9 in the opioid group (SD, 2.1) vs 3.3 in the nonopioid group (SD, 2.6); difference, −0.4 (95% CI, −1.2 to 0.3); BPI severity was 3.7 in the opioid group (SD, 1.8) vs 3.6 in the nonopioid group (SD, 2.0); difference, 0.1 (95% CI, −0.5 to 0.8). For the hip or knee osteoarthritis pain subgroup at 12 months, BPI interference was 4.4 in the opioid group (SD, 2.8) vs 3.4 in the nonopioid group (SD, 2.6); difference, 1.1 (95% CI, −0.1 to 2.3); BPI severity was 4.5 in the opioid group (SD, 2.2) vs 3.4 in the nonopioid group (SD, 1.8); difference, 1.1 (95% CI, 0.2 to 2.0).

In a post hoc sensitivity analysis, adjusting for baseline smoking status, results did not substantially change (BPI interference adjusted overall, P = .65; BPI severity adjusted overall, P = .05; medication-related adverse symptoms adjusted overall, P = .03).

Discussion

Among patients with chronic back pain or hip or knee osteoarthritis pain, treatment with opioids compared with nonopioid medications did not result in significantly better pain-related function over 12 months. Nonopioid treatment was associated with significantly better pain intensity, but the clinical importance of this finding is unclear; the magnitude was small (0.5 points on the 0-10 BPI severity scale) and was less than the MCID of 1.0. Opioids caused significantly more medication-related adverse symptoms than nonopioid medications. Overall, opioids did not demonstrate any advantage over nonopioid medications that could potentially outweigh their greater risk of harms.

Among the secondary outcomes, only anxiety symptoms were statistically better in the opioid group. This finding is consistent with the role of the endogenous opioid system in stress and emotional suffering.[31] The importance of this finding is uncertain because the magnitude of the difference in anxiety was small and the overall level of anxiety

was low (9% of patients had moderate severity anxiety symptoms at baseline).

Recent systematic reviews have concluded that opioids have small beneficial effects on pain compared with placebo that may be outweighed by common adverse effects.[5,32-34] Observational studies have found that treatment with long-term opioid therapy is associated with poor pain outcomes, greater functional impairment, and lower return to work rates.[35-37] In this trial, pain-related function improved for most patients in each group. Poor pain outcomes associated with long-term opioids in observational studies may be attributable to overprescribing and insufficient pain management resources rather than to direct negative effects of opioids.[31,38] This trial did not have sufficient statistical power to estimate rates of death, opioid use disorder, or other serious harms associated with prescribed opioids.[39-41]

This trial's pragmatic design has several advantages. First, enrolled patients had characteristics similar to those of patients receiving opioids in VA primary care, including patients with depression and posttraumatic stress disorder.[6] Second, flexibility of treatment within assigned groups facilitated high study retention. Third, the treat-to-target approach reflects clinical practice more closely than approaches comparing single drugs or fixed dosages and allowed maximized benefit for patients.[9,10] Because individual medications are effective for only a minority of patients with chronic pain,[33,42] structured reassessment and adjustment of medications is likely necessary for effective pharmacological treatment.

Few data are available regarding optimal opioid dosing for pain, function, and tolerability. A meta-analysis of chronic back pain trials found incremental benefits of larger opioid dosages, but concluded benefits were too small "to be clinically important even at high doses."[32] Another meta-analysis of opioid trials for musculoskeletal pain in older adults found no association of dosage with pain or function.[34] Recent opioid prescribing guidelines recommend keeping daily dosages low.[2-4] This study was designed to identify the medication regimen with the best balance of benefits and tolerability for each patient and allowed treatment with a range of low to moderately high opioid dosages.

By pragmatic design, this trial did not require high levels of adherence to study medications. This study had high active treatment continuation and study retention rates, so results reflect outcomes across a range of treatment adherence.

Limitations

This study has several limitations. First, the complexity of interventions precluded masking of patients. Because primary outcomes were patient-reported, results are subject to potential reporting bias that would likely favor opioids. Second, there was an imbalance in prerandomization treatment preference. Any effect of this imbalance would likely favor opioids. Third, because this study was conducted in VA clinics, patient characteristics differ from those of the general population, most notably in sex distribution. Fourth, patients with physiological opioid dependence due to ongoing opioid use were excluded, so results do not apply to this population.

Conclusions

Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

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Concept and design: Krebs, Kroenke, Bair.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Krebs, Jensen, DeRonne, Bair.
Critical revision of the manuscript for important intellectual content: Gravely, Nugent, DeRonne, Goldsmith, Kroenke, Bair, Noorbaloochi.
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