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Long-Term Evaluation of Opioid Treatment in Fibromyalgia

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Running Title: Opioid treatment and patient outcomes in fibromyalgia

Abstract

Objectives: In a 12-month observational study, we evaluated the effect of opioid use on outcomes in 1700 adult patients with fibromyalgia (FM).

Methods: Data were evaluated using propensity-score-matching after patients were divided into cohorts based on their baseline medication use:1) taking an opioid (concurrent use of tramadol was permitted); (2) taking tramadol (but no opioids); and (3) not taking opioids or tramadol. Changes in outcomes were assessed using the Brief Pain Inventory for severity and pain-related interference (BPI-S, BPI-I), Fibromyalgia Impact Questionnaire (FIQ), Patient Health Questionnaire for depression (PHQ-8), Insomnia Severity Index (ISI), Sheehan Disability Scale (SDS), 7-item Generalized Anxiety Disorder scale (GAD-7) and economic factors. Time to opioid or tramadol discontinuation was analyzed using Kaplan-Meier survival analyses.

Results: Compared with the opioid cohort, the non-opioid cohort demonstrated significantly greater reductions ($P<0.05$) in BPI-I, FIQ, PHQ-8, SDS and ISI; the tramadol cohort compared with the opioid group showed greater reductions on FIQ and ISI. Reductions in BPI-S and GAD-7 did not differ significantly among cohorts. Compared with the opioid cohort, patients in the tramadol cohort had fewer outpatient visits to healthcare providers. Few significant differences were found between the tramadol and non-opioid cohorts across outcomes.

Discussion: While pain severity was reduced over time in all cohorts, opioid users showed less improvement in pain-related interference with daily living, functioning, depression, and insomnia. Overall, the findings show little support for the long-term use of opioid medications in patients with FM given the poorer outcomes across multiple assessment domains associated with this cohort.

Introduction

Fibromyalgia (FM) is characterized by widespread pain and various symptoms, including fatigue and mood and sleep disturbances, which can complicate treatment decision making.[1,2,3,3,4] Current FM treatment guidelines recommend a multidisciplinary approach including nonpharmacologic and pharmacologic interventions.[3,5] The American Pain Society guidelines recommend that opioid analgesics be used with caution after all other therapeutic options have been exhausted.[6–8] Caution is recommended partly due to the paucity of clinical trial data evaluating the role of opioids in long-term FM treatment,[10] potential side-effects and risk of addiction associated with opioids in patients with FM.[11,12] Additionally, because patients with FM may have decreased central-opioid receptor availability or a lower binding potential, opioids may have less efficacy than when they are used in patients in whom binding potentials are higher.[13]

There are no known studies comparing the effects of opioids with those of other medication classes in patients with FM.[14] Tramadol, which was approved by the Food and Drug Administration for treatment of moderate to moderately severe pain in adults, is not specifically approved for FM treatment but it is the only opioid-like agent that has been systematically evaluated and included in FM treatment guidelines.[14,15] Because tramadol is a centrally acting synthetic opioid analgesic with activity on mμ receptors and serotonin and norepinephrine reuptake inhibition, we categorized tramadol separately from opioids or non-opioids.

A meta-analysis of studies examining the effectiveness and adverse effects of opioids for non-malignant chronic pain, including FM-related pain, showed that opioids were generally effective for pain relief and improving functional outcomes across a range of chronic conditions, and that this may be a reason some practitioners turn to opioid treatment for FM.[7] However, the

lack of scientific support of opioid use in this patient population remains a concern in terms of physiological factors (e.g., side effects) and the risks of abuse, addiction, or overdose associated with opioid use.[3,7,12,13] Evidence-based recommendations from the European League Against Rheumatism released in 2008 suggested that weak opioids may be considered for treatment of FM syndrome, but strong opioids were not recommended.[16]

Despite these recommendations and a lack of scientific support, many patients with FM are being prescribed and are taking opioid medications.[17] In our 12-month, prospective observational study, identified as REFLECTIONS (Real World Examination of Fibromyalgia: Longitudinal Evaluation of Costs and Treatments) two of the most commonly reported medications used for FM were opioids (24.2%) and tramadol (15.3%).[18] For the overall sample in that study, opioids had the highest mean medication possession ratio (defined as the number of days that supply of medication was supplied to number of days in the 12-month study) at 0.27. Among patients who had any opioid use at baseline (36.5%), the ratio was particularly high at 0.72.[18]

The purpose of this analysis was to evaluate the effects of long-term opioid treatment relative to tramadol or non-opioids on outcomes of relevance to FM and on the length of time patients remained on these treatments in the REFLECTIONS study.[19]

Methods

Study Setting and Participants

The study methodology has been described in detail by Robinson et al.[18,19] In brief, study participants were enrolled in various regions throughout the United States (northeast, north central, southeast, south central, west) and in Puerto Rico by their treating physicians (n=91) at 58 health care settings, including outpatient practices of rheumatology (59.3%), primary care (37.4%), neurology (2.2%), psychiatry (3.3%), pain specialties (3.3%), physical medicine (2.2%), obstetrics and gynecology (1.1%), and osteopathy (1.1%).

Minimal inclusion and exclusion criteria were used to increase the degree to which our sample represented patients with FM who are seen in real-world practice (ie, study generalizability); to be eligible, patients were ≥18 years of age and agreed to participate in the study for 12 months. Eligible patients were initiating a "new" treatment for FM (ie, were naive to FM treatment over the last 6 months), starting a new therapy to replace a previously used therapy, or adding a new therapy to their current FM treatment regimen. The treating physicians' decisions regarding the proper FM diagnosis, treatment, and care of the patients were made in the course of normal clinical practice.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was consistent with good clinical practices and applicable local laws and regulations. The ethical review boards of each investigator's institution approved the protocol and informed consent was obtained from each patient prior to study participation. This study was registered in ClinTrials.gov (identifier: NCT00725101).

Study Design and Measures

Study data were collected via a physician survey and patient visit form at baseline, and via computer-assisted telephone interviews at baseline, and 1, 3, 6, and 12 months postbaseline. Patients were invited to participate during a regular outpatient visit in which pharmacologic treatment for FM was prescribed, including but not limited to pain medications, antidepressants, anticonvulsants, stimulants, sleep agents, and anxiolytics.

Information about the type of medications used by patients was collected at each data collection wave from baseline to 12 months, including all concurrent medications, as well as which medications were discontinued during the study and reasons for discontinuation (multiple responses were allowed, including "felt better," "didn't help," "adverse events," "too costly," and "other").

The computer-assisted telephone interviews included the following outcome measures: Brief Pain Inventory (BPI) average pain severity (BPI-S; range 0 to 10) and average pain interference (BPI-I; range 0 to 10);[20] the total Sheehan Disability Scale total score, which incorporates disability across domains of work/school, social life, and family life/home responsibilities (SDS; range 0 to 30);[21] Fibromyalgia Impact Questionnaire total score across items of physical functioning; number of days the patient felt well; number of days the patient felt unable to work due to FM symptoms; and patient ratings of work difficulty, pain intensity, fatigue, morning tiredness, stiffness, anxiety, and depression (Fibromyalgia Impact Questionnaire [FIQ]; range 0 to 80);[22] Patient Health Questionnaire 8-item depression severity measure (PHQ-8, range 0 to 24);[23,24] PHQ physical symptoms measure (PHQ-15; range 0 to 30);[24,25] 7-Item Generalized Anxiety Disorder scale of anxiety disorder severity (GAD-7; range: 0 to 21);[24,26] Insomnia Severity Index (ISI; range 0 to 28);[27] and Massachusetts General Hospital

Cognitive and Physical Functioning Questionnaire (MGH-CPFQ; range 7 to 42).[28] For all of these measures, higher scores indicated worse status. To minimize patient burden, at the 1-month and 6-month visits, only the BPI-S, BPI-I, and PHQ-8 were administered.

The computer-assisted telephone interviews also assessed health care utilization measures, including the number of outpatient and hospital visits, over the 12 months.

Statistical Analysis

Patients were hierarchically classified into 3 mutually exclusive cohorts based on their baseline medication use: (1) opioids: currently taking an opioid (concurrent use of tramadol was permitted); (2) tramadol: currently taking tramadol but not opioids; and (3) non-opioid: not currently taking opioids or tramadol. Concurrent use of non-opioids was allowed in each cohort. The list of opioid medications reported included: bezitramide, buprenorphine, butorphanol, codeine, codeine plus N-acetyl-p-aminophenol (APAP), dextropropoxyphene, dextropropoxyphene napsilate, doxyphene, fentanyl, fortagesic, hydrocodone, hydrocodone plus APAP, hydromorphone, levorphanol, methadone, morphine, opioids (not specified), oxycodone, oxycodone plus APAP, oxymorphone, pentazocine, pethidine, phenazocine, propoxyphene, propoxyphene plus APAP, thebaine, and tilidine. Descriptive statistics were used to characterize patients' demographic and baseline clinical characteristics, physician characteristics, baseline outcome measures, and economic measures. Summary statistics were calculated for all enrolled patients (N =1700), and for patients in each of the 3 cohorts. Overall *P* values were provided with chi-square test for categorical variables and *F* test (analysis of variance) for continuous variables.

The propensity score matching method was used to construct matched-cohorts with similar demographics, and clinical and economic characteristics, for 3 pairwise cohort

comparisons 1) opioids vs. tramadol; 2) opioids vs. non-opioids; and 3) tramadol vs. non-opioids. The variables used in propensity score regression models included: patient demographic variables (age, sex, race, region [where the patient was receiving treatment]), body mass index, insurance type (private or public insurance), socioeconomic status (whether the patient was comfortable, had just enough to pay the bills, or not enough to pay the bills); baseline clinical variables (time since diagnosis and each total score for the BPI-I, BPI-S, FIQ, PHQ-8, GAD-7, MGH-CPFQ, PHQ-15, ISI, and SDS); and physician specialty (rheumatologists, primary care, or other specialties). For each cohort pair, first a propensity score for each patient was estimated using logistic regression, then a greedy 1:1 matching algorithm (which is commonly used to match cases to controls in observational studies) was used to form propensity score–matched samples. Standardized differences were computed to confirm that the propensity matching provided appropriate balance between cohorts for the above covariates, and the propensity matching process was finalized prior to initiating the outcome analysis.

Pairwise cohort differences in outcome measures (BPI-S, BPI-I, FIQ, PHQ-8, GAD-7, SDS, and ISI) were examined using repeated-measures models on the matched samples, with cohort, visit, and the interaction between cohort and visit as covariates. For the binary economic outcomes, repeated measures logistic regression analyses were performed to examine association of patients' outcomes (including resource utilization) with their baseline pain medication. A sensitivity analysis was also performed for the outcome measures. In the matched sample, patients who were taking both opioids and tramadol, and their matched counterparts, were excluded. Repeated-measures models were run on this modified sample. This analysis was conducted to evaluate the treatment effect associated with opioid use without the additional influence of tramadol use.

Time to discontinuation of opioids and time to discontinuation of tramadol were analyzed using Kaplan-Meier survival analyses among patients taking either medication at baseline. Opioid and tramadol discontinuation rates at 3, 6, and 12 months were estimated from the Kaplan-Meier survival curves.

Results

Patient Baseline Characteristics

A total of 2115 patients were recruited into the study, and 1700 were successfully enrolled. Participants were mostly female (94.6%) and white (82.9%). Mean (standard deviation [SD]) age was 50.5 (11.9) years, duration of FM diagnosis was 5.6 (6.3) years, BPI-S score was 5.5 (1.8), and BPI-I score was 6.1 (2.2); these scores indicated moderate levels of pain severity and pain-related interference with daily functioning.[20] Of the 1700 baseline patients, 1205 (70.9%) completed the 12-month assessment, and 1073 (63.1%) completed all of the assessments; further details on the overall sample and patient disposition are reported elsewhere.[19]

Table 1 contains the demographic and baseline characteristics of patients in each of the 3 medication cohorts: taking opioids (could include concurrent use of tramadol) (n = 412, 24.2%), taking tramadol but no opioids (n = 232, 13.6%); and not taking any opioids or tramadol (n = 1056, 62.1%). Statistical evaluation of baseline characteristics among these cohorts revealed overall significant differences between the groups on: sex, race, region, income level, years since diagnosis, physician specialty, and mean scores on BPI-S, BPI-I, FIQ, SDS, PHQ-8, PHQ-15, GAD, ISI and MGH-CPFQ; patients in the opioid cohort had higher scores, indicating more severe symptoms, on all of these outcome measures except the GAD-7. After propensity-score matching, there were no statistically significant between-cohort differences (Table 2; number of

patients in the opioid versus tramadol comparisons = 197 in each group; in the opioid versus non-opioid comparisons = 398 in each group). All patients were receiving FM treatment, either starting a new therapy or augmenting existing treatment.[19] Among the patients who were not taking any opioids or tramadol at baseline, the mostly commonly used medications were: nonsteroidal anti-inflammatory drugs (31.3%), duloxetine (28.5%), pregabalin (24.9%), cyclobenzaprine (14.2%), benzodiazepines(13.8%), selective serotonin reuptake inhibitors (13.5%), non-benzodiazepine sedative/ hypnotics (13.4%), and gabapentin (12.1%).

Outcome Measures

As shown in Table 3, pairwise comparisons between medication cohorts (opioid versus tramadol, and opioid versus non-opioid) revealed several statistically significant differences. Compared with patients in the opioid cohort, patients in the tramadol cohort reported greater improvement on the FIQ and ISI during the 12-month study period (P=.011 and P=.015, respectively) and at 3 months postbaseline (P=.005 and P=.004, respectively).

Compared with patients in the opioid cohort, patients in the non-opioids cohort reported greater reduction in BPI-I overall (P=.029) and at 1 month and 6 months postbaseline (P=.045 and P=.025, respectively). They also reported greater improvements overall and at 3 months postbaseline on the FIQ total score (P=.014 and P=.003, respectively), the SDS (P=.039 and P=.036, respectively), and the ISI (P=.017 and P=.009, respectively), as well as greater improvement on the PHQ-8 overall (P=.004) and at 1, 3, and 6 months postbaseline (P=.007, P=.029, and P=.012, respectively).

Patients who used tramadol were compared with those who did not use opioids at all; pairwise comparisons (N = 231) revealed no statistically significant differences in any of the outcome measures included in Table 3, with one exception: on the SDS patients taking tramadol

reported a greater reduction overall (estimated mean difference = 1.26 [standard error = 0.61], *P*=.040).

Sensitivity analyses were conducted in which patients who were counted as part of the opioid cohort but were also taking tramadol (n = 28) were removed from the analyses. The results of these analyses were consistent with the original findings. Compared with patients in the opioid cohort, patients in the tramadol cohort reported greater overall improvement on the mean FIQ total score and the ISI. Compared with patients in the opioid cohort, patients in the non-opioids cohort reported overall greater improvement on the BPI-I, FIQ, SDS, ISI, and PHQ-8.

Health Care Utilization

For the overall sample, patients reported approximately 20 visits annually for outpatient care (20.3 at baseline, 21.2 over 12 months). Pairwise comparisons are presented in Table 4. Over the 12-month study period, patients in the opioid cohort were significantly more likely to report having attended outpatient visits compared with patients in the tramadol cohort (overall cohort effect *P*<.001). Health resource utilization variables were evaluated also as continuous variables; compared with patients in the tramadol cohort, patients in the opioid cohort reported more outpatient visits (*P*<.001) and visits to a primary care doctor (*P*=.002). Compared with patients in the non-opioid cohort, patients in the opioid cohort reported more visits to a primary care physician (*P*=.008).

Time to treatment discontinuation

Time to discontinuation of medication for patients in the opioid cohort is presented in Figure 1; most patients receiving opioids continued treatment throughout the 12-month study period, with 16% (66 of 412 patients with observed data) discontinuing opioids during the study.

From the Kaplan-Meier survival analysis, the estimated percentage of patients who discontinued opioid use at 3 months was 11.9%, at 6 months was 15.3%, and at 1 year was 22%.

Evaluation of hazard ratio (HR) comparisons revealed that patients with a higher baseline BPI pain-related interference score were more likely to discontinue opioids (HR = 1.57, *P*=.003). Older patients (HR = 0.97, *P*=.024) as well as those with higher baseline PHQ-15 somatization scores (HR = 0.93, *P*=.048) were less likely to discontinue opioids.

Among the 16% (66/412 patients with observed data) of patients who did discontinue opioids during the study, the following reasons for discontinuation were reported: "adverse events" (n = 22, 33.3%), "did not help" (n = 20, 30.3%), "too costly" (n = 6, 9.1%), "felt better" (n = 5, 7.6%) and "other" (n = 23, 34.8%); 2 patients (3.0%) did not provide a reason.

A similar time-to–treatment-discontinuation pattern emerged for tramadol (Figure 1); 21.1% (49/232 patients with observed data) of patients using tramadol at baseline discontinued during the study. The estimated discontinuation rates at 3, 6, and 12 months were 12.3%, 16.6%, and 26.9%, respectively. Evaluation of HRs revealed that none of the variables tested were significantly associated with tramadol discontinuation.

Discussion

The findings from this longitudinal, observational study of patients with FM suggest that health outcomes and resource use among patients taking opioids at baseline were not significantly different from those of patients taking tramadol (no opioids) or those not using any opioid medications. In fact, after adjustment for confounders, significantly less improvement was observed on measures of pain-related interference with daily activities, functioning, depression, and insomnia for patients taking opioids compared with patients in the other two groups.

With regard to resource use, the study results suggest that taking opioids does not decrease the need for various resources including outpatient or emergency room visits; opioid-treated patients had more outpatient visits than tramadol-treated or non-opioids-treated patients. A potential reason for this finding is that controlled substance regulations often prohibit multiple opioid refills, requiring patients instead to come in for prescriptions at 1- to 3-month intervals. The tramadol and non-opioids cohorts achieved similar treatment outcomes; there were no significant between-group differences on health outcome measures except the SDS, on which patients taking tramadol reported a greater reduction in disability during the study period. Tramadol has a mechanism of action that differs from that of opioids, in that it includes not only weak agonist activity at the μ-opioid receptor but also inhibition of the reuptake of serotonin and norepinephrine.[29] Tramadol has been shown to have less addictive potential than opioids,[24] and is not classified as a controlled medication. For these reasons, both tramadol and non-opioid medications might be considered before opioid use, as has been suggested in the literature.[7–9]

Only a minority of patients on either opioids or tramadol at baseline discontinued these medications during the 12-month follow-up period. Previous trials of opioids for FM have been 12 weeks or less,[7] thus comparison with other studies is limited. To our knowledge this is the only 12-month observational study of patients with FM that assessed treatment selection and outcomes. One study that reported the results of an internet survey indicated that opioids were perceived as "helpful" by patients with FM;[17] however, no additional information or outcome measures were provided to understand the benefits for which the patients perceived them as helpful. Outcomes in our study were either similar or worse in patients with FM who were receiving opioids compared with patients receiving tramadol or non-opioid medications. There is

insufficient evidence to evaluate the long-term impact of opioid use in FM,[10] and studies are limited in part because of the potential for adverse events or for abuse.[30]

The evaluation of treatment effectiveness in FM includes not only pain severity but also the associated symptoms, health status, and quality of life. The results of this study do not show an advantage for opioid use on health outcomes such as pain-related interference with functioning, depressive symptoms, overall well-being and functioning, or insomnia. These findings are consistent with a recent review article suggesting that opioid use in patients with FM syndrome was not efficacious, possibly due to an inability of opioids to target the pathophysiologic processes involved in this central sensitization syndrome.[30]

There were several limitations to this study. The lack of randomization meant that unmeasured confounding was possible. To adjust for differences in measured baseline confounders, propensity score matching was used. However, this led to the exclusion of a subgroup of patients who had no matches in the comparison cohort; thus our results may not generalize to the full population of patients being treated for FM. An important limitation is that we did not have information on medication dose; it is uncertain how often opioids were being used. Also, patients in the opioid and the tramadol cohorts may have been taking non-opioid medications as well, and the patients might stop, switch, or continue concomitant medications, or add new medications at any time during 12-month study period. In fact, patients in this study were taking 1 or more of 182 different types of medications,[18] and although we attempted to look at homogenous cohorts, an inability to control for medication use in a naturalistic study does limit the conclusions that can be drawn. It should be noted that patients taking opioids tended to have more severe symptoms at baseline than those not taking opioids and although propensity score matching adjusted for measurable factors, patients who could not be matched were

excluded. Additionally, some unmeasured differences between the cohorts may have been missed from the analyses.

In summary, the use of opioids should be carefully considered by practitioners treating patients with FM, as their use may have low utility relative to potential side effects. Understanding of when and how an opioid may best be used in patients with FM is still incomplete; future studies could compare patients who improve while taking an opioid medication with those who do not in order to identify factors associated with improvement. More research is needed to identify effective treatment approaches for FM from the perspectives of both patients and resource utilization.

Conflicts of Interest and Source of Funding:

Xiaomei Peng, Rebecca Robinson, Douglas Faries, and Madelaine Wohlreich are employees of and/or shareholders in Eli Lilly and Company. David Williams is a consultant for Eli Lilly and Company, Forest Pharmaceuticals, Pfizer, Jazz Pharmaceuticals, and Bristol Meyers Squibb. Yi Chen is an employee of PharmaNet/i3. Bill McCarberg is an advisor for NeurogesX. Philip Mease receives research funding and consulting fees and is an honoraria speaker for Eli Lilly and Company, Forest Pharmaceuticals, and Pfizer. Danette Hann is a medical writer with INC Research. The REFLECTIONS study was sponsored by Eli Lilly and Company or one of its subsidiaries.

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Figure Legends

Figure 1. Time to opioid or tramadol treatment discontinuation. Most patients receiving either opioids or tramadol continued treatment throughout the 12-month study. The estimated discontinuation rates for opioid use at 3, 6, and 12 months were 11.9%, 15.3% and 22%, respectively. The estimated discontinuation rates for tramadol at 3, 6, and 12 months were 12.3%, 16.6%, and 26.9%, respectively.

Table 1. Baseline characteristics of the medication cohorts

		Opioid Cohort N = 412	**Tramadol Cohort N = 232**	**Non-opioid Cohort N = 1056**	***P* value** †	**Total Sample N = 1700**
Age, mean (SD)		50.6 (11.5)	50.7 (11.9)	50.3 (12.21)	0.830	50.5 (11.9)
Sex, n (%)	Female	379 (92.2)	225 (97.0)	997 (95.0)	0.023	1601 (94.6)
Race, n (%)	White	364 (89.4)	191 (82.7)	836 (80.4)	<0.001	1391 (82.9)
	Hispanic	21 (5.2)	32 (13.9)	156 (15.0)		209 (12.5)
	Other	22 (5.4)	8 (3.5)	48 (4.6)		78 (4.6)
Region, n (%)	North Central	74 (18.5)	51 (22.5)	216 (20.9)	<0.001	341 (20.5)
	Northeast	62 (15.5)	45 (19.8)	224 (21.7)		(331) 19.9
	Puerto Rico	9 (2.2)	22 (9.7)	130 (12.6)	<0.001	161 (9.7)
	South	148	50 (22.0)	214 (20.7)		412

	Central	(36.9)				(24.8)
	Southeast	62 (15.5)	32 (14.1)	161 (15.6)		255 (15.4)
	West	46 (11.5)	27 (11.9)	87 (8.4)		160 (9.6)
BMI, mean (SD)		31.5 (7.3)	31.9 (7.8)	31.1 (7.5)	0.354	31.3 (7.5)
Insurance, n (%)	Private/ combination insurance	315 (76.6)	173 (74.6)	834 (79.2)	0.233	1322 (77.9)
	Public/no insurance	96 (23.4)	59 (25.4)	219 (20.8)		374 (22.1)
Income level, n (%)	Enough to pay bills / not enough to pay	281 (68.7)	133 (58.8)	631 (60.5)	0.008	1045 (62.3)
	Comfortable	128 (31.3)	93 (41.2)	412 (39.5)		633 (37.7)
Years since diagnosis, mean (SD)		6.3 (6.4)	6.3 (6.2)	5.2 (6.2)	0.004	5.6 (6.3)
Doctor	Rheumat	262	155 (66.8)	713 (67.5)		1130

specialty, n (%)	ology	(63.6)				(66.5)
	Primary care	52 (12.6)	47 (20.3)	172 (16.3)	0.001	271 (15.9)
	Other specialty[a]	98 (23.8)	30 (12.9)	171 (16.2)		299 (17.6)
Pain severity, BPI-S, mean (SD)		6.0 (1.6)	5.4 (1.6)	5.4 (1.8)	<0.001	5.5 (1.8)
Pain interference, BPI-I, mean (SD)		6.6 (2.0)	6.0 (2.1)	5.8 (2.3)	<0.001	6.1 (2.2)
Disease impact, FIQ, mean (SD)		57.1 (12.6)	53.9 (12.9)	53.5 (14.1)	<0.001	54.4 (13.7)
Disability severity, SDS, mean (SD)		19.9 (7.3)	18.1 (7.5)	17.7 (7.6)	<0.001	18.3 (7.6)
Depression severity, PHQ-8, mean (SD)		13.8 (5.9)	12.8 (6.1)	12.7 (6.1)	0.003	13.0 (6.1)
Physical symptoms,		14.7 (4.7)	14.2 (4.7)	13.3 (4.6)	<0.001	13.7 (4.7)

PHQ-15, mean (SD)						
Anxiety severity, GAD-7, mean (SD)		11.1 (5.8)	11.0 (5.7)	10.7 (5.8)	0.364	10.8 (5.8)
Insomnia severity, ISI, mean (SD)		18.5 (6.1)	16.9 (5.9)	17.3 (6.0)	<0.001	17.5 (6.0)
Cognitive functioning, MGH-CPFQ, mean (SD)		27.6 (6.6)	25.8 (6.3)	26.2 (6.4)	<0.001	26.4 (6.5)

BMI, body mass index; BPI-I, Brief Pain Inventory-Interference; BPI-S, Brief Pain Inventory–Severity; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; GAD-7, 7-Item Generalized Anxiety Disorder scale; ISI, Insomnia Sleep Index; MGH-CPFQ, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; PHQ-8, Patient Health Questionnaire 8-item depression severity measure; PHQ-15, Patient Health Questionnaire physical symptoms measure; SD, standard deviation; SDS, Sheehan Disability Scale

[a]Other specialty areas included neurology, psychiatry, pain, physical medicine, obstetrics and gynecology, and osteopathy.

[†]After propensity score matching, no statistically significant differences ($p<.05$) existed (see Table 2).

Table 2. Baseline Characteristics for Matched Cohorts

		Opioid versus Tramadol Cohort		Opioid versus Non-opioid Cohort	
		Opioid N = 197	Tramadol N = 197	Non-opioid N = 398	Opioid N = 398
Age, mean (SD)		50.2 (12.1)	50.8 (12.2)	50.3 (11.9)	50.5 (11.5)
Sex, n (%)	Female	192 (97.5)	190 (96.4)	364 (91.5)	369 (92.9)
Race, n (%)	White	176 (89.8)	173 (88.3)	354 (89.8)	352 (89.3)
	Hispanic	13 (6.6)	15 (7.7)	16 (4.1)	21 (5.3)
	Other	7 (3.6)	8 (4.1)	24 (6.1)	21 (5.3)
Region, n (%)	Puerto Rico	6 (3.0)	6 (3.0)	3 (0.8)	9 (2.3)
	United States	191 (97.0)	191 (97.0)	395 (99.2)	389 (97.7)
BMI, mean (SD)		31.5 (7.8)	31.6 (7.6)	31.8 (8.3)	31.5 (7.3)
Insurance, n (%)	Private/combination insurance	148 (75.1)	150 (76.1)	304 (76.4)	307 (77.3)
Income level, n	Comfortable	77 (39.1)	77 (39.5)	131 (33.3)	124 (31.4)

(%)					
Years since diagnosis, mean (SD)		7.1 (6.7)	6.5 (6.4)	6.4 (6.8)	6.3 (6.4)
Doctor specialty, n (%)	Rheumatology	129 (65.5)	134 (68.0)	256 (64.3)	252 (63.3)
	Primary care	37 (18.8)	35 (17.8)	43 (10.8)	51 (12.8)
	Other specialty[a]	31 (15.7)	28 (14.2)	99 (24.9)	95 (23.9)
Pain severity, BPI-S, mean (SD)		5.5 (1.5)	5.4 (1.6)	5.9 (1.6)	5.9 (1.6)
Pain interference, BPI-I, mean (SD)		6.1 (2.0)	6.1 (2.0)	6.5 (2.0)	6.5 (2.0)
Disease impact, FIQ, mean (SD)		54.3 (13.0)	54.2 (12.7)	56.5 (12.2)	56.9 (12.6)
Disability severity, SDS, mean (SD)		18.4 (7.3)	18.4 (7.2)	19.3 (7.2)	19.8 (7.4)
Depression severity, PHQ-8, mean (SD)		13.1 (5.9)	13.0 (6.1)	13.7 (5.9)	13.8 (5.9)

Physical symptoms, PHQ-15, mean (SD)		14.5 (4.7)	14.1 (4.6)	14.3 (4.6)	14.5 (4.6)
Anxiety severity, GAD-7, mean (SD)		10.9 (5.6)	10.9 (5.7)	11.1 (5.7)	11.1 (5.8)
Insomnia severity, ISI, mean (SD)		17.3 (6.2)	17.3 (5.7)	18.3 (5.9)	18.4 (6.1)
Cognitive functioning, MGH-CPFQ, mean (SD)		26.3 (6.6)	26.0 (6.2)	27.3 (6.2)	27.6 (6.5)

Abbreviations: BMI, body mass index; BPI-I, Brief Pain Inventory–Interference; BPI-S, Brief Pain Inventory–Severity; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; GAD-7, 7-Item Generalized Anxiety Disorder scale; ISI, Insomnia Sleep Index; MGH-CPFQ, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; PHQ-8, Patient Health Questionnaire 8-item depression severity measure; PHQ-15, Patient Health Questionnaire physical symptoms measure; SD, standard deviation; SDS, Sheehan Disability Scale.

[a]Other specialty areas included neurology, psychiatry, pain, physical medicine, obstetrics and gynecology, and osteopathy.

Note: There were no significant differences between the cohorts at $p<.05$

Table 3. Change in Outcome Measures

		Opioid Cohort versus Tramadol Cohort, Change from Baseline, LS Means Estimate (Standard Error)	Opioid Cohort versus Nonopioid Cohort, Change from Baseline, LS Means Estimate (Standard Error)
Pain severity, BPI-S, mean (SD)	1-month	–0.12 (0.15)	0.00 (0.10)
	3-month	0.26 (0.16)	0.10 (0.12)
	6-month	0.30 (0.18)	0.06 (0.13)
	12-month	0.06 (0.19)	–0.11 (0.13)
	Overall	0.13 (0.12)	0.01 (0.09)
Pain interference, BPI-I, mean (SD)	1-month	0.03 (0.17)	**0.26 (0.13)**
	3-month	**0.47 (0.21)**	0.26 (0.14)
	6-month	0.36 (0.22)	**0.32 (0.14)**
	12-month	0.16 (0.24)	0.08 (0.16)
	Overall	0.26 (0.16)	**0.23 (0.11)**
Disease impact, FIQ,	3-month	**3.65 (1.29)**	**2.60 (0.88)**

mean (SD)	12-month	2.32 (1.53)	1.19 (1.00)
	Overall	**2.98 (1.16)**	**1.90 (0.77)**
Insomnia, ISI, mean (SD)	3-month	**1.48 (0.52)**	**0.89 (0.34)**
	12-month	0.82 (0.61)	0.57 (0.42)
	Overall	**1.15 (0.47)**	**0.73 (0.30)**
Disability severity, SDS, mean (SD)	3-month	0.98 (0.63)	**1.03 (0.49)**
	12-month	0.87 (0.83)	0.76 (0.56)
	Overall	0.93 (0.60)	**0.90 (0.43)**
Depression severity, PHQ-8, mean (SD)	1-month	0.26 (0.43)	**0.83 (0.31)**
	3-month	0.88 (0.47)	**0.75 (0.35)**
	6-month	0.95 (0.51)	**0.91 (0.36)**
	12-month	0.60 (0.56)	0.43 (0.41)
	Overall	0.67 (0.36)	**0.73 (0.26)**
Anxiety severity, GAD-7, mean (SD)	3-month	0.39 (0.48)	0.21 (0.35)
	12-month	0.10 (0.55)	0.40 (0.39)

	Overall	0.24 (0.42)	0.30 (0.30)

Abbreviations: BPI-I, Brief Pain Inventory–Interference; BPI-S, Brief Pain Inventory–Severity; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; GAD-7, 7-Item Generalized Anxiety Disorder scale; ISI, Insomnia Sleep Index; LS means, least squares means; PHQ-8, Patient Health Questionnaire 8-item depression severity measure; PHQ-15, Patient Health Questionnaire physical symptoms measure; SD, standard deviation; SDS, Sheehan Disability Scale

Notes: Differences with significant *P* values ($p<.05$) are in boldface type. Only the BPI-S, BPI-I, and PHQ-8 were administered at the 1-month and 6-month assessments to reduce patient burden. LS mean change > 0 indicates less improvement in the opioid cohort.

Table 4. Resource Use

	Opioid Cohort versus Tramadol Cohort	Opioid Cohort versus Nonopioid Cohort
	OR (95% CI)	OR (95% CI)
Had outpatient visits	**1.81 (1.29, 2.53)**	1.11 (0.87, 1.42)
Had visits to primary care	1.23 (0.92, 1.64)	1.04 (0.85, 1.29)
Had visits to physical therapist	1.28 (0.83, 2.00)	0.91 (0.69, 1.20)
Had visits to ER	1.22 (0.74, 2.01)	1.17 (0.88, 1.56)
Hired caregiver	1.34 (0.67, 2.69)	1.37 (0.87, 2.16)
Missed work due to FM	1.03 (0.72, 1.49)	0.87 (0.68, 1.11)

CI, confidence interval; ER, emergency room, FM, fibromyalgia; OR, odds ratio.

Note: Differences with significant *P* values are in boldface type.

Figure
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