JAMA Internal Medicine | Original Investigation

Nonsteroidal Anti-inflammatory Drugs vs Cognitive Behavioral Therapy for Arthritis Pain
A Randomized Withdrawal Trial

Liana Fraenkel, MD, MPH; Eugenia Buta, PhD; Lisa Suter, MD; Maureen Dubreuil, MD; Charles Levy, MD; Catherine Najem, MD; Matthew Brennan, MS; Barbara Corn, PhD; Robert Kerns, PhD; Joseph Goulet, PhD

IMPORTANCE Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for knee osteoarthritis. However, they are associated with uncertain long-term clinical benefit and significant toxic effects.

OBJECTIVE To evaluate whether discontinuing NSAIDs and engaging in a telephone-based cognitive behavioral therapy (CBT) program is noninferior to continuing NSAIDs for patients with knee osteoarthritis.

DESIGN, SETTING, AND PARTICIPANTS The Stopping NSAIDs for Arthritis Pain multicenter randomized withdrawal trial was conducted for 364 patients taking NSAIDs for knee osteoarthritis pain on most days of the week for at least 3 months between September 1, 2013, and September 30, 2018. Analysis was performed on an intent-to-treat basis.

INTERVENTIONS Participants discontinued their current NSAID and took 15 mg per day of meloxicam daily during a 2-week run-in period. Those who remained eligible were randomized in a 1:1 ratio to receive meloxicam or placebo for 4 weeks (blinded phase 1). Participants receiving meloxicam then continued this medication for 10 weeks, while those receiving placebo participated in a 10-week CBT program (unblinded phase 2).

MAIN OUTCOMES AND MEASURES The primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score at 4 weeks with the noninferiority margin set at 1. Secondary outcomes included the area under the curve of the pain score after 4 weeks as well as the WOMAC pain score, area under the curve of the pain score, WOMAC disability score, and global impression of change after treatment at 14 weeks.

RESULTS A total of 180 participants (161 men; mean [SD] age, 58. 2 [11.8] years) were randomized to receive placebo followed by CBT, and a total of 184 participants (154 men; mean [SD] age, 58.5 [10.0] years) were randomized to receive meloxicam. After adjustment for baseline pain and study site, the estimated mean difference in WOMAC pain score between the placebo and meloxicam groups after 4 weeks was 1.4 (95% CI, 0.8-2.0; noninferiority test $P = .92$). At week 14, the adjusted mean difference in WOMAC pain score between the placebo (followed by CBT) and meloxicam groups was 0.8 (95% CI, 0.2-1.4; noninferiority $P = .28$). There was no statistically significant difference in the global impression of change (mean difference in scores, −0.2; 95% CI, −0.4 to 0.1; $P = .15$) or lower extremity disability (mean difference in scores, 0.9; 95% CI, −1.4 to 3.2; $P = .45$) between the 2 groups after 14 weeks.

CONCLUSIONS AND RELEVANCE Among patients with knee osteoarthritis, placebo and CBT (after placebo) are inferior to meloxicam. However, the WOMAC pain score differences between the 2 groups were small, and there were no statistically significant differences in participants' global impression of change or function after 14 weeks.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01799213

JAMA Intern Med. doi:10.1001/jamainternmed.2020.2821
Published online July 20, 2020.

Supplemental content

Author Affiliations: Veterans Affairs Connecticut Healthcare System, West Haven (Fraenkel, Buta, Suter, Brennan, Corn, Goulet); Section of Rheumatology, Yale University School of Medicine, New Haven, Connecticut (Fraenkel, Suter); Yale University School of Medicine, New Haven, Connecticut (Buta, Brennan, Kerns, Goulet); Veterans Affairs Boston Healthcare System, Boston, Massachusetts (Dubreuil); Boston University School of Medicine, Boston, Massachusetts (Dubreuil); North Florida/South Georgia Veterans Health System, Gainesville, Florida (Levy); Providence Veterans Affairs Medical Center, Providence, Rhode Island (Najem).

Corresponding Author: Liana Fraenkel, MD, MPH, Section of Rheumatology, Yale University School of Medicine, 300 Cedar St, PO Box 208031, TAC Building, Room 525, New Haven, CT 06520 (liana.fraenkel@yale.edu).

Knee osteoarthritis (OA) affects more than 31 million US adults and is an important cause of disability worldwide.[1] Treatment is aimed at management of symptoms and maintenance or improvement of lower extremity function. Short-term trials have demonstrated that nonsteroidal anti-inflammatory drugs (NSAIDs) are more effective at decreasing knee pain in OA compared with both placebo and acetaminophen.[2] However, the effect sizes are small.[3,4] Gregori et al[5] published a systematic review and network meta-analysis examining the association of pharmacologic options with knee OA pain over at least 1 year. Of the 7 NSAIDs studied, only celecoxib was associated with a significant, albeit small, decrease in pain.

Despite their limited benefits, NSAIDs are the most commonly prescribed medications for OA. The widespread use of NSAIDs for OA warrants scrutiny because of the significant toxic effects associated with this class of medications.[6,7] Thus, while NSAIDs may play a role in treatment of knee OA, there is a need to examine safer alternatives. The objective of this trial was to determine whether replacing NSAIDs with cognitive behavioral therapy (CBT) is a viable option for patients with knee OA. Cognitive behavioral therapy is a psychological treatment that aims to change maladaptive thinking or behavior patterns and teach coping skills. It has demonstrated efficacy for reducing pain and improving function in persons with a broad spectrum of conditions, including OA.[8-12] Most trials examining the efficacy of CBT have compared this modality with usual care or a wait-list control group.[13,14] Few studies have included an active comparator, and whether CBT can be used to replace or minimize chronic use of analgesics is not known.

We conducted a 2-phase, noninferiority randomized withdrawal trial. Participants discontinued their current NSAID and took meloxicam daily during a 2-week run-in period. To examine whether placebo is noninferior to continued NSAID use, participants who remained eligible after the run-in period were randomized to receive meloxicam or placebo for 4 weeks (double-blinded phase 1). After 4 weeks, participants in the NSAIDs group continued meloxicam. Those in the placebo group stopped taking the placebo and participated in a 10-week telephone-based CBT program. The objective of the second phase was to determine whether CBT (after placebo) is noninferior to continued NSAIDs. Placebo was not continued during phase 2 because it may potentiate the effects of CBT.

Key Points

Question Is replacing meloxicam with placebo noninferior to continued meloxicam, and is engaging in a telephone-based cognitive behavioral therapy program noninferior to continuing meloxicam for patients with knee osteoarthritis?

Findings In this multicenter randomized withdrawal trial, the pain scores of patients randomized to stop meloxicam were inferior at 4 weeks to the pain scores of patients who continued meloxicam; the pain scores of patients who engaged in cognitive behavioral therapy after placebo were also inferior to the pain scores of patients who continued meloxicam. However, the pain score differences between the 2 groups were small (less than the minimal clinically important difference), and there were no statistically significant differences in patients' reported global impression of change or function.

Meaning Among patients with knee osteoarthritis, placebo and cognitive behavioral therapy (after placebo) are inferior to meloxicam.

Methods

Study Overview

Details of the study protocol have been previously published (trial protocol in Supplement 1).[15] The study was a 2-phase randomized withdrawal trial preceded by a 2-week run in period. During the 2-week run-in period, participants replaced their current NSAID with the study drug (meloxicam, 15 mg per day). Participants remaining eligible at the end of the run-in period were randomized to receive placebo or meloxicam. After 4 weeks, participants were unblinded and either continued meloxicam or began a 10-week telephone-based CBT program. The original protocol specified a 12-week CBT program with outcomes measured over a total of 16 weeks. Prior to starting the trial, however, the CBT protocol was shortened to 10 weeks and data were measured over 14 weeks. The trial was approved by the Veterans Affairs (VA) Central institutional review board. Participants provided written informed consent.

Participants

Participants were drawn from veterans with knee OA currently enrolled in the VA Connecticut Healthcare System, Providence VA Medical Center, North Florida/South Georgia Veterans Health System, or the VA Boston Healthcare System. The eligibility criteria were age 20 years or older, radiographic evidence of knee OA, and use of an NSAID (other than daily aspirin) for knee pain on most days of the month for at least the past 3 months. Continued use of tramadol and non-NSAID oral and topical analgesics was permitted. Exclusion criteria included significant hearing impairments, current opioid prescriptions excluding tramadol, contraindications to NSAID use, recent or scheduled intra-articular injections or surgery, comorbid conditions other than knee pain that limited walking, and bilateral knee replacements or knee pain in the replaced knee only. Additional eligibility criteria are described in a previous publication.[15]

Recruitment

We identified potential participants from electronic health record data. Veterans meeting initial eligibility criteria were mailed a letter informing them of the purpose of the study and enabling them to opt out of a screening telephone call from the study recruiter. All eligibility criteria were verified during the screening telephone call, and participants agreeing to participate were mailed a consent form. Primary care physicians were notified by encrypted email each time one of their patients was enrolled in the study. Recruitment started September 1, 2013, and data collection ended September 30, 2018. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Run-in Period

All participants (including those who were already taking meloxicam) discontinued their current NSAID and took the study drug (blue gel capsule) once a day with breakfast. Participants remained eligible if they reported taking the study drug on 10 days or more, denied developing any adverse events to the study drug, denied using arthritis medications for knee pain other than acetaminophen or other allowable medications, did not report worsening of knee pain on a global impression of change scale, and did not develop a specified exclusion criterion during the 2-week run-in period. Global impression of change after treatment was measured on a 5-point scale (where 1 indicates much better and 5 indicates much worse).

Randomization

Participants eligible after the run-in period were randomly assigned to the meloxicam or placebo group in a 1:1 ratio using a permuted block design with variable block size (2-6) with stratification by site and baseline knee pain intensity (≤8 vs >8 on the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] knee pain subscale; range, 0-20, with higher scores reflecting worse pain).[16] For participants with bilateral symptoms, the most painful knee was chosen as the study knee.

Study Capsules

Active meloxicam and indistinguishable placebo capsules (both blue gel) were supplied by the VA Connecticut's Research Pharmacy. The active capsules included 15 mg of meloxicam, and the placebo capsules included excipients only.

CBT Protocol

The CBT protocol included 10 modules delivered over 10 weeks in 30- to 45-minute telephone contacts with an experienced psychologist using a treatment manual modified for knee OA based on previously developed and tested materials for chronic back pain.[17] We allowed the time frame to be extended to account for missed sessions. The CBT program consisted of 1 introductory module, 8 pain coping skills modules (deep breathing and visual imagery, progressive muscle relaxation, physical activity and bodily mechanics, identifying unhealthy thoughts, balancing unhealthy thoughts, managing stress, time-based pacing, and sleep hygiene), and concluded with a module emphasizing skill consolidation and relapse prevention. Participants unblinded to the CBT group were mailed a binder with handouts for the pain coping skills included in the treatment, a compact disc to facilitate deep breathing and progressive muscle relaxation, and tracking goals sheets noting the coping skills to be practiced in between each session as well as a personal goal of their choosing to work on during that week.

Data Collection

Data were collected over the telephone by a trained project coordinator blinded to treatment allocation during phase 1. Demographic and clinical characteristics were assessed at baseline. The primary outcome was the WOMAC pain score 4 weeks after randomization. Secondary outcomes included WOMAC pain scores at the end of phase 2, the area under the curve (AUC) of the WOMAC pain scale score at the end of phases 1 and 2, and the WOMAC disability scale score and participants' global impression of change at the end of phase 2. The WOMAC is a disease-specific health status questionnaire. Of the instruments used to assess change in persons with knee OA, the WOMAC has been the most extensively validated and is both recommended for (by the Osteoarthritis Research Society International) and widely used in OA trials.[18,19] The WOMAC pain scale consists of 5 questions that ask about pain during walking, stair use, lying in bed at night, sitting, and standing. Each question is scored on a 5-point scale, where 0 indicates no pain; 1, mild pain; 2, moderate pain; 3, severe pain; and 4, very severe pain. Total pain scores range from 0 to 20, with higher scores reflecting worse pain. The WOMAC also includes a lower extremity physical function subscale containing 17 items that assess the amount of difficulty individuals say they have with climbing stairs, rising from a chair, walking, and other activities of daily living. Responses are measured and scored in the same way as the pain scale. Both the pain scale and disability scale (17 items) can be analyzed separately. The WOMAC pain scale score was collected at baseline and weekly during the trial, while the WOMAC lower extremity disability scale score was collected at baseline and in the final week of treatment. Participants' global impression of change after treatment was measured on a 5-point scale (where 1 indicates much better and 5 indicates much worse) at baseline and in the final week of treatment. Adherence to study medication, use of cotherapies, and adverse events were measured weekly.

Sample Size Calculation

The study was powered to test whether placebo was noninferior to meloxicam as measured by the WOMAC pain scale score 4 weeks after randomization. The range of the WOMAC pain subscale is 0 to 20, and the minimum clinically important difference is 2.1.[16,20] We set the noninferiority margin to 1, which is less than 50% of the minimum clinically important difference. A sample size of 434 (217 per group) would achieve 90% power to detect noninferiority using a 1-sided, 2-sample *t* test at a significance level (α) of .025, assuming the true difference between the means to be 0 and an SD of 3.2.[21]

Statistical Analysis

Analysis was performed on an intent-to-treat basis. We originally planned to use a linear regression model to test the noninferiority of placebo compared with meloxicam as measured by the WOMAC knee pain score 4 weeks after randomization (day 28 ± 3 days), with the margin of noninferiority prespecified as 1.[15] However, we changed this analysis to a linear mixed model over all weeks of data because it can better handle missingness and is more efficient with longitudinal data. The model included treatment group (placebo vs meloxicam), week (continuous), an interaction between group and week, and the 2 stratification variables: baseline WOMAC knee pain and site. To account for the nonlinear time trend, week was modeled using truncated quadratic splines with a knot at week 4 (end of phase 1). Random effects (intercept and slope) and a homogenous autoregressive correlation structure were used to

account for correlations within a subject. Specifically, the primary analysis tested (at α = .025) the hypothesis that the mean WOMAC pain score in the placebo group minus the mean WOMAC pain score in the meloxicam group at 4 weeks would be less than 1. We used the same mixed model to test a similar hypothesis at 14 weeks (secondary outcome). Analyses of the other secondary outcomes (except cotherapies used) were conducted using regression models including treatment group, baseline WOMAC knee pain score, and site. As planned, we conducted a noninferiority test (α = .025) for one secondary outcome (pain at week 14) and 2-sided difference tests ($P < .05$) for the other secondary outcomes. We also analyzed pain in the last week of treatment (last observation carried forward); this analysis was not prespecified but was added to supplement the pain comparison at week 14 because the participants in the CBT group were allowed extra weeks to complete their CBT sessions, so that some of them finished their treatment in week 15 or later. To accommodate different lengths of follow-up across participants, AUC was computed as time-averaged AUC (ie, AUC divided by the length of follow-up in weeks). Results for the continuous outcomes are presented as least-squares mean (SE) values. Because the variables indicating the number of days participants used cotherapies per week had a large proportion of zeroes, we dichotomized these variables (no use during week vs any use during week) and analyzed the resulting variables using logistic generalized linear mixed models for longitudinal data. The models included week, treatment group, baseline WOMAC knee pain score, and site as fixed effects plus a random intercept and slope as random effects. Results are reported as adjusted odds ratios with 95% CIs and represent the difference between groups averaged across all weeks. We also considered models with an interaction between week and treatment.

As a sensitivity analysis to examine the effect of missing data, we used multiple imputation (100 imputations) to impute the missing data for all participants.[22] Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc) and R, version 3.4.2 (R Foundation for Statistical Computing).

Results

A total of 490 participants (427 men; mean [SD] age, 58.4 [11.1] years; 318 non-Hispanic white) were enrolled and underwent the run-in period. The mean (SD) pain score at the start of the run-in period was 9.6 (3.4). A total of 364 participants (74%) remained eligible at the end of the run-in period and were randomized: 180 (161 men; mean [SD] age, 58.2 [11.8] years) to receive placebo followed by CBT and 184 (154 men; mean [SD] age, 58.5 [10.0] years) to receive meloxicam. The CONSORT flow diagram for both phase 1 and phase 2 is described in **Figure 1**. Baseline demographic and clinical characteristics were well balanced across the 2 groups (**Table 1**).

Primary Outcome

The WOMAC pain score was available for 84% (152 of 180) of participants in the placebo group and 92% (169 of 184) of participants in the meloxicam group 4 weeks after randomization. The overall mean (SD) pain score at baseline was 5.6 (3.8). After 4 weeks, the raw mean (SD) pain score increased to 7.8 (4.0) in the placebo group and to 6.7 (3.8) in the meloxicam group. Based on the mixed model of repeated pain measurements including all 355 participants (98%) with at least 1 postrandomization pain score, the estimated mean difference in pain score between the placebo and meloxicam groups at 4 weeks was 1.4 (95% CI, 0.8-2.0; noninferiority $P = .92$) (**Table 2**). The result from the sensitivity analysis for missing data (multiple imputation including all 364 participants [100%]) was similar, with the corresponding estimate being 1.4 (95% CI, 0.7-2.1; noninferiority $P = .85$).

Secondary Analyses

Participants in the placebo-followed-by-CBT group had a mean (SD) weekly pain measurement of 12.1 (3.3), and those in the meloxicam group had a mean (SD) pain measurement of 11.8 (2.9). A total of 9 participants (5 in the meloxicam group and 4 in the placebo group) had no postrandomization pain measurements. At week 14, 286 participants (79%) had pain score data available, and the adjusted mean difference in pain scores between the placebo-followed-by-CBT group and the meloxicam group based on the mixed model was 0.8 (95% CI, 0.2-1.4; noninferiority $P = .28$) (Table 2). Results from the sensitivity analysis for missing data were similar: from multiple imputation, the corresponding estimated difference in mean pain score was 1.1 (95% CI, 0.3-1.8; noninferiority $P = .57$). The median last week of follow-up when pain was reported was week 16 (interquartile range, 15-18) in the placebo-followed-by-CBT group and was week 15 (interquartile range, 14-15) in the meloxicam group. The adjusted difference in pain score between the placebo (followed by CBT) group and the meloxicam group in the final week of follow-up (last observation carried forward) was 0.6 (95% CI, −0.1 to 1.3; noninferiority test $P = .12$) (Table 2). Mean pain scores over time are illustrated in **Figure 2**. In terms of time-averaged AUC of pain scores, meloxicam was superior to placebo in both phase 1 and across all weeks (Table 2). There was no evidence of a difference in the global impression of change (mean difference in scores, −0.2; 95% CI, −0.4 to 0.1; $P = .15$) or lower extremity disability (mean difference in scores, 0.9; 95% CI, −1.4 to 3.2; $P = .45$) between the two groups (Table 2). The sensitivity analysis (multiple imputation) provided similar results.

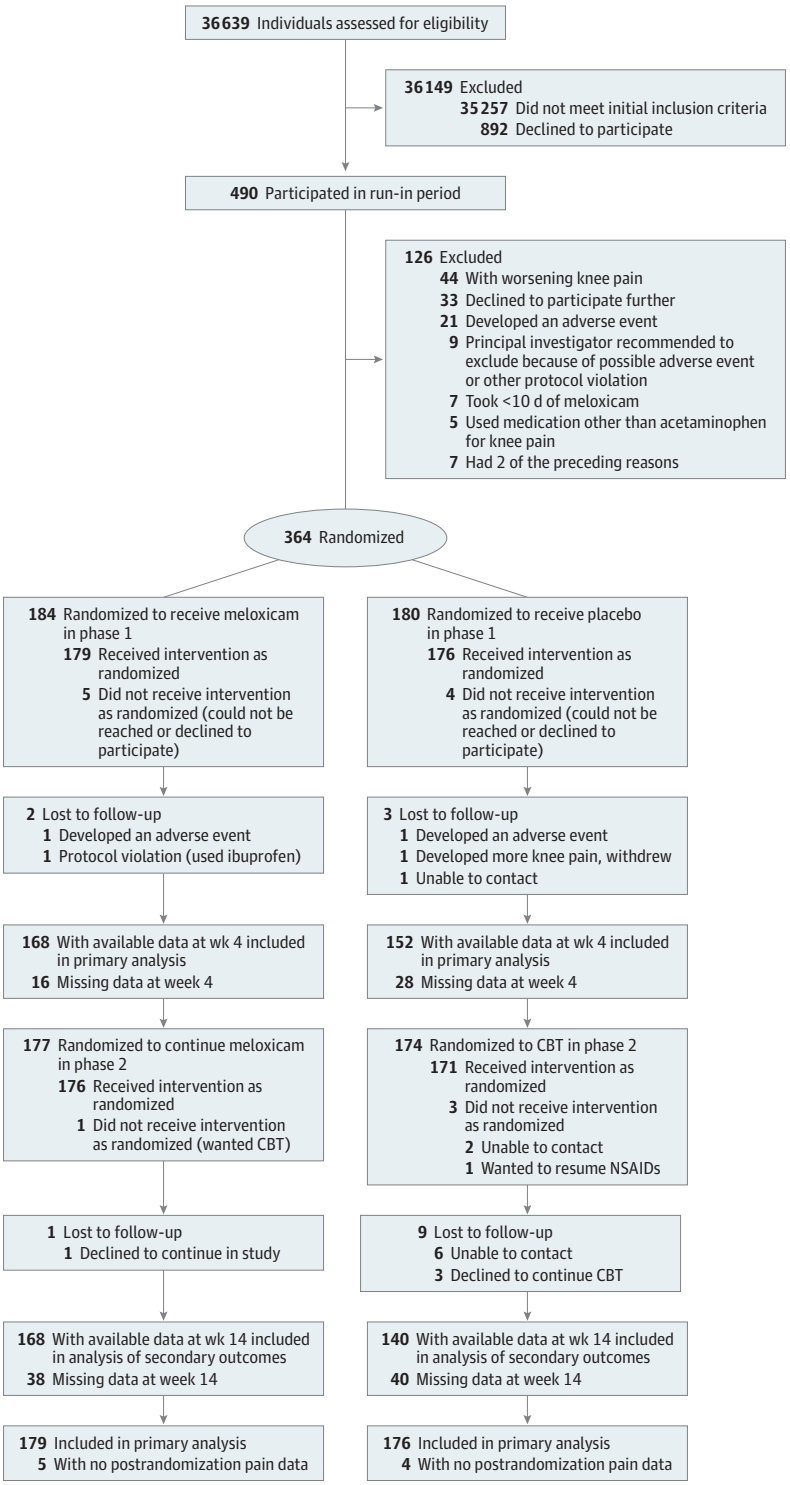
Safety

The number of participants experiencing a serious adverse event was similar in both groups (3 in the placebo-followed-by-CBT group and 4 in the meloxicam group; **Table 3**). Twice as many participants in the meloxicam group reported a gastrointestinal adverse effect compared with the placebo-followed-by-CBT group (12 vs 6).

Adherence to Study Medication

Participants reported adherence data for a median of 4 weeks (interquartile range, 3-4 weeks) in the placebo group and 13 weeks (interquartile range, 11-14 weeks) in the meloxicam group. Participants perfectly adhered (ie, 7 days out of 7) to their study medication in 90% (575 of 639) of the weeks in the pla-

Figure 1. CONSORT Diagram



CBT indicates cognitive behavioral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.

cebo group and 87% (1892 of 2175) of the weeks in the meloxicam group.

Use of Cotherapies

Across all weeks, participants in the placebo group used acetaminophen in 46% (1005 of 2186) of the weeks and participants in the meloxicam group in 26% (558 of 2180) of the weeks. The corresponding percentages for the other cotherapies were as follows: 8% (178 of 2186) in the placebo group vs 5% (99 of 2179) in the meloxicam group for other prescribed medications for knee pain and 27% (592 of 2185) in the placebo group vs 21% (448 of 2179) in the meloxicam group for

Table 1. Participant Characteristics by Treatment Group

Characteristic	Participants, No. (%)	
	Placebo (n = 180)	Meloxicam (n = 184)
Age, mean (SD), y	58.2 (11.8)	58.5 (10.0)
Male sex	161 (89)	154 (84)
Race/ethnicity		
Non-Hispanic		
White	120 (67)	112 (61)
Black	45 (25)	51 (28)
Hispanic	9 (5)	8 (4)
Other	6 (3)	13 (7)
Marital status		
Single	36 (20)	42 (23)
Married or partner	104 (58)	97 (53)
Widowed	9 (5)	8 (4)
Separated or divorced	31 (17)	37 (20)
Highest educational level		
≤8th Grade	0	2 (1)
Some high school	8 (4)	2 (1)
High school graduate or GED	42 (23)	41 (22)
Some college or 2-y degree	64 (36)	83 (45)
4-y College degree	33 (18)	30 (16)
Graduate degree or higher	32 (18)	26 (14)
Employment status		
Employee or student		
Full-time	73 (41)	73 (40)
Part-time	15 (8)	24 (13)
Unemployed	9 (5)	9 (5)
Disabled	22 (12)	25 (14)
Retired	61 (34)	53 (29)
Current housing		
Homeowner	116 (64)	110 (60)
Rents apartment or room	45 (25)	52 (28)
Lives rent free with friend or relative	11 (6)	12 (7)
Group, assisted living, or nursing home	0	2 (1)
Other	8 (4)	8 (4)
Overall health status		
Excellent	9 (5)	12 (7)
Very good	40 (22)	54 (29)
Good	100 (56)	82 (45)
Fair	28 (16)	31 (17)
Poor	3 (2)	5 (3)
BMI, mean (SD)	33.9 (7.1)	33.4 (7.2)
Psychiatric comorbidity	88 (49)	96 (52)
Social support score, median (IQR)[a]	75 (50-100)	75 (50-100)
Comorbidities		
High blood pressure	100 (56)	103 (56)
High cholesterol	81 (45)	84 (46)
Type 2 diabetes	43 (24)	39 (21)
Mental illness	43 (24)	55 (30)
Lung disease	5 (3)	6 (3)
Kidney disease	4 (2)	1 (1)
Heart disease	14 (8)	14 (8)
Stroke	0	1 (1)
Cancer[b]	7 (4)	8 (4)
Stomach ulcer	4 (2)	4 (2)
Baseline WOMAC score, mean (SD)		
Pain (0-20)	5.4 (3.8)	5.9 (3.9)
Disability (0-68)	17.5 (12.1)	17.9 (11.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, General Educational Development certification; IQR, interquartile range; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Measured on a scale from 0 to 100, where 0 indicates no support available and 100 indicates support always available.

[b] Excluding nonmelanoma skin cancer.

other unprescribed medications, creams, or supplements for knee pain (eAppendix, eFigure, and eTable in Supplement 2).

Discussion

In this randomized withdrawal trial, both placebo and CBT (after placebo) were inferior to meloxicam. The difference between placebo and meloxicam during the first 4 weeks of the trial was slightly less than the minimum clinically important difference of the WOMAC pain scale score. Nonetheless, the upper limit of the CI (2.09) exceeded the prespecified noninferiority margin of 1; therefore, we cannot conclude that placebo is noninferior to meloxicam. The difference in pain scale score between the placebo followed by CBT group and the meloxicam group after 14 weeks was also smaller than the minimum clinically important difference of the WOMAC pain scale score. However, the upper limit of the CI exceeded the noninferiority margin of 1; therefore, we cannot conclude that CBT is noninferior to meloxicam. Moreover, use of cotherapies for knee pain was higher in participants randomized to the placebo followed by CBT group vs those in the meloxicam group. However, we found no statistically significant difference in participants' function as measured by the WOMAC subscale or global impression of change or function after 14 weeks.

Although noninferiority trials are more complex than superiority trials, because the clinical question of interest was to determine whether placebo and CBT (after placebo) is no worse than continued NSAIDs, a superiority trial is not well suited to this proposal. A noninferiority trial is appropriate in this context because the new strategy under investigation is safer than the current widespread long-term use of NSAIDs for knee OA.[23] Moreover, a superiority trial would not allow us to determine whether patients who discontinue NSAIDs do not experience more pain compared with those who continue NSAIDs, even if the superiority trial was to be well powered and negative.[24] Although superiority trials that fail to reject the null hypothesis are frequently interpreted as negative

Table 2. Primary and Secondary Analysis Results

Outcome	Placebo		Meloxicam		Adjusted difference, placebo minus meloxicam	
	Participants with available outcome data, No.	LS mean (SE) value	Participants with available outcome data, No.	LS mean (SE) value	Mean (95% CI)	*P* value
Primary analysis						
WOMAC knee pain at week 4 (possible range, 0-20)[a]	152	8.0 (0.2)	169	6.6 (0.2)	1.4 (0.8 to 2.0)	.92[b]
Secondary analyses						
WOMAC knee pain						
At week 14[a]	140	6.9 (0.2)	146	6.0 (0.2)	0.8 (0.2 to 1.4)	.28[b]
In final week[c]	176	6.6 (0.3)	179	6.1 (0.3)	0.6 (−0.1 to 1.3)	.12[b]
Time-averaged AUC[d]						
Weeks 1-4	167	7.7 (0.2)	173	6.7 (0.2)	1.1 (0.5 to 1.6)	<.001[e]
Over all weeks	175	7.5 (0.2)	179	6.4 (0.2)	1.1 (0.5 to 1.6)	<.001[e]
Global impression of change in final week (possible range, 1-5)[f,g]	160	2.1 (0.1)	176	2.3 (0.1)	−0.2 (−0.4 to 0.1)	.15[e]
WOMAC function in final week (possible range, 0-68)[g]	160	19.7 (0.9)	176	18.8 (0.9)	0.9 (−1.4 to 3.2)	.45[e]

Abbreviations: AUC, area under the curve; LS, least-squares; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Results for the first 2 outcomes (WOMAC knee pain at week 4 and 14) were obtained from a linear mixed model. The model included all participants with at least 1 postrandomization pain score (176 placebo and 179 meloxicam). Results for the other outcomes were obtained from linear regression models. All models were adjusted for the stratification variables (baseline WOMAC knee pain score and site).

[b] Noninferiority (1-sided); $P < .03$.

[c] Last observation carried forward.

[d] Time-averaged AUC = AUC divided by the length of follow-up in weeks.

[e] Difference (2-sided); $P < .05$.

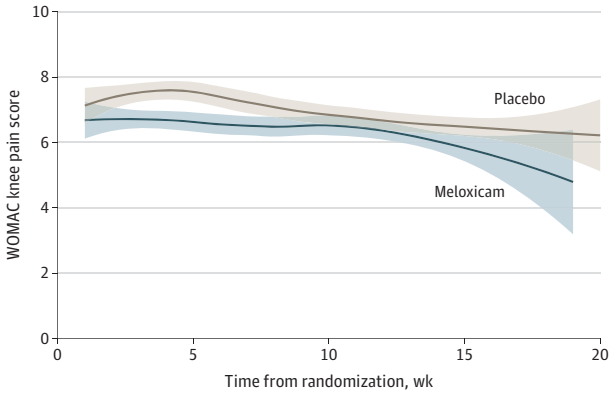
[f] Global impression of change range: 1 indicates much better and 5 indicates much worse.

[g] Final week (≥12 for all participants).

(ie, no difference between the 2 groups), they should be interpreted as indeterminate (uncertain).[24]

Several alternative therapies to NSAIDs are available. We chose CBT because it is a widely used nonpharmacologic intervention, has established efficacy in OA,[12,25,26] and can be safely administered to all patients with OA and tailored to benefit patients based on their individual needs. To facilitate access to CBT, we delivered the intervention by telephone. Use of telephone-delivered CBT may be especially appealing for older adults or patients living in rural communities with limited transportation who have difficulty attending hospital- or clinic-based programs. Although fewer data are available on the efficacy of telephone-based CBT, previous controlled studies have demonstrated that telephone-based programs can improve functional status in patients with OA.[27-30] Coping skills were selected from a larger collection of possible skills because they were judged by participants in a previous study[31] of chronic back pain to be the most important and appealing and the skills they were most confident they could engage in.

Figure 2. Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Scale Scores Over Time



Pain scales scores range from 0 to 20, with higher scores reflecting worse pain. Means are smoothed LOESS (locally estimated scatterplot smoothing) estimates. The gray shaded areas indicate 95% CIs.

Strengths and Limitations

This study has some strengths, including recruitment of patients across multiple sites, implementation of a rigorous study design, and inclusion of a patient-centered treatment strategy that addresses barriers to care that frequently affect older adults with OA. This trial supports the feasibility of examining whether other nonpharmacologic treatment modalities for knee OA, such as exercise and physical therapy, may help patients limit their use of NSAIDs.

This randomized withdrawal trial also has some important limitations. We did not reach our target sample size, and therefore our study may have been underpowered. However, the number of completers provided 80% power to detect noninferiority, assuming the same assumptions described in the protocol. Our results are applicable to a single NSAID, and individual patients may respond differently to different NSAIDs. To mitigate against a response or intolerance to meloxicam biasing our results toward the null, we included a 2-week run-in period in which participants replaced their NSAID with the study drug. The duration of the run-in period was chosen based on data demonstrating that patients with OA respond to meloxicam by 2 weeks.[32] Although run-in periods have been shown to improve efficiency, they may also decrease generalizabil-

Table 3. Adverse Events

Adverse event	No. of participants (%)		*P* value[a]
	Placebo (n = 180)	Meloxicam (n = 184)	
Organ system affected			
Gastrointestinal	6 (3)	12 (7)	.23
Renal	0	1 (1)	>.99
Liver	0	0	
Cardiovascular	4 (2)	1 (1)	.21
Other	15 (8)	13 (7)	.70
Serious adverse event	3 (2)	4 (2)	>.99

[a] Obtained from Fisher exact test.

ity by selecting a more adherent population. Both 7.5-mg and 15-mg meloxicam doses have been used in randomized clinical trials before. We chose the higher dose to improve the assay sensitivity of the trial (that is, the ability of a trial to demonstrate a difference between the 2 groups if one truly exists). Tramadol was not classified as a controlled substance when this trial was designed and, because of the prevalent use of this medication, patients taking tramadol at study baseline were eligible to participate and were permitted to continue taking tramadol. Although the CBT delivered in this trial was adapted to the needs of patients with OA, it is possible that the limited module content for specific concerns, such as sleep, were not intensive enough to provide as much benefit as other CBT programs that include multiweek content on specific topics.[33,34]

Conclusions

Among patients with knee OA, placebo and CBT (after placebo) are inferior to meloxicam. However, clinicians may inform patients that the pain score differences between the 2 groups are smaller than those considered to be clinically important and that there are no meaningful differences in patients' perceptions of whether they have improved or not or in how they are functioning after 14 weeks. Although the overall results of the trial are negative, they provide clinicians with data to support shared decision-making and reassure patients willing to taper NSAIDs and consider self-management approaches, such as CBT.

ARTICLE INFORMATION

Accepted for Publication: May 25, 2020.

Published Online: July 20, 2020. doi:10.1001/jamainternmed.2020.2821

Author Contributions: Drs Fraenkel and Buta had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Fraenkel, Suter, Corn, Kerns, Goulet.
Acquisition, analysis, or interpretation of data: Fraenkel, Buta, Dubreuil, Levy, Najem, Brennan, Corn, Kerns, Goulet.
Drafting of the manuscript: Fraenkel, Buta, Brennan, Goulet.
Critical revision of the manuscript for important intellectual content: Fraenkel, Buta, Suter, Dubreuil, Levy, Najem, Corn, Kerns, Goulet.
Statistical analysis: Buta, Goulet.
Obtained funding: Fraenkel, Kerns, Goulet.
Administrative, technical, or material support: Suter, Levy, Brennan, Corn.
Supervision: Fraenkel, Kerns.

Conflict of Interest Disclosures: Drs Fraenkel and Goulet reported receiving grants from the Veterans Affairs Health Services Research and Development during the conduct of the study. Dr Suter reported other support from Veterans Health Administration during the conduct of the study and other support from the Centers for Medicare & Medicaid Services outside the submitted work. Dr Levy reported receiving salary support from the North Florida/South Georgia Veterans Health System during the conduct of the study. No other disclosures were reported.

Funding/Support: This trial was funded by grant IIR 11-113 from the Veterans Affairs Health Services Research and Development Service.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Information: Research resources generated with funds from this grant will be freely distributed, as available, to qualified academic investigators for noncommercial research. Deidentified data will be shared with the research community once the project has been completed and the resulting manuscripts have been accepted for publication. The study protocol and results will be uploaded to Clinical Trials.gov. The proposed research will include data from all enrolled participants. The final data set will be stripped of identifiers prior to release for sharing. Even so, in order to ensure protection of participants, we will make the data and associated documentation available to users only under a data sharing agreement that provides for (1) a commitment to using the data only for research purposes and not to identify any individual participant, (2) a commitment to securing the data using appropriate computer technology, and (3) a commitment to destroying or returning the data after analyses are completed.

REFERENCES

1. Neogi T, Zhang Y. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am*. 2013;39(1):1-19. doi:10.1016/j.rdc.2012.10.004

2. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum*. 2004;51(5):746-754. doi:10.1002/art.20698

3. Jordan KM, Arden NK, Doherty M, et al; Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62(12):1145-1155. doi:10.1136/ard.2003.011742

4. Bjordal JM, Ljunggren AE, Klovning A, Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ*. 2004;329(7478):1317. doi:10.1136/bmj.38273.626655.63

5. Gregori D, Giacovelli G, Minto C, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis. *JAMA*. 2018;320(24):2564-2579. doi:10.1001/jama.2018.19319

6. Meek IL, Van de Laar MAFJ, Vonkeman HE. Non-steroidal anti-inflammatory drugs: an overview of cardiovascular risks. *Pharmaceuticals (Basel)*. 2010;3(7):2146-2162. doi:10.3390/ph3072146

7. Vonkeman HE, van de Laar MA. Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. *Semin Arthritis Rheum*. 2010;39(4):294-312. doi:10.1016/j.semarthrit.2008.08.001

8. Beck AT, Dozois DJA. Cognitive therapy: current status and future directions. *Annu Rev Med*. 2011; 62:397-409. doi:10.1146/annurev-med-052209-100032

9. Dixon KE, Keefe FJ, Scipio CD, Perri LM, Abernethy AP. Psychological interventions for arthritis pain management in adults: a meta-analysis. *Health Psychol*. 2007;26(3):241-250. doi:10.1037/0278-6133.26.3.241

10. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *Am Psychol*. 2014;69(2):153-166. doi:10.1037/a0035747

11. Keefe FJ, Lumley M, Anderson T, Lynch T, Studts JL, Carson KL. Pain and emotion: new research directions. *J Clin Psychol*. 2001;57(4):587-607. doi:10.1002/jclp.1030

12. Niknejad B, Bolier R, Henderson CR Jr, et al. Association between psychological interventions and chronic pain outcomes in older adults: a systematic review and meta-analysis. *JAMA Intern Med*. 2018;178(6):830-839. doi:10.1001/jamainternmed.2018.0756

13. Bernardy K, Klose P, Busch AJ, Choy EHS, Häuser W. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev*. 2013;9 (9):CD009796.

14. Eccleston C, Fisher E, Craig L, Duggan GB, Rosser BA, Keogh E. Psychological therapies (internet-delivered) for the management of chronic pain in adults. *Cochrane Database Syst Rev*. 2014;2 (2):CD010152. doi:10.1002/14651858.CD010152.pub2

15. Goulet JL, Buta E, Brennan M, Heapy A, Fraenkel L. Discontinuing a non-steroidal anti-inflammatory drug (NSAID) in patients with knee osteoarthritis: design and protocol of a placebo-controlled, noninferiority, randomized withdrawal trial. *Contemp Clin Trials*. 2018;65:1-7. doi:10.1016/j.cct.2017.11.020

16. Zhao SZ, McMillen JI, Markenson JA, et al. Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. *Pharmacotherapy*. 1999;19(11):1269-1278. doi:10.1592/phco.19.16.1269.30879

17. Otis JD. *Managing Chronic Pain: A Cognitive-Behavioral Therapy Approach*. Oxford University Press; 2007.

18. Rogers JC, Irrgang JJ. Measures of adult lower extremity function: The American Academy of Orthopedic Surgeons Lower Limb Questionnaire, The Activities of Daily Living Scale of the Knee Outcome Survey (ADLS), Foot Function Index (FFI), Functional Assessment System (FAS), Harris Hip Score (HHS), Index of Severity for Hip Osteoarthritis (ISH), Index of Severity for Knee Osteoarthritis (ISK), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). *Arthritis Care Res (Hoboken)*. 2003;49 (S5):S67-S84. doi:10.1002/art.11401

19. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Rheum*. 2001;45(5):453-461. doi:10.1002/1529-0131(200110)45:5<453::AID-ART365>3.0.CO;2-W

20. Strand V, Kelman A. Outcome measures in osteoarthritis: randomized controlled trials. *Curr Rheumatol Rep*. 2004;6(1):20-30. doi:10.1007/s11926-004-0080-6

21. Angst F, Aeschlimann A, Steiner W, Stucki G. Responsiveness of the WOMAC osteoarthritis index as compared with the SF-36 in patients with osteoarthritis of the legs undergoing a comprehensive rehabilitation intervention. *Ann Rheum Dis*. 2001;60(9):834-840.

22. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1-67. doi:10.18637/jss.v045.i03

23. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med*. 2003;22(2):169-186. doi:10.1002/sim.1425

24. Alderson P, Chalmers I. Survey of claims of no effect in abstracts of Cochrane reviews. *BMJ*. 2003; 326(7387):475. doi:10.1136/bmj.326.7387.475

25. Keefe FJ, Caldwell DS, Williams DA, et al. Pain coping skills training in the management of osteoarthritic knee pain, II: follow-up results. *Behav Ther*. 1990;21(4):435-447. doi:10.1016/S0005-7894(05)80357-0

26. Kidd BL, Langford RM, Wodehouse T. Arthritis and pain: current approaches in the treatment of arthritic pain. *Arthritis Res Ther*. 2007;9(3):214. doi:10.1186/ar2147

27. René J, Weinberger M, Mazzuca SA, Brandt KD, Katz BP. Reduction of joint pain in patients with knee osteoarthritis who have received monthly telephone calls from lay personnel and whose medical treatment regimens have remained stable. *Arthritis Rheum*. 1992;35(5):511-515. doi:10.1002/art.1780350504

28. Maisiak R, Austin J, Heck L. Health outcomes of two telephone interventions for patients with rheumatoid arthritis or osteoarthritis. *Arthritis Rheum*. 1996;39(8):1391-1399. doi:10.1002/art.1780390818

29. Allen KD, Oddone EZ, Coffman CJ, et al. Telephone-based self-management of osteoarthritis: a randomized trial. *Ann Intern Med*. 2010;153(9):570-579. doi:10.7326/0003-4819-153-9-201011020-00006

30. Baker K, LaValley MP, Brown C, Felson DT, Ledingham A, Keysor JJ. Efficacy of computer-based telephone counseling on long-term adherence to strength training in elders with knee osteoarthritis: a randomized trial. *Arthritis Care Res (Hoboken)*. Published online May 10, 2019. doi:10.1002/acr.23921

31. Kerns RD, Burns JW, Shulman M, et al. Can we improve cognitive-behavioral therapy for chronic back pain treatment engagement and adherence? a controlled trial of tailored versus standard therapy. *Health Psychol*. 2014;33(9):938-947. doi:10.1037/a0034406

32. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P; The Meloxicam Osteoarthritis Investigators. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. *Arch Intern Med*. 2000;160(19):2947-2954. doi:10.1001/archinte.160.19.2947

33. Somers TJ, Blumenthal JA, Guilak F, et al. Pain coping skills training and lifestyle behavioral weight management in patients with knee osteoarthritis: a randomized controlled study. *Pain*. 2012;153(6): 1199-1209. doi:10.1016/j.pain.2012.02.023

34. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. *J Clin Sleep Med*. 2009;5(4):355-362. doi:10.5664/jcsm.27547