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Does Association of Opioid Use with Pain and Function Differ by Fibromyalgia/Widespread Pain Status?

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Abstract

Many consider chronic opioid therapy (COT) to be ineffective for fibromyalgia, but empirical evidence is limited. Among patients identified as initiating COT, we examined whether fibromyalgia was associated with different relationships of opioid use to pain and activity interference outcomes 12 months later. We obtained electronic data on diagnoses and opioid prescriptions. We obtained patient self-report data, including pain and activity interference measures, at baseline, 4 months, and 12 months. Among 1,218 patients, 429 (35%) met our definition of fibromyalgia. Patients with and without fibromyalgia who had intermittent/lower-dose or regular/higher-dose opioid use at 12 months had similar 12-month pain intensity scores. However, among patients with minimal/no opioid use at 12 months, 12-month pain intensity was greater for those with fibromyalgia (adjusted mean = 5.15 [95% CI = 4.80, 5.51]; 0-10 scale) than for those without (4.44 [4.15, 4.72]). Similar patterns were observed for 12-month activity interference. Among patients who discontinued opioids by 12 months, those with fibromyalgia were more likely to report bothersome side effects and less likely to report pain improvement as important reasons for discontinuation (P -values < 0.05). In sum, at 12 months, among patients who

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The other authors report no conflicts.

List of Supplemental Digital Content

Supplemental Digital Content 1. Supplemental Figure 1: Adjusted mean pain intensity at baseline, 4 months, and 12 months for individuals with baseline widespread pain scores at the 75th (A) and 25th (B) percentile by opioid use in the 120 days prior to the 12-month assessment. pdf

Supplemental Digital Content 2. Supplemental Figure 2: Adjusted mean activity interference at baseline, 4 months, and 12 months for individuals with baseline widespread pain scores at the 75th (A) and 25th (B) percentile by opioid use in the 120 days prior to the 12-month assessment. pdf

Supplemental Digital Content 3. Supplemental Table: Association of 12-month characteristic pain intensity and activity interference with opioid use over the prior 120 days by widespread pain score at baseline. pdf

had discontinued opioids or used them minimally, those with fibromyalgia had worse outcomes and were less likely to have discontinued due to pain improvement. Among patients continuing COT, pain and activity interference outcomes were worse than those of patients with minimal/no opioid use and did not differ for those with fibromyalgia versus those with diverse other chronic pain conditions.

Keywords

fibromyalgia; widespread pain; opioids; chronic opioid therapy; chronic pain

1. Introduction

Although patients with fibromyalgia are often treated with chronic opioid therapy (COT)^{14,30} and often report it as helpful,¹ COT is viewed by many experts as inappropriate for fibromyalgia.^{6,10,26} This argument is based largely on expert opinion and lack of evidence for efficacy of COT for fibromyalgia rather than on evidence that COT is ineffective or harmful for patients with fibromyalgia.^{6,26} A recent systematic review concluded that evidence was insufficient regarding whether opioid benefits and harms vary for different pain conditions.⁷

The conceptualization of fibromyalgia is evolving and the diagnosis is controversial.⁹ Current conceptualizations generally view fibromyalgia as a term for widespread musculoskeletal pain with the following characteristics: (a) no alternative cause can be identified; (b) frequently co-morbid with other chronic pain syndromes lacking specific identifiable causes; and (c) reflecting augmented pain or sensory processing in the central nervous system rather than a pathologic abnormality in the painful region of the body.¹⁰ The Modified American College of Rheumatology (ACR) 2011 Fibromyalgia Diagnostic Criteria self-report measure (which assesses pain in multiple body sites, fatigue, cognitive problems, and depression) can be scored dichotomously using cut-points. However, there is increasing appreciation that fibromyalgia is a constellation of symptoms and that an individual's degree of "fibromyalgianess" can be measured on a continuum.¹⁰ It has been proposed that higher scores on the ACR 2011 measure predict poor response to opioids.¹⁰

In parallel with these evolving conceptualizations of fibromyalgia, chronic widespread pain (CWP) is increasingly accepted as a diagnosis in its own right.¹¹ Empirical data regarding meaningful clinical differences and consensus on operational definitions of CWP and fibromyalgia are lacking.⁴ For both diagnoses, although there are advantages of dichotomous definitions (e.g., in treatment decision-making and epidemiological studies), evidence supports a continuous distribution of the extent of pain in the body and cut-points for classification as arbitrary.¹¹

To address the gap in knowledge concerning possible differential effects of opioids for patients with fibromyalgia or CWP, we used data from the Middle-Aged/Seniors Chronic Opioid Therapy (MASCOT)³⁵ longitudinal study of patients initiating COT for chronic pain. We examined whether the relationships of opioid use to pain and function at 12-month follow-up differed depending on whether the patient had fibromyalgia at baseline. We also

examined whether these relationships differed according to baseline scores on a continuous patient-reported widespread pain measure. We previously observed worse pain and function outcomes at 12 months among patients who sustained COT as compared with patients who transitioned to minimal or no opioid use.³⁵ For the current study, we hypothesized that the difference in 12-month outcomes for those with continued opioid use versus minimal/no opioid use would be greater for patients with fibromyalgia than for patients without fibromyalgia. In the subgroup of patients who sustained COT, we explored whether self-reported helpfulness of opioids differed by fibromyalgia status. In the subgroup of patients who discontinued opioids, we explored differences in reasons given for discontinuation.

2. Methods

2.1. Study participants, setting, and procedures

We previously described the methods of the MASCOT study.^{35,40} In brief, study participants were members of Group Health, a large nonprofit healthcare system in Washington State. This study was approved by the Group Health Institutional Review Board and all participants provided informed consent. Participants enrolled in the study between November 1, 2010 and March 5, 2013. Potential study participants were identified from Group Health electronic pharmacy records. We identified patients aged 45 years or older who appeared to have recently started opioid therapy and to be transitioning to long-term use. We operationalized this by identifying patients who, within the past 4 months, had filled an index opioid prescription followed by at least 2 more opioid prescriptions and had at least 60 days' supply of opioids within the 4-month period. The index prescription had to follow a period of at least 3 months without an opioid prescription fill. Preliminary analyses, conducted prior to enrolling study participants, indicated that about half of patients meeting these criteria would continue opioid use 1 year later. To ensure completeness of administrative data, we excluded patients not enrolled continuously at Group Health in the prior year. We also excluded patients with 2 or more visits for cancer diagnoses (other than non-melanoma skin cancer) in the prior year or receiving hospice or nursing home care. During telephone screening, we excluded patients who said that they had not taken prescription pain relievers on at least 7 days in the previous 2 weeks as well as those unable to speak English, unable to participate in a telephone interview, or planning to disenroll from Group Health in the next year. Trained survey staff conducted computer-assisted telephone interviews with study participants at baseline and again 4 and 12 months later.

Among 3,172 Group Health patients mailed MASCOT study invitation letters, 2,808 (89%) were contacted for eligibility screening; among these, 2,125 were not identified as ineligible for the study. Among these 2,125 patients, 1,477 (70%) enrolled and completed the baseline interview. Among the 1,477 MASCOT participants, 38 (3%) participants had missing information on important baseline covariates. Among the 1,439 individuals with relevant baseline information, 1,218 (85%) completed the 12-month interview and had complete data on the outcome and opioid use measures of interest in the current study.

2.2. Measures

2.2.1. Independent variables

2.2.1.1. Fibromyalgia: We defined presence of fibromyalgia based on physician-assigned diagnostic codes and/or patient self-report. At the time of this study, Group Health physicians used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)²⁸ to code patient diagnoses at office visits. There is not a specific ICD-9-CM code for fibromyalgia, but 729.1 (myalgia and myositis NOS) was commonly used for fibromyalgia and converts to myositis, unspecified; myalgia; or fibromyalgia in ICD-10-CM. We defined presence of fibromyalgia as (a) assignment of an ICD-9-CM diagnostic code of 729.1 at a visit in the 2 years prior to the baseline interview or (b) patient indication at baseline on a self-report measure of widespread pain bothersomeness (described below) of being ‘bothered a lot’ by ‘widespread pain, pain in most of your body, or fibromyalgia.’ For parsimony, we hereafter refer to this variable as *fibromyalgia*.

2.2.1.2. Widespread pain score: As a secondary measure, we used the baseline score on a continuous measure of widespread pain bothersomeness. Participants used the Patient Health Questionnaire-15 (PHQ-15)²¹ rating scale to rate how much they had been bothered (not at all [0], a little [1], or a lot [2]) by pain in each of 7 different body sites during the past 4 weeks. The sites included 5 sites from the PHQ-15 (stomach; back; arms, legs, or joints; headaches; chest) plus ‘neck’ and ‘widespread pain, pain in most of your body, or fibromyalgia.’ The score was calculated as the sum of the ratings and could range from 0 to 14, with higher scores indicating more bothersome and widespread pain. For parsimony, we hereafter refer to this as the *widespread pain score*.

2.2.1.3. Opioid use: Because pharmacy records accurately capture information on medication dispensed, but not on how patients use the medication, we defined opioid use with a categorical classification that combined information from pharmacy records and self-report.³⁵ Using Group Health electronic pharmacy data, we identified prescription opioid medication fills (including information on quantity and strength of medication dispensed, days’ supply, and prescription fill date) in the 120-day period prior to the 12-month interview. We calculated the mean morphine-equivalent dose (MED) per day³⁹ across the 120 days. We classified study participants into the following 3 opioid use groups at 12 months based on a combination of self-reported opioid use in the past 28 days as reported in the 12-month interview and opioid dose over the 120 days prior to the 12-month interview as calculated from pharmacy data:

Minimal/no use: Mean daily MED <5 mg in the previous 120 days or self-reported use of opioids less than twice a week (including no use) for the previous 28 days.

Intermittent/lower-dose use: Mean daily MED 5 to <15 mg in the previous 120 days and self-reported use of opioids at least twice a week within the previous 28 days.

Regular/higher-dose use: Mean daily MED ≥ 15 mg in the previous 120 days and self-reported use of opioids at least twice a week within the previous 28 days.

2.2.2. Outcome measures—Our co-primary outcomes were characteristic pain intensity and pain-related activity interference at 12 months. Characteristic pain intensity, from the Graded Chronic Pain Scale,^{37,38} is the mean of 0-10 ratings (0 = ‘no pain’ and 10 = ‘pain as bad as could be’) of pain right now, worst pain in the past month, and average pain in the past month; it has been shown to be valid, reliable, and sensitive to change.^{13,20,36-38} Pain-related activity interference was evaluated by the Graded Chronic Pain Scale item, “in the past month, how much has pain interfered with your daily activities, using a 0-10 scale where 0 is ‘no interference’ and 10 is ‘unable to carry on any activities’?”.³⁷

2.2.3. Descriptive variables and covariates—Following recommended methods for covariate selection,³³ we controlled for potential confounders identified in prior research as predictive of the study outcomes^{8,18,29,34} and of long-term prescription opioid use.^{5,31} The covariates included age; gender; disability status (categorized for analysis as permanently or temporarily disabled or unable to work because of pain or health versus working, in school, retired, unemployed, or homemaker); number of days with pain in the past 6 months; the GAD-2²² 2-item measure of anxiety (score range 0-6; higher scores indicate greater anxiety); and the PHQ-8²³ 8-item measure of depressive symptom severity (score range 0-24; higher scores indicate greater depressive symptom severity). All of these covariates were self-report measures obtained during the baseline assessment except for age and gender, which were obtained from Group Health electronic databases.

We also included as a covariate an indicator of recent COT initiation.³⁵ All study participants were identified by pharmacy data as initiating a new episode of opioid use as defined by a period of at least 3 months between the index opioid prescription fill and prior opioid prescription fills. Due to difficulty definitively identifying patients initiating COT using only pharmacy data, we also used patient-reported information to differentiate confirmed COT initiators from continuing COT users. We defined *COT initiators* as patients who (1) did not fill an opioid prescription with a run-out date (based on days’ supply) within 30 days of the index prescription fill date and (2) reported in the baseline interview that their current use of opioids use began (a) less than 6 months ago or (b) more than 6 months ago, but with a period of at least 1 month within the past 6 months of no opioid use, after which opioid use was re-initiated. We defined all patients who did not meet these criteria as *continuing opioid users*.

2.2.4. Reasons for stopping opioid medication use and helpfulness of opioid use—At 12 months, participants who reported that they had not used opioids in the past 2 weeks and that they had discontinued opioid use were read a list of possible reasons for discontinuing and asked to rate each as very, somewhat, or not important in deciding to stop.³⁵ Patients who were still using opioids were asked, “Over the past 3 months, how helpful have you found opiate pain medicines to be in relieving your pain?”. Response choices were ‘not at all,’ ‘a little,’ ‘moderately,’ ‘very,’ and ‘extremely’ helpful.

2.3. Statistical analysis

We used descriptive statistics to summarize characteristics of patients with versus without fibromyalgia at baseline, as defined using ICD-9-CM code and/or patient self-report. To

examine whether these groups differed in levels of opioid use at 12 months, we used a *chi*-square test. We also compared these groups in terms of baseline characteristics that might be prognostic of pain outcomes or response to opioids using *t*-tests and *chi*-square tests. Our analysis sample consisted of study participants with data on the outcomes at baseline and at 12 months, covariates assessed at baseline, and opioid use in the 120 days preceding the 12-month outcome assessment. In the regression analyses described below, we used inverse probability of missingness weights to account for bias in measured covariates that might result from this ‘complete case’ analysis.^{24,32}

To examine whether the associations of opioid use with 12-month outcomes differed depending on presence of fibromyalgia at baseline, we constructed separate regression models for each outcome (pain and activity interference). The dependent variable was the 12-month value of the outcome measure. The independent variables were baseline fibromyalgia and opioid use prior to the 12-month interview (minimal/no, intermittent/lower-dose, regular/higher-dose use). The models adjusted for the covariates and the baseline values of both outcome measures. Each model included a fibromyalgia by opioid use interaction term. We assessed statistical significance of the interaction term using a Wald test⁴¹ to evaluate whether the coefficients for the interaction terms differed from zero. We estimated the adjusted mean scores (with associated 95% confidence intervals [CI]) on the outcome measures in the 3 opioid use categories by baseline fibromyalgia status. We also estimated the adjusted mean differences (and 95% CI) between the opioid use groups on the outcome measures at 12 months. For descriptive purposes, we also estimated adjusted mean (95% CI) pain and activity interference scores at 4 months for each opioid use group for individuals with and without fibromyalgia at baseline.

We repeated the regression analyses using the baseline widespread pain score as a predictor. We estimated the adjusted mean (95% CI) pain and activity interference scores for each opioid use group at the 25th and 75th percentiles of the baseline widespread pain score in our sample.

We repeated the primary analyses examining the association of baseline fibromyalgia diagnosis with the 12-month pain and activity interference outcomes in three sets of sensitivity analyses. First, because depressive symptoms are sometimes included in diagnosing fibromyalgia, we repeated the analyses excluding the PHQ-8 depression measure as a covariate in the regression models to determine whether results changed when not adjusting for depression. Second, because tramadol could be more effective than other opioids for fibromyalgia because it inhibits serotonin and norepinephrine reuptake,¹⁷ we repeated the analyses excluding patients with prescriptions for tramadol in any of the 3 120-day periods examined in this study (prior to baseline, 4 months, and 12 months). Finally, because results could differ for patients with confirmed recent initiation of COT versus those with continuing opioid use, we repeated the analyses restricting the sample to the confirmed COT initiators.

For the subgroup of patients who at 12 months were in the minimal/no opioid use group and reported that they had stopped using opioids, we calculated the number and percent of patients with and without fibromyalgia at baseline. We used *chi*-square tests to compare the

2 groups in terms of reported reasons for discontinuing opioid use. For the subgroup of patients who were still using opioids at 12 months on an intermittent/lower-dose or regular/higher-dose basis, we used *chi*-square tests to compare those with versus without fibromyalgia on their ratings of helpfulness of opioids in relieving their pain.

3. Results

3.1. Sample baseline characteristics

At baseline, among the 1,218 patients in the sample, 429 (35%) met our definition of fibromyalgia based on physician-assigned diagnostic code or self-report and 789 (65%) did not. Among the 429 patients who met this definition, 25.5% had the physician-assigned diagnostic code but did not describe themselves as being bothered a lot by widespread pain or fibromyalgia, 54.0% met the self-report criterion but did not have the diagnostic code, and 20.5% met both criteria.

Patients with versus without fibromyalgia were similar in age, race/ethnicity, and education, but differed significantly on all other baseline characteristics examined (**Table 1**). Patients with fibromyalgia were more likely to be female and continuing opioid users, and had higher scores on measures of pain and physical and psychosocial dysfunction. As expected, the widespread pain score was significantly higher for individuals with fibromyalgia than for those without. Twelve months later, patients with fibromyalgia were less likely than those without fibromyalgia to have used opioids minimally or not at all (41.7% versus 54.1%) and more likely to have used opioids on a regular/higher-dose basis (31.2% versus 23.2%) in the preceding 120 days. Among the 606 patients in the minimal/no use category at 12 months, 441 (73%) reported that they used opioids less than twice a week (including no use) during the previous 28 days, 532 (88%) had a mean daily opioid dose <5 mg MED over the previous 120 days, and 367 (61%) met both of these criteria.

3.2. Patients with versus without fibromyalgia: differences in association of opioid use with 12-month pain and activity interference

Figures 1 and 2 show the baseline, 4-month, and 12-month adjusted mean scores on the pain intensity and activity interference measures for patients grouped according to their opioid use in the 120 days prior to the 12-month assessment, separately for patients with and without fibromyalgia at baseline. These figures show that among patients both with and without fibromyalgia, those with regular/higher-dose or intermittent/lower-dose opioid use at 12 months improved less in the year after baseline in pain and interference outcomes than did those with minimal/no opioid use prior to the 12-month follow-up. Among these patients who had sustained opioid use through the year, the improvement in pain and interference was similar for patients with and without fibromyalgia, irrespective of whether their opioid use was regular/higher-dose or intermittent/lower-dose. In contrast, among patients with minimal/no opioid use by 12 months, improvement from baseline was somewhat greater for those without fibromyalgia than for those with fibromyalgia. For example, the adjusted mean pain intensity at 12 months for patients in the regular/higher-dose group was 6.04 (95% CI, 5.74, 6.34) among patients with fibromyalgia (**Figure 1A**) and 5.98 (95% CI, 5.70, 6.25) among patients without fibromyalgia (**Figure 1B**). However, in the minimal/no use

group, pain outcomes were better for patients without fibromyalgia (4.44 [95% CI, 4.15, 4.72]) than for patients with fibromyalgia (5.15 [95% CI, 4.80, 5.51]).

A similar pattern was observed for activity interference (**Figure 2**), although the difference between those with and without fibromyalgia in the minimal/no use group at 12 months was smaller. The adjusted mean activity interference at 12 months in the regular/higher-dose group was similar for those with fibromyalgia (5.08 [95% CI, 4.64, 5.52]; **Figure 2A**) and those without fibromyalgia (4.99 [95% CI, 4.57, 5.42]; **Figure 2B**). The adjusted mean activity interference at 12 months in the minimal/no opioid use group was 3.72 (95% CI, 3.25, 4.20) among patients with fibromyalgia (**Figure 2A**) and 3.41 (95% CI, 3.04, 3.79) among those without fibromyalgia (**Figure 2B**).

Table 2 shows the results of the regression models examining the interaction between baseline fibromyalgia and opioid use in the 120 days prior to the 12-month assessment in predicting 12-month outcomes, adjusting for the baseline values of the outcome measures and the covariates. The interaction coefficient in the model predicting 12-month characteristic pain intensity differed significantly from zero ($P = 0.006$), indicating a differing relationship between opioid use and pain intensity for those with versus without fibromyalgia. Among patients without fibromyalgia, 12-month adjusted mean pain scores were 1.54 points higher (95% CI, 1.26, 1.82) in the regular/higher-dose group than in the minimal/no use group; among patients with fibromyalgia, pain scores were 0.88 (95% CI, 0.53, 1.24) points higher (adjusted mean difference between those with and without fibromyalgia of 0.66 points; **Table 2**). A similar pattern of smaller differences relative to the minimal/no use group among individuals with fibromyalgia than among those without was seen in the intermittent/lower-dose group. Among individuals without fibromyalgia, adjusted mean pain intensity was 1.44 points (95% CI, 1.16, 1.72) higher in the intermittent/lower-dose group than in the minimal/no use group; among individuals with fibromyalgia, it was 0.83 (0.46, 1.21) points higher (adjusted mean difference between those with and without fibromyalgia of 0.61 points; **Table 2**).

In the model predicting activity interference at 12 months, the interaction between baseline fibromyalgia and opioid use prior to the 12-month assessment did not differ significantly from zero ($P = 0.68$), although the pattern of a decrease in the association between opioid use and activity interference among those with versus without fibromyalgia was similar to that observed for pain intensity (**Figure 2, Table 2**). The reduction in the magnitude of the effect was 0.27 points in the intermittent/lower-dose group and 0.22 points in the regular/higher-dose group as compared with the minimal/no use group for activity interference (**Table 2**), in contrast to 0.61 points and 0.66 points for pain intensity.

3.3. Patients with low versus high baseline widespread pain scores: differences in association of opioid use with 12-month pain and activity interference

The relationship between opioid use and pain intensity at 12 months differed significantly (Wald test $P < 0.001$) based on widespread pain score at baseline. Similar to the pattern seen for the baseline fibromyalgia variable, differences in 12-month pain intensity between the minimal/no opioid use group and the other 2 opioid use groups were smaller for those with higher versus lower widespread pain scores at baseline. This was largely due to the more

favorable pain outcomes in the minimal/no opioid use group for those with lower widespread pain scores. For example, in the minimal/no use group, the adjusted mean pain intensity (95% CI) at 12 months was 4.11 (3.81, 4.40) for someone scoring at the 25th percentile on the widespread pain measure at baseline and 5.22 (4.94, 5.50) for someone scoring at the 75th percentile. (See Supplemental Digital Content 1, which is a figure showing adjusted mean pain intensity scores at baseline, 4 months, and 12 months for individuals with baseline widespread pain scores at the 25th and 75th percentile by opioid use in the 120 days prior to the 12-month assessment.)

A similar pattern was observed for adjusted mean activity interference scores. Interference outcomes at 12 months were better for those scoring at the 25th percentile than for those scoring at the 75th percentile on the widespread pain measure at baseline. This was especially the case for patients with minimal/no opioid use at 12 months. In this group, the adjusted mean (95% CI) activity interference score at 12 months was 3.07 (2.67, 3.46) for those at the 25th percentile versus 3.96 (3.58, 4.34) for those at the 75th percentile on the widespread pain measure at baseline. (See Supplemental Digital Content 2, which is a figure showing adjusted mean activity interference scores at baseline, 4 months, and 12 months for individuals with baseline widespread pain scores at the 25th and 75th percentile by opioid use in the 120 days prior to the 12-month assessment.) However, the interaction between baseline widespread pain score and 12-month opioid use in predicting activity interference at 12 months was not statistically significant ($P = 0.06$). (See Supplemental Digital Content 3, which is a table showing the results of the analyses of the interaction between baseline widespread pain score and opioid use prior to the 12-month interview in predicting 12-month characteristic pain and activity interference.)

3.4. Sensitivity analyses: without adjusting for baseline depression scores, excluding patients who used tramadol, and limited to confirmed opioid initiators

We repeated the regression analyses predicting 12-month characteristic pain and activity interference in 3 separate sensitivity analyses: (1) without adjusting for baseline PHQ-8 depression scores; (2) excluding the 199 patients (16.3% of the sample) who used tramadol in the 120-day period prior to the baseline, 4-month, and/or 12-month assessment; and (3) limited to confirmed COT initiators ($n = 469$). There were no meaningful changes in the results of the first 2 sensitivity analyses. Compared to the analysis for the entire sample, the analysis limited to confirmed COT initiators showed a similar pattern of coefficient estimates (adjusted mean differences). The estimates were slightly larger for the main effects of fibromyalgia and intermittent/lower-dose and regular/higher-dose opioid use relative to minimal/no use on pain, and for the main effects of intermittent/lower-dose and regular/higher-dose opioid use relative to minimal/no use on activity interference. There were no meaningful changes in the fibromyalgia by opioid use interaction effects.

3.5. Patients with versus without fibromyalgia: helpfulness of opioids and reasons for discontinuing opioid use at 12 months

At 12 months, among patients who reported still using opioids and were classified as either intermittent/lower-dose or regular/higher-dose users ($n = 605$; 358 without fibromyalgia and 247 with fibromyalgia), there was no significant difference between those with and without

fibromyalgia in proportion who said that opioids were very or extremely helpful in relieving their pain (66% of those with fibromyalgia and 69% of those without fibromyalgia; *chi-square* test, $P = 0.49$). Among patients in the minimal/no opioid use group who reported having stopped using opioids entirely at 12 months ($n = 360$), 89 met our definition of fibromyalgia at baseline (20.7% of the 429 patients with fibromyalgia at baseline) and 271 did not (34.3% of the 789 patients classified as not having fibromyalgia at baseline). **Table 3** shows the reasons endorsed as very or somewhat important in discontinuing opioid use by patients with and without fibromyalgia. Significantly fewer patients with fibromyalgia reported pain getting better as a reason for discontinuation (66.3% of patients with fibromyalgia versus 80.1% of patients without fibromyalgia, $P = 0.008$) and significantly more patients with fibromyalgia said that they stopped due to physical side effects (45.5% versus 31.5%, $P = 0.02$) or cognitive side effects (40.5% versus 26.9%, $P = 0.02$) of the medication. More patients with fibromyalgia reported that an important reason for discontinuation was that the medicine was not very effective in relieving their pain (43.4% versus 32.2% of those without fibromyalgia), but this difference was not statistically significant ($P = 0.06$).

4. Discussion

This study addresses the need for empirical data concerning pain outcomes associated with COT for patients with fibromyalgia. Using data from the MASCOT cohort of patients initiating COT for chronic pain,³⁵ we tested the hypothesis that patients with fibromyalgia would have worse pain outcomes with long-term opioid use when compared to patients without fibromyalgia. As expected given previous MASCOT findings,³⁵ outcomes were worse for patients who continued to use opioids long-term than for those with minimal/no opioid use at 12 months. However, our hypothesis regarding worse outcomes with opioids for patients with fibromyalgia was not confirmed. Among patients who continued to use opioids at the 12-month follow-up, pain and activity interference outcomes were similar for those with and without fibromyalgia. This was true for both intermittent/lower-dose and regular/higher-dose opioid users. In contrast, among patients with minimal or no opioid use at 12 months, outcomes were less favorable for those with fibromyalgia than for those without.

This pattern of findings was similar when using a continuous measure of widespread pain instead of a dichotomous definition of fibromyalgia. It has been proposed that higher scores on the ACR 2011 fibromyalgia diagnostic measure indicate likelihood of poor response to opioids.¹⁰ Using a similar measure but not including cognitive, affective, and fatigue symptoms, higher baseline widespread pain scores did not predict worse response to opioids. Both patients with low scores and those with high scores showed less improvement in pain over the next 12 months if they continued using opioids than if they discontinued opioids or used them minimally. The more favorable outcomes among patients with minimal/no opioid use may reflect opioid discontinuation among patients whose pain improved.³⁵ However, among patients with minimal or no opioid use by 12 months, pain outcomes were worse for those with higher widespread pain scores than for those with lower scores at baseline.

Reasons given for the view that COT is inappropriate for treating fibromyalgia include lack of evidence for efficacy. Furthermore, findings of positive associations between fibromyalgia survey scores and post-operative opioid consumption in observational studies of patients undergoing total knee and hip arthroplasty³ and hysterectomy¹⁹ could reflect decreased opioid responsiveness, although other explanations are also possible (e.g., greater post-operative pain severity among those with fibromyalgia, pre-operative characteristics associated with both fibromyalgia and post-operative opioid consumption but not controlled for in analyses).² There are also concerns about possible increased vulnerability of patients with fibromyalgia to opioid-related augmentation of central nervous system pain processing, risks for abuse, and other adverse effects.^{10,25,26} Differences between patients in our study with versus without fibromyalgia who discontinued opioid use in reasons reported for discontinuation bear on these issues. Patients with fibromyalgia were significantly less likely to cite pain improvement as an important reason for discontinuation (66% of those with fibromyalgia versus 80% of those without fibromyalgia) and significantly more likely to report that negative physical and cognitive side effects were important reasons for stopping. These data support previous observations that patients with fibromyalgia are more likely to report adverse effects of treatment in general and of opioids specifically (e.g., fatigue, constipation, sedation).²⁶ Cognitive problems (e.g., problems with attention, concentration, memory) are part of the constellation of fibromyalgia symptoms.¹⁵ It is possible that patients with fibromyalgia tended to attribute these problems to opioids and/or were more sensitive to effects of opioids on cognitive functioning. Patients with fibromyalgia did not differ from those without fibromyalgia in citing concerns about dependency or addiction, or concerns that they were having trouble controlling how much medication they took, as reasons for stopping.

Only a minority of patients with fibromyalgia (21%) discontinued opioid use by the 12-month follow-up. This proportion was similar to the estimated proportion of patients with fibromyalgia using opioids at baseline who discontinued opioid use at 12 months (22%) in a prior large, longitudinal, observational study comparing propensity score-matched cohorts of patients with fibromyalgia using versus not using opioids at baseline.²⁷ In that study, reasons given for discontinuation included adverse events (33%), lack of helpfulness (30%), and “felt better” (8%). Although differences in wording of reasons make direct comparisons of our study to theirs difficult, both studies indicate that undesirable side effects and lack of helpfulness are common reasons for opioid discontinuation among patients with fibromyalgia; our study also sheds light on how these reasons may differ for patients with fibromyalgia versus other chronic pain problems.

In the study of matched patients with fibromyalgia using versus not using opioids at baseline,²⁷ patients in the non-opioid cohort had greater improvement in activity interference over the 12-month study period than did patients in the opioid cohort. Taken together, that study and ours suggest that even with matching or adjusting for baseline patient characteristics predictive of outcomes, chronic pain patients who continue using opioids long-term, whether or not they have fibromyalgia, are more likely to have worse pain outcomes as compared with patients who do not use opioids long-term. Our findings that patients with fibromyalgia were less likely to discontinue opioids due to pain improvement and more likely to discontinue because of side effects may help explain why, among patients

with minimal or no opioid use at 12 months, those with fibromyalgia had worse pain and function outcomes.

We note study limitations. Patients were not systematically clinically assessed for fibromyalgia and did not complete the Modified ACR 2011 Fibromyalgia Diagnostic Criteria self-report measure. However, there is no consensus on fibromyalgia or CWP diagnostic criteria and we used a self-report measure of pain in multiple body sites that was similar to the ACR measure except for lack of items assessing fatigue, cognitive problems, and depression. Results for this measure did not change depending on whether analyses adjusted for scores on the PHQ-8 depression scale, which assesses cognitive, affective, and fatigue symptoms. Patients without an ICD-9-CM diagnosis indicating fibromyalgia or self-report of widespread pain or fibromyalgia were combined into a single group of “other diagnoses.” This group was mixed in pain sites and likely mixed in terms of level of centralized pain state. The diagnostic data available to us were not sufficiently detailed to distinguish other chronic pain conditions for which the risks of COT are believed to outweigh the benefits (e.g., headache, nonspecific low back pain) from nociceptive pain conditions, which are believed to be more responsive to opioids.^{10,12,16} We assessed pain and activity interference outcomes at only 2 follow-up time points and examined relationships to opioid use averaged over the prior 120 days. Although this can shed light on longer-term patterns, we were unable to examine more finely-grained relationships between opioid use and pain. Finally, our sample was restricted to adults aged 45 years and older in an integrated healthcare system; the extent to which our findings generalize to patients and settings with different characteristics is unknown. Despite these limitations, our study had notable strengths, including the prospective design, large sample size, adjustment for multiple baseline variables predictive of opioid use and pain outcomes, and use of both electronic medical record and self-report measures.

In conclusion, among patients identified as initiating COT for chronic pain, many had discontinued opioid use or used opioids only minimally 12 months later. In this group, those with fibromyalgia had worse outcomes as compared to those without fibromyalgia. Reasons for discontinuing opioid use also differed for patients with versus without fibromyalgia. Among patients without fibromyalgia, those who discontinued opioids were largely individuals whose pain had improved. In contrast, patients with fibromyalgia were less likely to have discontinued opioid use because of pain improvement and more likely to have discontinued because of bothersome side effects. Among the patients who continued to use opioids long-term, either on an intermittent/lower-dose or regular/higher-dose basis, those with fibromyalgia or widespread pain had no worse and no better pain outcomes as compared with patients with other chronic pain problems. Regardless of baseline fibromyalgia status or scores on a measure of widespread pain, long-term pain and activity interference outcomes were worse for those who continued to use opioids long-term than for those who discontinued opioids or used them minimally by 12 months. Many patients without fibromyalgia may have had other chronic pain conditions for which the risks of COT are believed to outweigh the benefits. Although it is possible that individuals continuing to use opioids long-term could have had even greater pain and activity interference without opioids, the worse scores on those measures for patients both with and without fibromyalgia

who continued on opioid therapy long-term may reflect unfavorable outcomes with opioids in both groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Adjusted mean characteristic pain intensity at baseline, 4 months, and 12 months by opioid use in the 120 days prior to the 12-month assessment among patients with (A) and without (B) fibromyalgia at baseline. Baseline means are adjusted for gender and baseline age, pain days in past 6 months, disability status, opioid initiator status, GAD-2, and PHQ-8. 4-month and 12-month means are adjusted for gender and baseline age, characteristic pain intensity, activity interference, pain days in past 6 months, disability status, opioid initiator status, GAD-2, and PHQ-8.

Figure 2.

Adjusted mean activity interference at baseline, 4 months, and 12 months by opioid use in the 120 days prior to the 12-month assessment among patients with (A) and without (B) fibromyalgia at baseline. Baseline means are adjusted for gender and baseline age, pain days in past 6 months, disability status, opioid initiator status, GAD-2, and PHQ-8. 4-month and 12-month means are adjusted for gender and baseline age, characteristic pain intensity, activity interference, pain days in past 6 months, disability status, opioid initiator status, GAD-2, and PHQ-8.

Table 1

Patients with versus without fibromyalgia at baseline: baseline characteristics and opioid use at 12-month follow-up (N = 1,218).

Characteristics	Baseline fibromyalgia status		<i>P</i> -value [*]
	No fibromyalgia n = 789	Fibromyalgia n = 429	
Baseline characteristics			
Age, yr, M (SD)	64.6 (10.9)	64.4 (10.2)	0.80
Female, n (%)	460 (58.3)	320 (74.6)	<0.001
Non-Hispanic white, n (%)	678 (86.5)	355 (84.1)	0.27
College graduate, n (%)	263 (33.3)	125 (29.1)	0.13
Disabled, n (%)	76 (9.6)	87 (20.3)	<0.001
Characteristic pain intensity (0-10), M (SD)	6.0 (1.6)	6.9 (1.4)	<0.001
Activity interference (0-10), M (SD)	5.7 (2.3)	6.6 (2.2)	<0.001
Number of days with pain, past 6 mo (0-180), M (SD)	136.7 (55.9)	155.7 (46.3)	<0.001
GAD-2 (0-6), M (SD)	1.4 (1.6)	2.0 (2.0)	<0.001
PHQ-8 (0-24), M (SD)	6.5 (5.3)	9.0 (5.8)	<0.001
Widespread pain bothersomeness (0-14), M (SD)	4.8 (2.0)	7.9 (2.5)	<0.001
Confirmed opioid initiator, n (%)	531 (67.3)	218 (50.8)	<0.001
Opioid use at 12 months			<0.001
Minimal/no use, n (%)	427 (54.1)	179 (41.7)	
Intermittent/lower-dose use, n (%)	179 (22.7)	116 (27.0)	
Regular/higher-dose use, n (%)	183 (23.2)	134 (31.2)	

GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire

^{*} *P*-value is from *t*-test for continuous variables, *chi*-square test for categorical variables.

Table 2

Association of 12-month characteristic pain intensity and activity interference with opioid use over the prior 120 days by presence of fibromyalgia at baseline.

	Characteristic pain intensity, 12 months	Activity interference, 12 months
	Adjusted mean difference (95% CI)	Adjusted mean difference (95% CI)
Fibromyalgia at baseline *	0.72 (0.37, 1.06)	0.31 (−0.15, 0.77)
Opioid use at 12 mo. (reference=minimal/no use) †		
Intermittent/lower-dose use	1.44 (1.16, 1.72)	1.32 (0.90, 1.73)
Regular/higher-dose use	1.54 (1.26, 1.82)	1.58 (1.16, 2.00)
Baseline fibromyalgia X 12 mo. intermittent/lower-dose interaction ‡	−0.61 (−1.07, −0.14)	−0.27 (−0.93, 0.39)
Baseline fibromyalgia X 12 mo. regular/higher-dose interaction ‡	−0.66 (−1.10, −0.22)	−0.22 (−0.87, 0.42)

Analyses controlled for gender, confirmed opioid initiator status, baseline disability status, and baseline values of age, characteristic pain intensity, activity interference, pain days in past 6 months, GAD-2, and PHQ-8. The interaction between fibromyalgia status at baseline and opioid use prior to 12 months was statistically significant in predicting 12-month characteristic pain intensity ($P = 0.006$), but not in predicting 12-month activity interference ($P = 0.68$).

* The adjusted mean differences for fibromyalgia indicate differences in the outcomes for those with versus without fibromyalgia. Positive values indicate higher scores (worse outcomes) for those with fibromyalgia.

† The adjusted mean differences for opioid use at 12 months indicate differences in the outcomes for those with each level of opioid use as compared with minimal/no use. Positive values indicate higher scores (worse outcomes) for those with greater opioid use.

‡ The adjusted mean differences associated with interaction terms are estimates for the different associations of opioid use with the outcomes in patients with versus without fibromyalgia. An interaction estimate of 0 would indicate that the adjusted mean difference in the opioid use category compared to minimal/no use is the same for individuals with and without fibromyalgia. The negative values here indicate smaller differences between the minimal/no opioid use group and the other two opioid use groups among patients with fibromyalgia than among those without fibromyalgia.

Table 3

Reasons for discontinuing opioid use among patients with and without fibromyalgia who had stopped using opioids at 12 months (n = 360).

Reason	Fibromyalgia n = 89 % (n)	No fibromyalgia n = 271 % (n)	P-value
You prefer to manage pain without using strong pain medicines.	84.3 (75)	87.4 (236)	0.45
Your pain had gotten better.	66.3 (57)	80.1 (217)	0.008
You were worried about becoming dependent on or addicted to the medicine.	47.2 (42)	50.2 (136)	0.62
The medicine made you feel bad physically; for example, made you constipated, drowsy, nauseated, or itchy.	45.5 (40)	31.5 (85)	0.02
The medicine was not very effective in relieving your pain.	43.4 (36)	32.2 (86)	0.06
Your health care provider had expressed concerns about your use of the medicine.	37.2 (32)	27.0 (73)	0.07
The medicine caused problems with concentration, alertness or memory.	40.5 (36)	26.9 (73)	0.02
The medicine made you feel bad emotionally; for example, you felt sad, depressed, irritable, moody, or anxious.	21.4 (19)	20.7 (56)	0.89
You felt like you were having a hard time controlling how much pain medicine you took.	23.6 (21)	16.2 (44)	0.12
Your family, friends, or other person had expressed concerns about your use of the medicine.	18.0 (16)	13.7 (37)	0.32

Percents (n) indicate those who endorsed the reason as very or somewhat important in discontinuing prescription opioid use. *P*-values are from *chi*-square tests.