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Effects of prescription non-steroidal anti-inflammatory agents on symptoms and disease progression among patients with knee osteoarthritis

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Abstract

Objective—The effect of short and long term non-steroidal anti-inflammatory agents (NSAIDs) use on structural change is equivocal. We estimate the extent to which recent and long-term use of prescription NSAIDs relieve symptoms and delay structural progression among patients with radiographically confirmed osteoarthritis (OA) of the knee.

Methods—We applied a new-user design among participants with confirmed OA not reporting NSAID use at enrollment in the Osteoarthritis Initiative. Participants were evaluated for changes in the Western Ontario and McMaster Universities Arthritis Index, WOMAC (n=1,846) and joint space width measured using serial x-rays and a customized software tool (n=1,116) over 4 years. We used marginal structural modeling to estimate the effect of NSAIDs.

Results—Compared to participants who never reported prescription NSAID use, those reporting use at 1 or 2 assessments had no clinically important changes, but those reporting prescription NSAID use on all 3 assessments had on average 0.88 point improvement over the follow-up period (95% Confidence Interval (CI): -0.46 to 2.22) in Pain, 0.72 point improvement (95% CI: -0.12 to 1.56) in Stiffness, 4.27 points improvement (95% CI: -0.31 to 8.84) in Function, and decreased by 0.28mm in joint space width (95% CI: -0.06 to 0.62) less than no use. Recent NSAID use findings were not clinically or statistically significant.

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Conclusions—Long term but not recent NSAID use was associated with a priori defined minimally important clinical change in stiffness, function and structural change but not in pain. While showing modest clinical importance, estimates did not reach statistical significance.

Osteoarthritis (OA) affects ~27 million people in the U.S. (1). Management of OA traditionally has focused on treating pain and disability. Clinical guidelines recommend both pharmacological and non-pharmacological therapies to relieve symptoms as no effective remedies to cure OA exist (2). Nonsteroidal anti-inflammatory drugs (NSAIDs) help with symptoms and pain relief (3-5), but the evidence of long-term effects from oral NSAIDs is still lacking (6,7). Moreover, their effect on joint structural changes has not been well established. *In vitro* and animal studies suggest that conventional NSAIDs may have deleterious effects on articular cartilage (8,9), whereas COX-selective NSAIDs might have beneficial or neutral effects (10-12). In observational studies of people with knee and hip OA over 55 years of age, the long-term use of diclofenac appeared to accelerate disease progression (13).

Despite controversial efficacy, prescription NSAIDs are widely used. Prescriptions for generic ibuprofen and naproxen exceed 500 million per year, with over 45 million prescriptions written for cyclooxygenase-2 (COX-2) inhibitors (14). Given the widespread use of NSAIDs and the mounting evidence of their adverse effects (15), understanding the effectiveness of long-term prescription NSAID use in persons suffering from OA is warranted. We sought to estimate the extent to which prescription NSAIDs used long-term may not only relieve symptoms, but also delay disease progression. This study builds on previous research in several ways. First, we used data from the Osteoarthritis Initiative (OAI), a study which recruited a large number of persons with radiographically confirmed OA and followed them annually with validated patient reported outcomes and measures of disease progression. Second, this rich data source allowed us to evaluate NSAID use over a three year period. Typically, studies of NSAIDs on OA symptoms are of much shorter duration (16). Last, we used advanced statistical techniques to estimate effects from the non-experimental OAI study design. This allowed us to quantify the effect of NSAIDs in a more heterogeneous population than most clinical trials (17).

Patients and Methods

This study was approved by the Institutional Review Boards of the University of Massachusetts Medical School and the Memorial Hospital of Rhode Island.

Study sample

Publicly available OAI data was used. For detailed information about the OAI protocol, please see the OAI protocol for the cohort study (18). From 2004-2006, the OAI collected baseline data from four study sites (i.e., Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI) totaling 4,796 patients with established OA or at high risk for developing knee OA (18). Up to four years of annual follow-up assessments were collected. We developed two samples from the 2,539 participants with radiographic confirmed OA of the knee at the time of enrollment. A Kellgren-Lawrence grade (K-L) ≥2 was deemed radiographic confirmation of OA. For both samples, we included “new users” who did not

report any NSAID use at baseline (n=2,070) given that study designs identifying new users (19) improve validity by allowing adjustment for pre-treatment disease severity. We also required at least one follow-up assessment, and all 2,070 participants met that requirement. For the sample used to evaluate symptoms, we excluded patients with missing data on the outcome variables or confounders (n=224). The final sample included 5,263 assessments of 1,846 unique participants. Six percent contributed 1 assessment, 4% two assessments and 90% three follow-up assessments. To evaluate structural disease progression, we excluded participants who had K-L grade 4 or primarily lateral joint space narrowing in both knees (n=212) or those missing either confounders or outcome measures (n=742). The final sample to evaluate structural changes included 2,890 assessments on 1,116 unique participants. Fourteen percent contributed 1 assessment, 13% two assessments and 73% three follow-up assessments. Fourteen NSAID users and forty non-users had a total knee replacement surgery during the follow-up.

Definition of non-steroidal anti-inflammatory agent use

The operational definition of NSAIDS was based on prescription NSAID use only. We intentionally did not include over the counter NSAID use for two reasons. First, we believed that prescription medication use would be more reflective of medication use throughout the year. Second, we believed that prescription NSAID use was likely at higher doses than over the counter NSAID use. Adjustments for over the counter use were conducted (see below). We defined prescription NSAID use in two ways using information from medication inventory. First, we defined NSAID use as any NSAID prescription use (regular and as needed use) in the 30 days preceding the interview as indicated by Iowa Drug Information System (IDIS) (codes 28080400 through 28080610) with oral tablet or capsule use indicated (99% of all reported use). Respondents had to indicate that they were still using the medication at the time of the assessment (94% reported that they were). Second, we defined prescription NSAID use as regular use only (vs as needed use or non-use). Frequency of medication use was considered regular if the participant was taking the medication as prescribed on a regular schedule. We provided this alternative operational definition of prescription NSAID use because we were concerned that as needed use may not have the same impact on the outcomes of interest. Sixty-seven percent of prescription NSAID users indicated their use was regular. We classified users according to the number of years for which any prescription NSAID use was reported as part of the medication inventory of the annual assessment process. We assumed that use was continued between annual assessments.

Outcome definitions

We evaluated two conceptually distinct outcomes: symptoms and structural disease progression. Each outcome variable was defined as change from baseline. To create comparability with the companion piece (20), we used the same operational definitions of the outcomes. Briefly, symptoms evaluated included pain, stiffness, and physical function. The OAI used the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale to evaluate knee-specific symptoms (21) with assessments collected at annual visits. Higher WOMAC scores are suggestive of worse symptoms (Pain: range 0 to 20; Stiffness: range 0 to 8; Physical function: range 0 to 68). We selected WOMAC information from the

knee with worse pain at baseline and included information from that knee throughout the follow-up period. For structural progression, we used joint space width (JSW) as the primary outcome. Bilateral standing knee X-rays were collected annually using posterior anterior projection. Knees were flexed to 20-30 degrees, with feet rotated to 10 degrees (18). Using serial knee x-rays, a customized software tool automatically delineated the margin of the femoral condyle and the tibial plateau and provided longitudinal measurements of JSW across different locations within the knee (22). The distance from tibial plateau to tibial rim closest to femoral condyle was measured to indicate knee positioning (23). The JSW measure at x=0.25 (in the medial compartment) was used because it was demonstrated to have best responsiveness to changes (24). JSW measures were considered missing if the distance between plateau and rim was > 6.5mm (n=280 out of the 2,070 participants who were non-users of any NSAIDs at baseline) or the change between visits was >2mm (n=314). Minimally important clinical improvements for WOMAC Pain range from 1.2 to 4.6, for WOMAC Stiffness range from 0.5 to 1.5, and for WOMAC Physical Function range from 4.1 to 9.9. Minimally important changes in JSW range from 0.12 to 0.84 mm (25-27).

Confounders

Potential confounders included sociodemographics, clinical characteristics of OA, indices of general health status, body mass index (BMI), and use of alternative treatments other than prescription NSAIDs. If data were collected annually, the confounder was treated as time-varying in the analysis. Income was measured with personal family income for the last year, including all sources such as wages, salaries, social security and retirement benefits.

OAI administered comprehensive measurements on participants' clinical characteristics, including knee alignment, multi-joint symptoms, K-L grade, and history of having a knee injury or surgery (18). When K-L grade was missing (5.2%), we carried the last observation forward (28). Knee malalignment was measured with a goniometer. Varus or valgus deformity was recorded if malalignment was found. We considered multi-joint symptoms present if participants had frequent pain, aching, or stiffness in at least two joints other than knee (29). Information was collected on prior knee injuries that limited ability to walk for at least two days, and history of knee surgery including arthroscopy, ligament repair or meniscectomy.

The 12-item Short-Form Health Survey (SF-12) was employed to assess general health status (30). A summary Physical and Mental Component Summary score was calculated ranging from 0 to 100, with higher scores indicating better health status. The SF-12 Scores were missing in 148 participants and we carried their last observation forward. BMI is a risk factor for OA progression due to its potential local biomechanical effect and systemic metabolic effect (31). Participants were categorized in the following manner: BMI less than 25, normal weight; BMI 25 to less than 30, overweight; and BMI 30 and over, obese.

We also considered concomitant analgesic medications and over the counter NSAID use as potential confounders. At each visit, acetaminophen, aspirin, over the counter NSAID and opioid use was assessed for the previous 30 days. Both over-the-counter and prescription medications captured in the Medications Inventory File or reported by patients in the medication history survey were used to define these variables.

Statistical analyses

Before conducting the model-building exercise, we compared the clinical and sociodemographic characteristics of prescription NSAID initiators to non-users in year 1. We identified predictors of prescription NSAID initiation, as well as continuation of prescription NSAID use from the previous assessment. Then, we estimated the crude effect of prescription NSAIDs on the symptom and disease progression using a repeated measure model which adjusted for within-participant correlation using an unstructured correlation matrix (32). The distribution of the outcome variables were inspected for departures from normality (and ruled out). Using generalized estimating equations (GEE), this correlation structure maximized the quasi-likelihood information criterion (33). We adjusted the crude estimate for baseline and time-varying confounders.

Recognizing that estimates derived from multivariable regression models may be biased (34), we used marginal structural modeling (MSMs) because the OAI data structure allowed us to analytically adjust for time-varying confounders which may lie on the causal path from previous treatments to the study outcomes (35). The methodology used is described in detail in the companion article in this issue (20). For each year, we developed an individual probability of prescription NSAID use given sociodemographic and clinical covariates using logistic regression models. If covariates considered in the model were highly correlated, the variable more strongly associated with the outcome was included in the logistic regression model. The inverse of the conditional probability was stabilized to provide a more precise estimate than what is derived from models using unstabilized weights. We also classified each participant's censoring status at each assessment (censored due to illness or death or total knee replacement, loss to follow-up owing to refusal or missing data, or not censored). Conditional probabilities for censoring were estimated from multinomial logistic models and stabilized. Final weights were calculated as the products of the weights calculated at each assessment for treatment and censoring. We truncated the weights at 99^{th} percentile to lessen violations to the positivity assumption (36).

Using these weights, we created weighted linear models to estimate the effect of long-term prescription NSAID use on the outcome variables. From the final model, we were able to estimate the effect of prescription NSAID use for 3 years, 2 years and 1 year on each outcome with 95% confidence intervals (CI). The final beta coefficients provided an estimate of the average changes from baseline in WOMACs and JSW among participants using prescription NSAIDs for certain time periods relative to those who never used the treatment.

Results

Among non-users at baseline, 6% initiated prescription NSAID use by year 1 with 52% indicating regular use (Table 1). Seventy-three percent of regular users were women and 55.3% of non-users were women. Multi-joint symptoms were present in 65.5% of regular users and 47.3% of non-users. Use of over the counter NSAIDs/aspirin (34.6% versus 25.5%), acetaminophen (21.8% versus 11.1%), opioids (10.9% versus 3.4%) were higher in regular prescription NSAID users relative to non-users. Concurrent use of proton pump inhibitors or histamine-2 receptor antagonists was more common among NSAIDs users than

those not using NSAIDs. Ibuprofen, naproxen, and celecoxib were the most commonly reported prescription NSAIDs among those reporting any prescription NSAID use, whereas naproxen, celecoxib, and meloxicam were the most commonly reported prescription NSAIDs among regular users (Table 2). Compared to men, women had increased odds of initiating any prescription NSAIDs (adjusted odds ratio (aOR): 1.48; 95% confidence interval (CI): 1.09-2.01) (data not shown). Opioid users had increased odds of initiating prescription NSAIDs (aOR: 3.43; 95% CI: 2.22-5.29), but those using over the counter NSAIDs had decreased odds of initiating NSAIDs relative to non-users (aOR: 0.62; 95% CI: 0.44-0.89). Pain was positively associated with initiation of prescription NSAIDs (aOR per one standard deviation increase in pain score: 1.26; 95% CI: 1.10-1.44), whereas the physical component score was a negative correlate (aOR per one standard deviation increase: 0.69; 95% CI: 0.60-0.80).

Across all person visits, persons not using prescription NSAIDs were using other analgesics including over the counter acetaminophen (10.8%) and over the counter NSAIDs (17.9%) (Table 3). Prescription NSAID users were commonly using other analgesics in addition to their prescription NSAIDs with use of opioids (18.7%) and acetaminophen (17.1%) common.

Tables 4 shows the effect of most recent use of NSAIDs on patient-reported outcomes and JSW. Any prescription NSAIDs reported on the most recent assessment was not associated with pain, stiffness, function or JSW (Table 4). Crude GEE estimates, multivariable adjusted GEE estimates and marginal structural model based estimates of effects did not achieve a priori defined minimally important clinical differences suggesting improvement. Regular use of prescription NSAIDs was not associated with minimally important clinical improvements on patient reported symptoms including pain, stiffness, and function, nor changes in JSW. Table 5 focusses on the cumulative effect of any NSAID use as participants were categorized by the number of assessments with NSAID use reported. When considering the number of assessments NSAID use was reported, crude GEE estimates, multivariable adjusted GEE estimates and marginal structural model based estimates of effect were not supportive of improvements in pain for use of prescription NSAIDs (Table 5). The strongest effect observed was among those reporting prescription NSAIDs at all 3 year assessments (beta = -0.88; 95% CI: -2.22 to 0.46), but it was not consistent with minimal clinically important differences in pain. For those reporting prescription NSAID use at all 3 assessments, but not 1- or 2- year use, marginal structural model effects for stiffness (beta = -0.72; 95% CI: -1.56 to 0.12) and function (beta = -4.27; 95% CI: -8.84 to 0.31) met a priori definitions of minimal clinically important differences, although the confidence intervals were wide and included no effect. For disease progression, prescription NSAID use for 3 years changed joint space width by 0.28 mm (95% CI: -0.06 to 0.62) relative to changes observed in non-users. Although reaching the minimal clinically important difference, the 95% confidence intervals were wide. Shorter term use (1 and 2 years) was not associated with changes in joint space width.

Discussion

Among persons with radiographically confirmed OA of the knee, initiation of prescription NSAIDs in a year period was low. While prescription NSAID use one year preceding outcomes measurement showed no effect, the data were suggestive of long-term use (prescription NSAID use reported at all assessments over 3 year period) improving patient reports of stiffness and function and a delay in disease progression. The precision of the latter estimates were limited by the number of NSAID initiators whose NSAID use persisted across the 3 years of follow-up.

The findings relating to long term use of prescription NSAIDs are consistent with evidence from clinical trials of shorter duration (3,5). It is likely that NSAID use reported at three assessments is more likely reflective of habitual use relative to persons reporting NSAID use at one or two study visits. That we found no short term effects of NSAIDs on patient reported outcomes conflicts with evidence from clinical trials (5). There are several non-causal explanations for this. First, prescription NSAIDs likely improve patient reported outcomes only during active treatment. Discontinuation rates of prescription NSAIDs have been reported to exceed 85% within six months of initiation (37), with time to discontinuation slightly longer for those initiating cyclooxygenase inhibitors (38). If the timing of assessments of patient reported outcomes were months after discontinuation, our study would underestimate the short term beneficial effects of prescription NSAIDs. Indeed, the majority of NSAID users reported use at one assessment only. Second, the challenges of pain assessment have been documented (39). Non-differential measurement error of the outcome can attenuate the estimate of the prescription NSAID effect. Lastly, many participants reported use of other analgesics including opioids and over the counter acetaminophen and NSAIDs. While we adjusted for the use of these medications in the analysis, it is possible that residual confounding may have attenuated the observed effect of NSAIDs.

The proportion of participants reporting long term prescription NSAID use in our study was low. Discontinuation of analgesics may be owing to inadequate relief of pain or intolerable side effects of NSAIDs (40,41). The extent to which NSAIDs' gastrointestinal side effects may be lessened with gastroprotective agents is unknown. We do know that among long-term users of NSAIDs, concomitant use of gastroprotective agents was relatively low (one in five). Given there is no cure for OA, understanding how to balance NSAIDs' adverse side effects with potential gains in delaying disease progression is important.

The strengths of this study include its prospective nature, the sophisticated analyses, and the detailed valid measures used to evaluate structural progression and patient reported outcomes. The validity and reliability of the WOMAC is noted (21). The OAI provided a large diverse sample of participants with OA followed for a long period of time. To address threats to the validity of the study, the MSM technique reduced bias owing to time-varying confounding, intermediaries, and attrition. However, we experienced a loss of precision around the estimates of effect. That MSM often can result in a tradeoff between reduction of bias and increased variance is well-known.

Several limitations must be considered. Few participants reported prescription NSAID use at all three assessments (spaced approximately 1 year apart). This may have contributed to the lack of precision around the clinically important differences. No information about NSAID doses was available. The OAI used a medication inventory in 30 days preceding interview which is more reliable than patient recall (42). Misclassification likely attenuated the observed effects for those reporting NSAID use sporadically. Over-the-counter analgesic use and opioid use was common. While we adjusted for this in the analysis, residual confounding may have attenuated the NSAID effect. Finally, we adjusted for the concurrently measured disease characteristics as potential confounders. This may reduce the measurement error in the time-varying confounders, but may also induce bias due to the possible adjustment for intermediate variables.

In conclusion, long term NSAIDs use was associated with improved patient reports of stiffness and function and changes in measures of JSW. The NSAID discontinuation rates call for further understanding of the extent to which potential side effects can be mitigated with gastroprotective agents. Understanding how best to balance benefits of treatment with risks among persons with knee OA is important.

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Table 1

Sociodemographic and clinical factors among people with radiographically confirmed OA of the knee by initiation of NSAIDs in year one (n= 1,846 persons)

Baseline Characteristics	Initiate Any NSAID use (n=102)	Initiate Regular NSAID Use (n=55)	Non-users of any NSAID (n=1,744)
		Percentage	
Age (in years)			
<65	55.9	50.9	54.6
65-74	35.3	38.2	33.8
≥75	8.8	10.9	11.6
Women	65.7	72.7	55.3
Ethnicity/Race			
Non-Hispanic White	76.5	83.6	78.9
Non-Hispanic Black	19.6	12.7	18.1
Other	3.9	3.6	3.0
Education			
High school or less	16.7	12.7	16.8
Some college	36.3	32.7	21.7
College graduate	12.8	9.1	22.9
Graduate school	34.3	45.5	38.7
Income ($)			
<25,000	19.6	16.4	14.1
25,000 - 50,000	22.6	20.0	27.1
>50,000	57.8	63.6	58.8
KL grade 3 or 4	45.1	41.8	38.6
Multi-joint symptoms	61.8	65.5	47.3
Use of OTC NSAIDs or aspirin	29.4	34.6	25.5
Use of acetaminophen	17.7	21.8	11.1
Use of opioids	7.8	10.9	3.4
History of knee injury	30.4	27.3	39.0
History of knee surgery	33.3	30.9	30.2
Body Mass Index (kg/m^2)			
<25	10.8	14.6	18.8
25 - <30	37.3	43.6	39.1
≥30	52.0	41.8	42.2
Knee alignment			
Normal	22.6	25.5	27.2
Varus	31.4	30.9	30.2
Valgus	46.1	43.6	42.7
Proton pump inhibitor	15.7	20.0	11.4
Proton pump inhibitor/ histamine-2 receptor antagonist	18.6	23.6	12.9
		Mean (*standard deviation*)	

Baseline Characteristics	Initiate Any NSAID use (n=102)	Initiate Regular NSAID Use (n=55)	Non-users of any NSAID (n=1,744)
WOMAC Pain	4.8 (4.2)	4.9 (4.0)	3.4 (3.7)
WOMAC Stiffness	2.4 (1.8)	2.4 (1.8)	1.9 (1.7)
WOMAC Physical Function	14.6 (13.1)	15.5 (12.8)	10.4 (11.6)
SF-12 Physical Component Score	45.5 (10.3)	44.7 (10.2)	49.0 (8.7)
SF-12 Mental Component Score	53.4 (8.5)	53.2 (7.7)	54.1 (7.6)
Joint space width (mm)*	4.8 (1.0)	4.7 (1.0)	5.2 (1.2)

*Based on information on 1,116 participants included in analyses on JSW, among whom 60 initiated any NSAIDs use and 37 initiated regular NSAID use.

Table 2

NSAID use among persons with radiographically confirmed OA

	Any NSAID use (N= 335 person-visits*)	Regular NSAID use (N= 257 person-visits)
	N (%)	
Prescription Drugs		
Ibuprofen	85 (25.4)	34 (13.2)
Naproxen	79 (23.6)	59 (23.0)
Celecoxib	54 (16.1)	50 (19.5)
Meloxicam	41 (12.2)	45 (17.5)
Diclofenac sodium	24 (7.2)	17 (6.6)
Etodolac	18 (5.4)	15 (5.8)
Nabumetone	18 (5.4)	16 (6.2)
Piroxicam	10 (3.0)	10 (3.9)
Indomethacin	6 (1.8)	7 (2.7)
Sulindac	3 (0.9)	3 (1.2)
Ketoprofen	2 (0.6)	0
Oxaprozin	1 (0.3)	1 (0.4)

*Combination use of prescription NSAIDs occurred at 6 person-visits (in 5 unique persons): ibuprofen and naproxen (at 5 person-visits), and etodolac and diclofenac sodium (at one person-visit).

Table 3

Concomitant use of analgesics among persons with radiographically confirmed OA*

	Any prescription NSAID use (N=335 person-visits)	Regular prescription NSAID use (N=257 person-visits)	No NSAID use (N=4,928 person-visits)
		Percentage	
Prescription aspirin	1.8	1.2	1.7
Acetaminophen, Prescription or over-the-counter	18.2	17.1	10.8
Over-the-counter NSAIDs or aspirin	13.7	9.3	17.9
Opioids	18.2	18.7	4.5
Steroid injection	9.3	10.2	2.7
Hyaluronic acid injection	2.1	2.7	0.9

*Information from all person-visits included in this analysis.

Table 4

Effect of most recent use[#] of prescription NSAIDs, beta coefficients (95% confidence intervals (CI))

	Any NSAID use versus non-use Beta coefficients (95%CI)	Regular NSAID use versus non-regular use Beta coefficients (95%CI)	Minimal clinically important difference (MCID)
Pain			
Crude GEE[§]	−0.29 (−0.64 to 0.05)	0.15 (−0.29 to 0.58)	1.2 - 4.6, negative beta indicates improvement
Multivariable-adjusted GEE[§]	−0.12 (−0.44 to 0.21)	0.26 (−0.15 to 0.67)	
Marginal Structural Model[*]	0.02 (−0.38 to 0.41)	0.34 (−0.21 to 0.89)	
Stiffness			
Crude GEE[§]	−0.18 (−0.36 to 0.00)	0.06 (−0.14 to 0.26)	0.5 - 1.5, negative beta indicates improvement
Multivariable-adjusted GEE[§]	−0.07 (−0.23 to 0.10)	0.13 (−0.05 to 0.32)	
Marginal Structural Model[*]	−0.05 (−0.26 to 0.16)	0.04 (−0.23 to 0.31)	
Function			
Crude GEE[§]	−0.77 (−1.86 to 0.33)	0.22 (−1.13 to 1.58)	4.1 - 99, negative beta indicates improvement
Multivariable-adjusted GEE[§]	−0.09 (−1.11 to 0.93)	0.63 (−0.62 to 1.89)	
Marginal Structural Model[*]	−0.09 (−1.33 to 1.14)	0.24 (−1.57 to 2.05)	
Joint Space Width			
Crude GEE[§]	−0.16 (−0.27 to −0.06)	−0.09 (−0.20 to 0.02)	0.12 - 0.84, negative beta indicates improvement
Multivariable-adjusted GEE[§]	−0.07 (−0.16 to 0.01)	−0.05 (−0.14 to 0.04)	
Marginal Structural Model[*]	−0.08 (−0.21 to 0.05)	−0.07 (−0.20 to 0.06)	

[#]"Most recent use" was operationally defined as a binary variable with value 1 indicating NSAID use at the previous visit. Any NSAID use included regular and as needed use.

[§]Crude and multivariable adjusted estimates were derived from an analysis using GEE with an unstructured correlation matrix. The multivariable-adjusted GEE estimates adjusted for baseline characteristics including gender, age, race/ethnicity, education and income and time-varying confounders (including follow-up time, obesity status, knee malalignment, Kellgren-Lawrence grade, multi-joint symptoms, history of knee injuries, use of other complementary/alternative medicine, use of other analgesic medications, WOMAC subscale score, SF-12 physical and mental health scores) that were measured at the same visit as NSAID use. Any NSAID use was reported (3 years (n=25), 2 years (n=62), 1 year (n=136), or never-use (n=1,623)) and the number of years that regular prescription NSAID use was reported (3 years (n=21), 2 years (n=45), 1 year (n=104), or never-use (n=1,805)) for the analyses of patient-reported outcomes.

[*]Inverse Probability Weighted analyses with final weights truncated at the 99th percentile.

Table 5

Estimated effects of any prescription NSAID use[≠] by number of assessments reported on symptoms and disease progression among participants with radiographic knee OA, beta coefficients (95% confidence intervals (CI))[*]

Models	Use of any NSAIDs (relative to non-use)		
	Reported on all 3 annual assessments	Reported on 2 of 3 annual assessments	Reported on 1 annual assessments
WOMAC Pain (Minimal clinically important difference (MCID) *1.2 - 4.6), negative beta coefficient indicates improvement*			
Crude GEE[§]	−0.79 (−1.86 to 0.28)	−0.77 (−1.46 to −0.09)	−0.41 (−0.80 to −0.02)
Multivariable-adjusted GEE[§]	−0.04 (−1.08 to 1.00)	−0.29 (−0.81 to 0.23)	−0.16 (−0.45 to 0.13)
Marginal Structural Model[#]	−0.88 (−2.22 to 0.46)	−0.26 (−0.94 to 0.42)	−0.13 (−0.54 to 0.28)
WOMAC Stiffness (MCID *0.5 – 1.5), negative beta coefficient indicates improvement*			
Crude GEE[§]	−0.51 (−1.19 to 0.17)	−0.23 (−0.54 to 0.08)	−0.16 (−0.36 to 0.04)
Multivariable-adjusted GEE[§]	−0.21 (−0.88 to 0.45)	−0.01 (−0.26 to 0.24)	−0.06 (−0.21 to 0.09)
Marginal Structural Model[#]	−0.72 (−1.56 to 0.12)	−0.01 (−0.40 to 0.38)	−0.08 (−0.29 to 0.13)
WOMAC Function (MCID *4.1 - 9.9), negative beta coefficient indicates improvement*			
Crude GEE[§]	−2.10 (−5.75 to 1.55)	−1.66 (−3.59 to 0.27)	−1.09 (−2.28 to 0.09)
Multivariable-adjusted GEE[§]	−0.40 (−3.75 to 2.95)	−0.67 (−2.38 to 1.04)	−0.37 (−1.23 to 0.48)
Marginal Structural Model[#]	−4.27 (−8.84 to 0.31)	−0.71 (−3.10 to 1.67)	−0.40 (−1.64 to 0.84)
Joint space width (MCID 0.12 - 0.84), *negative beta coefficient indicates worsening*			
Crude GEE[§]	−0.39 (−0.58 to −0.21)	−0.38 (−0.53 to −0.22)	−0.26 (−0.38 to −0.14)
Multivariable-adjusted GEE[§]	0.08 (−0.04 to 0.19)	−0.04 (−0.19 to 0.11)	−0.07 (−0.15 to 0)
Marginal Structural Model[#]	0.28 (−0.06 to 0.62)	−0.06 (−0.31 to 0.18)	−0.08 (−0.25 to 0.09)

[≠] Any NSAID use (including regular and as needed) was operationally defined by the number of assessments when participants reported use of NSAIDs up to the visit before the study outcomes were measured.

[*] The reference group includes persons reporting no NSAID use up to “previous visit”.

[§] Estimates were derived from an analysis using GEE with an unstructured correlation matrix. The multivariable-adjusted GEE estimates adjusted for baseline characteristics including gender, age, race/ethnicity, education, income and history of knee surgery and time-varying confounders (including follow-up time, obesity status, knee malalignment, Kellgren-Lawrence grade, multi-joint symptoms, history of knee injuries, use of other complementary/alternative medicine, use of other analgesic medications, WOMAC subscale score, SF-12 physical and mental health scores) that were measured at the same visit as NSAID use.

#Inverse Probability Weighted analyses with final weights truncated at the 99th percentile.