Research Article

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Characteristics of fibromyalgia patients prescribed opioid medications: data from the Cleveland clinic fibromyalgia registry

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Objective: Determine the prevalence, socioeconomic, clinical characteristics of fibromyalgia (FM) patients and the factors associated with narcotic drug prescription.

Methods: New patients with FM referred for rheumatology evaluation are compared based on narcotic drugs use. Demographic, socioeconomic, clinical, and medication data are collected.

Results: Of 305 FM patients 34.8% are taking narcotic medication and these patients ($p \leq 0.05$) are older, have longer duration of FM, are socioeconomically more disadvantaged by lower education and employment and higher disability rates; more are obese, and clinically report more extensive and severe pain, higher depression, more disability and higher FM severity, compared to FM patients not prescribed opioid drugs. Patients prescribed opioids are using more medical resources, they take more medications for FM and report more doctor visits and surgeries. Binomial regression analysis demonstrates that pain and stiffness severity, and functional impairment are independent predictors of being prescribed opioid medications. Taking narcotic medications is an independent predictor of FM severity along with pain and depressive symptoms.

Conclusion: About one third of patients with FM seen in a tertiary care rheumatology center are taking narcotic medications to treat pain. In this environment, opioid prescription for FM identifies a group of patients with severe FM who have failed the traditional therapeutic options.

Keywords: fibromyalgia • pain • narcotic drugs

Introduction

Fibromyalgia (FM) is a biopsychosocial disorder characterized by chronic pain, fatigue, impaired sleep, cognitive difficulties and a multitude of somatic problems [1].

The FDA approved drugs for the treatment of FM duloxetine, milnacipran and pregabalin, provide limited benefit. Only a third of patients report 50% pain reduction, and half report 30% pain reduction in clinical trials [2,3]. A survey of 1,555 FM patients from US rheumatology practices found that only 10% report substantial improvement over time, while most patients maintain high levels of distress and self-reported symptoms [2]. The lack of effective therapeutic interventions in fibromyalgia can be largely explained by an incomplete understanding of the clinical heterogeneity and complex FM pathophysiology [4-6]. Rather than the treatment of process variables, a parsimonious focus on outcome variables, especially pain, has become the fashion leading some physicians to prescribing opioid drugs for FM pain. In the general population, the focus on pain control and the inclusion of pain in the vital signs category led to the doubling of opioid prescriptions since 19946. Rates of opioid prescriptions for FM patients vary widely. Insurance claim databases show between 11.3 and 69% FM patients are prescribed opioid drugs [7-9]. Between 2000 and 2010 the percentage of FM patients prescribed opioid drugs increased from 40 to 46.6% as illustrated in a study of 3123 FM [10]. Patient preference may also play a role. An internet survey of 2,596 FM patients found responders perceived hydrocodone and oxycodone preparations among the most effective therapies for FM [11]. This opinion seems surprising given the lack of evidence for benefit in controlled trials [12,13] and guidelines that advocate against the use of opioids for the treatment of chronic non-

malignant pain and FM [13-15]. For instance, a critical review of 39 therapeutic trials for chronic pain found that the prevalence and severity of opioid toxicity rose with dose and that the evidence for efficacy as insufficient [16,17]. This patient preference may be related to the effects of opiates on the reward centers resulting in addiction potential. A body of literature directly links opioid and other addictions to increased levels of distress [18]. Fibromyalgia is a distress related condition. Therefore patients with FM are particularly likely to become addicted. This may be even more pronounced in patients with severe FM and FM with obesity [19-21].

A retrospective claims analysis of 96, 175 FM patients, between January 2008 and February 2012 found that more than half of the patients, 57% of patients were prescribed short acting opioids, while centrally acting drugs were prescribed less, 28% SSRIs (selective serotonin reuptake inhibitors) or SNRIs (serotonin norepinephrine reuptake inhibitors), 3% tricyclic antidepressants and 10% gabapentioids for FM [22].

A Canadian study of 457 FM patients referred to a multidisciplinary pain program found that opioid use was associated with lower socioeconomic status, unstable psychiatric disorders and with history of substance abuse [10]. Less is known about the individual characteristics of US tertiary care center FM patients who take narcotics. In this analysis of patients evaluated at an academic tertiary center we addressed the following questions:

- What is the prevalence of opioid medications prescriptions for FM patients presenting for their initial visit in rheumatology?
- What are the demographic, socioeconomic and clinical characteristics of FM patients prescribed narcotics?

Methods

New patients seen in the Cleveland Clinic Rheumatology Department (Cleveland, OH) by two physicians (WSW, CEG), and diagnosed clinically with FM, were enrolled in the Cleveland Clinic Fibromyalgia Cohort. This study was approved by Cleveland Clinic Institutional Review Board and includes the first 305 consecutive patients seen between September 1, 2008 and January 31, 2011. We determined whether patients met the ACR 1990 FM criteria [23], and the survey criteria [24]. The survey criteria include the regional pain score (RPS), a sum of 19 non-articular painful sites, also named widespread pain index (WPI), and the 0-10 visual analogue (VAS) fatigue scale. The symptom intensity scale (SIS) is calculated as (RPS/2 + VAS fatigue)/2; the score ranges from 0 to 9.75, the cut point for FM diagnosis is 5.7524,25. Clinical and survey criteria were found to be concordant in 74.8% of cases [25].

We collected demographic, socioeconomic and clinical data. The following FM related symptoms and conditions were recorded as yes/no: all over pain, pain worse at rest, fatigue, duration of morning stiffness for at least one hour, headaches, memory impairment, concentration impairment, sicca symptoms, sensitivity to lights, smells or noises, difficulty initiating swallowing, sensation of swollen glands in the neck, shortness of breath at rest, constipation alternating with diarrhea, urinary frequency at night, feeling faint or tired in hot shower, intermittent numbness in hands and/or feet, history of depression, anxiety, bipolar disorder, or other psychiatric disorders, family history of fibromyalgia, family history of mood disorders, exercising at least 30 minutes, at least three times a week, current illicit drug use, past illicit drug use, born premature, history of abuse and feeling stressed.

The following categories of medications were recorded (taking yes/no): serotonin reuptake (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic and tetracyclic antidepressants, other antidepressants (bupropion, trazodone), antipsychotics/mood stabilizing drugs, stimulants, barbiturates, benzodiazepines, analgesics non narcotics (paracetamol and tramadol), non steroidal anti-inflammatory drugs (NSAIDS), narcotics, anti-seizure analogues of gamma aminobutyric acid (gabapentinoids) (pregabalin or gabapentin), muscle relaxants, sleep medications, other medications for FM. The sum of all the medications taken in these categories was designated the total number of mediations taken for FM.

Narcotic medications were classified as weak (codeine, hydrocodone, propoxyphene) and strong (morphine, fentanyl, hydromorphone, buprenorphine, methadone). Tramadol, a weak opioid agonist with SNRI effects, was not included in the narcotic category, but in the analgesics category.

Duration of narcotic use was listed as: less than a week, more than a week but less than a month,

more than a month but less than a year, and a year or more.

As a measure of obesity we used the body mass index (BMI). The World Health Organization defines weight categories as follows: underweight, BMI <18.5 kg/m^2, normal weight, BMI 18.5 -24.9 kg/m^2, overweight, BMI 25-29.9 kg/m^2, and obese, BMI ≥ 30 kg/m^2.

The Patient Health Questionnaire-9 (PHQ-9) is a diagnostic tool to make a probable diagnosis of major depressive disorder, and is a continuous measure of depressive symptoms in the past two weeks, with scores ranging from 0 to 27 and cut points of 5, 10, 15, and 20, representing mild, moderate, moderately severe and severe levels of depressive symptoms [26]. To determine the presence of anxiety we used the yes/no answer to the question "In the last 4 weeks, have you had an anxiety attack-suddenly feeling fear or panic?" [27].

The MDQ is a self-reported inventory that screens for lifetime history of manic or hypomanic syndrome by including 13 yes/no items in question 1 [28,29]. A score of 7 or more plus concurrence of symptoms and at least moderate problems reported, was found to have a sensitivity of 29-91% and a specificity of 67-94% for the diagnosis of bipolar disorder [28,30]. Limiting the MDQ to the first 13 items of Question 1 increases the sensitivity to detect hypomania [30].

The Epworth Sleepiness Scale (ESS) rates, on a scale of 0-3, the chances of dozing in each of eight different situations (range 0-24); ESS ≥ 10 is encountered in patients with various sleep problems, such as sleep apnea, narcolepsy, restless leg syndrome [31].

The FM impact questionnaire (FIQ) was developed to capture the total spectrum of FM related symptoms and responses to therapy. The FIQ is composed of 10 subscales. The first question, FIQ physical impairment contains 11 items related to the ability to perform large muscle tasks, each rated on a 4 point Likert scale. Questions 2, FIQ feel good, and 3, FIQ work missed, ask the patient to mark the number of days they felt well and the number of days they were unable to work because of FM symptoms. Items 4 to 10 are visual analogue scales (VAS) marked in 10 increments on which the patients rate work difficulty FIQ do job, FIQ pain, FIQ fatigue, FIQ morning tiredness, FIQ stiffness, FIQ anxiety, and FIQ depression. The maximum possible score is 100.

The disability domain of the health assessment questionnaire (HAQ-DI) measures patients' usual abilities in the past week, through eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common activities on a Likert scale 0 to 4, and gives a total score in the 0 to 3 range [32,33].

Statistical methods

Continuous variables were presented as mean (standard deviation). Variables recorded as yes/no are presented as % of yes cases. Comparisons across groups were performed using one-way analysis of variance for continuous variables, and chi square tests for categorical variables. To ascertain effect of variables, on a continuous variable we performed linear regression analysis. Linear regression analysis and binomial logistic regression were performed to ascertain the effect of select variables on a continuous variable and respectively on the likelihood of patients to be prescribed opioid drugs. The significance level was set at alpha = 0.05 for all analyses. Data analysis was conducted in SPSS v 24 (SPSS Inc., Chicago, IL).

Results

Of 305 patients clinically diagnosed with FM, 79.7% met the ACR 1990 FM criteria, and 79.5% met the survey criteria (SIS score ≥ 5.75).

There were 34.8% FM patients, who, at the time of their first visit in rheumatology, were taking a form of opioid as treatment for FM. Opioid drugs were the second most prescribed medications after SSRI/SNRI drugs. Of other drug categories, 40% of patients were taking SSRI or SNRI drugs, 29.8% NSAIDs, 24.5% gabapentinoids, 29.4% pain medications (paracetamol and/or tramadol), 25.3% benzodiazepines, 9.4% tricyclic or tetracyclic antidepressants, 20.4% muscle relaxants, 12.2% sleep medications, 10.6% other antidepressants (bupropion and or trazodone), 10.2% antipsychotic drugs, 4.5% stimulants, and 2.4% barbiturates. The mean (standard deviation) number of medications taken for FM was 2.6 (2.1).

Of 106 FM patients taking narcotics, 94.1% were taking one narcotic drug, 5.2% were taking two, and 0.7% were taking three different narcotics. Weak narcotics were prescribed to 19.7%, strong narcotics to 12.5% and 2.6% of all FM patients were taking both weak and strong narcotic analgesics. We carefully reviewed each patient electronic medical record and we can state that none of these patients were prescribed opioids for

the first time the day of their visit in rheumatology, thus we concluded that they must have taken narcotics for at least one day. Duration of narcotic analgesic use was not specifically recorded at the time of the visit, and could not be retrospectively determined in 63.2% of patients, so these patients were recorded in the category taking opioids for less than 1 week, but more than 1 day. For the rest of the patient where duration could be ascertained from the electronic medical record, 17.9% were taking narcotic drugs for more than a year, 11.3% for at least a month and less than a year, 7.5% for more than a week, but less than one month.

We divided FM patients into four groups: no opioids, weak opioids, strong opioids and both strong and weak opioids and we compared demographic, socioeconomic Table 1 and clinical variables as well as utilization of care, medication use and type, depression (PHQ-9), disability (HAQ-DI) and fibromyalgia severity scores (FIQ total and subsets) Table 2. All the variables listed in methods, that demonstrated statistically significant differences between non narcotic and narcotic prescribed FM groups are presented in Tables 1 and 2.

Table 1. Demographic and socioeconomic of FM patients grouped according to opioid analgesics used. * no opioid *vs*. opioid group; ** no opioid *vs*. weak opioid; * no opioid *vs*. strong opioid; ****weak *vs*. strong opioid**

Variable	No opioid analgesics	All opioid analgesics	Opioid analgesics			p
			Weak	Strong	Both weak and strong	
N	199 65.2%	106 34.8%	60 19.7%	38 12.5%	8 2.6%	
Socioeconomic						
Age	42.1(11.6)	46 (11.5)	45.1 (11.8)	47 (10.8)	47.3 (13.7)	0.007* 0.024***
Employment status						0.01* 0.013***
Unemployed	23.90%	22.60%	25.40%	18.80%	22.20%	
Employed	52.30%	31.10%	35.60%	28.90%	22.20%	
Retired	4.10%	5.70%	8.50%	2.60%	0%	
Disabled	16.30%	37.70%	27.10%	47.40%	55.60%	
Student	3.60%	2.80%	3.40%	2.60%	0%	
Education level						0.017** 0.047***
Less than 12th grade	5.30%	13%	5.30%	16.20%	0%	
High school graduate	23.70%	17.40%	29.80%	18.90%	11.10%	
Some college	30.90%	47.80%	42.10%	43.20%	66.70%	
College graduate	26.80%	10.90%	17.55	10.80%	11.10%	
Post graduate	14.40%	10.90%	5.35	10.80%	11.10%	
Marital status						0.014* 0.019***
Married	28.10%	11.40%	13.80%	10.50%	0%	
Single	55.20%	71.40%	70.70%	65.80%	100%	
Divorced	14.10%	16.20%	15.50%	21.10%	0%	
Widowed	2.60%	1%	0%	2.60%	5	
BMI mean (SD)	29.5(7.5)	32.4(8.6)	32.9(9.6)	30.8 (6.6)	35.1(9.2)	0.011*
BMI =>30	38.80%	54.20%	54.1%-	44.40%	87.50%	0.023**
History of abuse	33.50%	38.70%	25.40%	52.60%	55.60%	0.035*** 0.009****
Stressors continue	39.50%	53.30%	59.30%	51.40%	22.20%	0.019* 0.005** 0.041****
Duration of FM symptoms (years)	9.2 (8.8)	11.6(10.5)	12.1(11.5)	11.9(9.7)	7.6(6)	0.021*
Family history of fibromyalgia	25.30%	38.70%	38.30%	34.20%	62.50%	0.018* 0.038**

* no opioid vs opioid group; ** no opioid vs weak opioid; *** no opioid vs strong opioid; ****weak vs strong opioid

Table 2. Clinical characteristics, medications, FIQ (fibromyalgia impact questionnaire) scores, PHQ-9 (depression scores) and HAQ-DI (health assessment questionnaire - disability index) and utilization of care in FM patients grouped based on opioid analgesics use

Variable	No opioid analgesics	All opioid analgesics	Opioid analgesics			p
Symptoms						
Pain worse at rest	78.40%	89.40%	89.80%	86.50%	100%	0.011* 0.033**
Dry eyes and/or dry mouth	62.80%	74.80%	76.30%	72.20%	75%	0.03* 0.041**
Duration of morning stiffness more than one hour	60.80%	73.10%	65.50%	86.50%	55.60%	0.025* 0.037****
Difficulty initiating swallowing	42.30%	59%	60.30%	55.30%	66.70%	0.005* 0.014**
Generalized weakness	83.60%	95.10%	96.60%	94.40%	88.90%	0.001* 0.004** 0.024***
Tender points >=12/18	77.20%	88.50%	86.20%	92.10%	87.50%	0.009* 0.024***
Questionnaires						
PHQ-9	11.3(6.1)	12.9(6.4)	12 (6.1)	14.7(6.9)	10.3(4.7)	0.04* 0.004*** 0.026****
FIQ physical impairment	13.2(9.2)	17.6(8.9)	16.5(9.2)	20.3(8)	14.4(8.9)	0.0001* 0.019** 0.0001*** 0.01****
FIQ work missed	3.2(2.5)	4.2(2.3)	3.9(2.4)	4.5(2.1)	4.6(2.6)	0.015* 0.001**
FIQ do work	6.5(2.5)	7.9(2)	7.7(8)	8.5(9)	7.1(2.2)	0.0001* 0.011** 0.0001*** 0.036****
FIQ pain	7(2.3)	8.2(1.7)	8 (1.6)	8.7(1.4)	7.5(2.4)	0.0001* 0.014** 0.0001*** 0.025****
FIQ stiffness	6.3(2.6)	7.7(2.2)	7.5(2.3)	8.1(1.9)	7.2(3.2)	0.0001* 0.006** 0.003***
FIQ depression	4.5(3.5)	5.8(3.2)	5.5(3.1)	6.2 (3.1)	5.1 (4.6)	0.002* 0.025** 0.004***
FIQ total	62.6(18.6)	72.5(14.9)	70.6(15.6)	76.1(13.4)	66.6(11.8)	0.0001* 0.003** 0.001***
WPI	10.6(4.6)	12.2(3.7)	12.3(3.8)	11.9(3.5)	12.4(4.2)	0.031* 0.009** 0.009***
HAQ-DI	0.9(0.6)	1.3(0.5)	1.3(0.5)	1.4(0.5)	1.3(0.5)	0.0001* 0.0001** 0.0001***
Treatment						
Aerobic exercise	17.80%	7.70%	0%	8.10%	0%	0.008* 0.043**
SSRI/SNRI	36.20%	52.80%	49.20%	55.30%	66.70%	0.026* 0.017***
Benzodiazepines	20.60%	38.70%	33.90%	47.40%	33.30%	0.004* 0.042** 0.004***
Gabapentinoids	21.70%	36.20%	23.70%	39.50%	22.20%	0.023*
Muscle relaxants	17.70%	31.90%	23.30%	34.20%	22.20%	0.021*

Sleep meds	10.10%	21.30%	15%	21.10%	22.20%	0.037*
Pain medications (paracetamol, tramadol)	21.10%	84%	98.30%	60.50%	77.80%	0.0001* 0.0001** 0.0001*** 0.0001****
Utilization of care						
Nr of medications taken for FM	2(1.8)	4.7(1.8)	4.4(1.8)	4.8(1.8)	5.3(2)	0.0001* 0.0001** 0.0001***
Nr of doctor visits in the past 6 months	8.3 (9.3)	11.4(11.1)	10.4(9.4)	10.5(9.7)	16.5(17.9)	0.028* 0.002** 0.033***
Number of surgeries	3 (3.1)	5(3.8)	4.6(3.5)	4.8(3.9)	7(4.8)	0.0001* 0.0001** 0.001***
Number of musculoskeletal surgeries	0.7(1.8)	1.7(2.5)	1.5(2.4)	1.7(2.4)	3.1 (3.4)	0.0001* 0.003** 0.003***

Compared to those not taking opioids, we found that FM patients taking opioid drugs were older, more were single, had longer duration of FM symptoms, felt more stressed and had worse socioeconomic status, indicated by lower education level, less employment and higher disability rates.

Of all the FM symptoms recorded, difficulty initiating swallowing, generalized weakness and morning stiffness more than an hour was significantly more prevalent with opioid use. Patients taking opioids had significantly more severe pain, stiffness, depression, physical impairment and disability, and overall more severe fibromyalgia measured by FIQ. Opioid takers were also using more medical resources as indicated by more doctor visits in the past 6 months, more past surgeries, and by taking more medications for FM, including more benzodiazepines and non-narcotic pain medications. We found no difference in the number of comorbidities between the two groups, opioid group 1.6 (1.4) compared to the non-opioid group 1 (1.2), p=0.086.

Because we were not able to establish duration of opioid use in all our patients and that prevented us from making comparisons based on duration of treatment, we present the data on FM patients prescribed narcotics, in whom we could confirm from the medical record that they were taking these medications for at least a week or longer (n=39) Table 3.

Table 4 presents the variables used for core OMERACT FM domains measurement.

To investigate if narcotic prescription is associated with FM symptoms severity we first performed a binomial logistic regression to ascertain the effects of core OMERACT FM domains, pain (FIQ pain), fatigue (FIQ fatigue), stiffness (FIQ stiffness), function (FIQ function), depression (PHQ-9), sleep (Epworth Sleepiness Scale), on the likelihood that patients are prescribed opioid drugs for FM. The logistic regression model was statistically significant, $X^2(4) = 32.994$, $P<0.0005$. The model explained 14.3% (Nagelkerke R^2) of the variance in opioid prescription, and correctly classified 66.1% of cases as patients taking opioid drugs, with a sensitivity of 29.2% and a specificity of 86.2%, positive predictive value 53.4% and negative predictive value of 69.1%. Increasing pain, stiffness and functional disability, remain statistically significantly associated with increased likelihood of being prescribed opioid medications Table 5. We performed the same model but replaced measures for the some of the OMERACT domains. We substituted FIQ stiffness with morning stiffness of more than an hour, and FIQ function with HAQ-DI. In this model only disability and pain were statistically significant predictors of opioid drug prescription (data not shown).

We also performed a multiple regression to predict FM severity as measured by FIQ from age, BMI, duration of FM symptoms, pain (WPI), sleep (Epworth Sleepiness Scale), depression (PHQ-9), number of medications taken for FM and use of narcotics. This multiple regression model statistically significantly predicted FIQ, $F(8,203)=26.607$, $P<0.0005$, adjusted $R2=0.49$. In this model, pain, depression and use of narcotic medications added statistically significantly to the prediction ($p<0.05$). Regression coefficients and standard errors can be found in Table 6.

Table 3. Characteristics of 39 FM patients taking narcotics for a week or longer. BMI – body mass index, PHQ-9 – patient health questionnaire -9, FIQ – fibromyalgia impact questionnaire, WPI – widespread pain index, HAQ-DI – health assessment questionnaire-disability index

Variable	N =39
Age	46.2(12.4)
BMI	33.5 (10.5)
PHQ-9	12.8(6.4)
Duration of morning stiffness in minutes	313.1 (493.4)
FIQ physical impact	17.6(8.9)
FIQ feel good	1.4 (1.9)
FIQ work missed	4.1(2.3)
FIQ do work	8 (1.8)
FIQ pain	8.5(1.7)
FIQ fatigue	8.7(1.7)
FIQ stiffness	8.2(1.8)
FIQ anxiety	6.3(3)
FIQ depression	6.1 (3.1)
FIQ total	74.7(15)
WPI	12.8(3.5)
HAQ DI	1.39(0.5)
Medications taken for FM	4.6(1.6)
Number of doctor visits in the past 6 months	12.4(10.8)

Table 4. Core FM OMERACT domains and their measures WPI Widespread Pain Index, also known as regional pain score; FIQ Fibromyalgia Impact Questionnaire; ESS Epworth Sleepiness Scale, PHQ-9 Patient Health Questionnaire -9; HAQ-DI Health Assessment Questionnaire Disability Index

OMERACT domain	Scale, subscale
Pain	WPI
	FIQ pain
Stiffness	Duration of stiffness more than an hour
	Duration of stiffness in minutes
	FIQ stiffness
Sleep	ESS
	Hours of sleep
	FIQ rested
Depression	PHQ-9
	FIQ depression
Function	FIQ physical impairment
	HAQ-DI

Table 5. Logistic regression predicting likelihood of being prescribed opioid medications based on OMERACT domains pain, stiffness, fatigue, sleep, depression and function. ESS Epworth Sleepiness Scale, FVAS Fatigue visual analogue scale, FIQ Fibromyalgia Impact Questionnaire, PHQ Patient health questionnaire

	B	S.E.	Wald	df	P	Odds Ratio	95% CI	
							Lower	Upper
FIQ pain	0.202	0.079	6.524	1	0.011	1.224	1.048	1.429
FIQ stiffness	0.116	0.058	4.065	1	0.044	1.123	1.003	1.257
FIQ fatigue	-0.084	0.084	1.002	1	0.317	0.919	0.78	1.084
Sleep (ESS Score)	0.006	0.023	0.063	1	0.801	1.006	0.962	1.052
Depression (PHQ-9)	-0.009	0.024	0.146	1	0.703	0.991	0.944	1.039
FIQ function	0.037	0.016	5.1	1	0.024	1.037	1.005	1.071
Constant	-2.81	0.733	14.71	1	0	0.06		

Table 6. Summary of multiple regression analysis to predict FIQ from age, BMI, duration of FM, pain, sleep, depression, number of medications used for FM, and narcotic prescription

Variable	Unstandardized regression coefficient B	SE B	Standardized coefficient	t	P	95% CI for B	
						Lower bound	Upper bound
(Constant)	36.511	4.93		7.406	0	26.791	46.231
Age	0.101	0.077	0.069	1.306	0.193	-0.051	0.253
BMI	-0.192	0.116	-0.086	-1.652	0.1	-0.421	0.037
Duration of FM (years)	0.117	0.093	0.065	1.255	0.211	-0.067	0.3
Pain (WPI)	0.738	0.207	0.186	3.559	0	0.329	1.147
Sleep (ESS)	-0.052	0.152	-0.017	-0.343	0.732	-0.351	0.247
Depression (PHQ-9)	1.606	0.154	0.561	10.438	0	1.302	1.909
Number of medications taken for FM	0.318	0.525	0.039	0.605	0.546	-0.717	1.352
Narcotics	7.251	2.36	0.19	3.073	0.002	2.598	11.903

BMI Body Mass Index; WPI Widespread Pain Index; ESS Epworth Sleepiness Scale; PHQ-9 Patient Health Questionnaire-9; FM Fibromyalgia

Discussion

Of the 305 patients with FM referred to a tertiary center rheumatology department, about a third of patients (34.8%) were prescribed opioid drugs, close to data reported in a 2011 Canadian study of 302 FM patients referred to a multidisciplinary care program10, and data from the REFLECTIONS study 33, and falling in the middle of the opioid prescription rates 11.3-69%, reported in a retrospective study of insurance claims databases of FM patients13-15. A study of 3123 US adult patients with FM found that in 2010, 46.7% were prescribed opioid drugs, including 12.5% strong opioids. The lower prevalence observed in our study may be partially accounted by our exclusion of Tramadol from the opioid category.

Differences in rates of opioid prescription for FM patients have been explained by factors such as: differences in access to health care and population densities [5,10]. Compared to internal medicine specialties, a higher percentage of primary care physicians prescribe opioids for FM pain [24]. Access to care measured by the number of physicians per capita per state was found to be significantly negatively associated with use of opioids in patients with FM; also patients from states with large populations such as New York, Ohio, were less likely to be prescribed opioid drugs for FM [34] suggesting that better access to care may be associated with lower opioid use for FM. These criteria do not apply to our FM opioid group who have a mean of 11.3 [11] doctor visits in the past 6 months, and are taking an average of 4.7 (1.7) drugs for FM, 63% taking at least one antidepressant. Our study shows that rather than poor access to care, the socioeconomic status, clinical characteristics, and the severity of FM are associated with opioid prescription in FM patients. We believe that many of these patients with more severe disease manifestations had already exhausted the usual therapeutic resources available to primary and specialty care, and were given opioids as a "last resort".

Narcotic drug prescription and socioeconomic status

Our study confirms and strengthens prior observations that those who are prescribed opioid drugs are faring poorly both socially and economically. Compared to FM patients not prescribed opioid drugs, patients taking narcotics are more likely to be single, 71.4% *vs.* 54.7%, less educated, 10.9% *vs.* 26.8 % have graduated college, more are disabled 37.7% *vs.* 16.3%, all factors associated with lower income. Fitzcharles and colleagues reported similar economic characteristics for opioid prescribed patients10; less FM patients on opioids were college educated 13% *vs.* 24%, and employed 16% *vs.* 40%, when compared FM patients not prescribed these drugs. In a much larger cohort of 1,700 FM patients opioid use was also associated with worse income level [17].

Higher disability scores on multiple measures, including FIQ physical impairment 17.7 (8.9) *vs.* 13.1 (9.2), and HAQ-DI 1.4 (0.5) *vs.* 1 (0.6), also explain why more FM patients taking narcotics reported more FIQ days of missed work 4.29 (2.3) *vs.* 3.25 (2.5), higher difficulty to do work, FIQ do work 7.9 (2) *vs.* 6.5 (2.5), and only 31.3% *vs.* 52.2% were employed. These results indirectly suggest that opiates prescribed to FM patients, do not have a positive impact

on disability rates, and workforce retention. In support of this conclusion, longitudinal studies of FM opioid users compared to non-opioid FM patients showed worse pain scores, worse function and higher FIQ for the opioid prescribed group [17,18]. Physical impairment and the ability to do work are significantly worse in the high compared to low narcotic group Table 2. This is not surprising, higher opioid doses are associated with a disability profile on the Minnesota Multiphasic Personality Inventory and predict poorer functional outcome in patients with chronic occupational musculoskeletal disorders [35,36]. The relationship between opioid prescription and FM disability is likely bidirectional. Disabled FM patients have higher FM symptoms burden therefore are more likely to be prescribed opioids. It is also possible that opioid prescription contributes to patients' disability, through opioid sedating and depressive effects; it was shown that opioid users have less improvement over time in pain related interference with functioning [37].

Narcotic drug prescription and FM symptoms and FM severity

We find that severity of pain, stiffness and disability are independent predictors of being prescribed opioids.

Patient taking opioids report statistically significant higher severity and extent of pain FIQ pain 8.2 (1.7) *vs.* 7.0 (2.3), WPI 12.2 (3.7) *vs.* 10.6(4.6), more experience at least 60 min of stiffness, 73.1% *vs.* 60.8%, and have more severe stiffness FIQ stiffness 7.5 (2.3) *vs.* 6.4 (2.6), compared to patients not taking opioids. Significantly more patients with FM taking narcotics have at least 12/18 tender points 88.5% *vs.* 77.2% compared to those not taking narcotics, indicating a higher level of distress. It has been demonstrated that tender points are associated with distress and patients with FM who meet ACR 1990 criteria have more severe fibromyalgia [38,39]. We observe that FM patients taking narcotics present with more severe disease FIQ 72.9 (14.9) *vs.* 62.6 [18], have longer duration of FM 11.6 (10.4) *vs.* 9.2 (8.8) years. In a multiple regression analysis the extent of pain, depression and being on narcotics remain independent predictors of fibromyalgia severity measured by FIQ total.

A study performed in a tertiary care center on patients with chronic pain, prescribed narcotic medication, found that almost half of the patients taking opioids continued to report severe pain [40]. A Canadian longitudinal study of 159 FM patients who had at least on follow up visit, compared FM patients taking opioids with those who did not, and found that opioid users scored significantly higher on all measures of symptom severity, particularly higher pain scores and higher functional impairment [41]. Also, not reported by others, of all the FM symptoms recorded, we find that statistically significant more FM patients prescribed narcotic drugs reported pain worse at rest, sicca symptoms, and difficulty initiating swallowing than those who were not on narcotic drugs Table 1, possibly due to the fact that this population was also taking more drugs, many with anticolinergic side effects. These observations are not specific to FM patients. A Danish study of a National Random sample of 16,684 patients, found chronic pain opioid users report moderate/severe or very severe pain, poor self rated health, not being engaged in employment, high use of health care system, and opioid treatment fails to fulfill key outcomes of opioid treatment goals such as pain relief, improved quality of life and improved functional capacity [42].

Narcotic drugs prescription and depression

We find that narcotic taking FM patients endorse more depressive symptoms PHQ-9 13 (6.5) *vs.* 11.2 (6) compared to non-opioid FM, and those taking strong opioids report higher depression than those prescribed weak opioid drugs, PHQ-9 14.7(6.9) *vs.* 12 (6.1). Numerous studies have demonstrated that psychological factors predict or are associated with opioid use (reviewed by Darnall *et al*) [43]. Depression preceding lumbar fusion or total joint arthroplasty is associated with increased opioid use following surgery [44,45]. Psychological factors, such as unstable mental illness, and higher depression rates than in controls, have been associated with opioid prescription and use in FM [37,41]. Increased prevalence of psychiatric disorders and prior suicidal attempts have been observed previously in FM patients taking narcotics [10,17] supporting the need for comprehensive psychiatric evaluations in patients with severe FM taking opioids.

The relationship between depression and opioid use is complex. Opioid drugs act as agonists of mu opioid receptors, key players for reward processing and likely for the success of opioid depression treatment. In the first half of the 20th century, treatment, often reported successful, of depression/melancholia consisted of low doses

of opiate mixture or opium. The antidepressant effect of mu-opioid agonists is complex, and while acute opioid exposure may result in antidepressant effects, possibly through the euphoric effect of opioids, long term exposure is associated with neuroadaptations in brain structures, including down regulation of mu receptors, that potentially lead to depressive disorders [46]. Interestingly, both FM and depression have been associated with decreased binding capacity of CNS mu opioid receptors compared to controls [47,48]. In patients with FM, mu opioid binding ability determined by positron emission tomography with carfentanil tagged with radiotracer was found to be decreased in areas relevant to pain processing such as amygdala, cingulate and nucleus accumbens [49]. Furthermore, a follow-up study has shown that reduced numbers of mu receptors or lower receptor affinity provides a plausible mechanism by which chronic exogenous opioids might worsen pain outcomes in FM [50]. Endogenous opioid neurotransmission on mu-opioid receptors, a system implicated in stress responses and emotional regulation is also altered in patients with major depressive disorder, with evidence for decreased biding potential of mu receptors in brain areas involved in the processing of stressful stimuli and sadness [46,51].

Our results suggest that FM patients prescribed opioid drugs have failed the resources available to primary and specialty care, and are likely in need of more intensive multidisciplinary and psychological interventions. The utility of comprehensive multidisciplinary interventions for weaning FM patients from narcotics has been demonstrated in a study of 55 patients admitted to Mayo Clinic pain rehabilitation program. Patients who successfully tapered opioids showed significant improvements in pain scores, depression, catastrophizing, health perception, and perceived life control [20].

There were important limitations to this study that may lead to further investigations. The cross-sectional design prevents analysis of cause and effect outcome of FM patients on opioids *vs.* those not prescribed opioids. Also, the length of time that the patients were treated with opioid therapy was not analyzed, and it was not recorded if opiates were initiated prior or after patients have shown incomplete response to centrally acting drugs. Nevertheless, the fact that FM patients currently taking opioids endorse higher pain scores, FIQ pain 8.2 (1.7) *vs.* 7 (2.3) than those not taking opioid drugs, supports the hypothesis that narcotic therapy is at the most, minimally effective in treating FM. Also, the small group of 39 patients for whom we had evidence that opioids were taken for at least one week continued to endorse high levels of pain severity FIQ pain 8.5 (1.7), pain extent WPI 12.8 (0.5) and report severe fibromyalgia, FIQ total 75.7 (15) Table 3. Only prospective controlled trials pitting opioids against recommended guideline therapy will answer important questions about relative efficacy and toxicity [22].

Conclusion

In a tertiary rheumatology setting prescription opioid use by FM patients identifies a subgroup with higher burden of disease, lower socioeconomic status, high disability and severe fibromyalgia, who have failed the traditional primary care and specialty care. These patients are in need of a biopsychosocial approach, such as structured intensive multidisciplinary interventions that integrate education, physical and occupational therapy, psychological and psychiatric interventions.

References

1. Wolfe F, Clauw DJ, Fitzcharles MA *et al.* The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis. Care. Res (Hoboken)*. 62(5), 600–610 (2010).

2. Mease PJ, Choy EH. Pharmacotherapy of fibromyalgia. *Rheum. Dis. Clin. North. Am*. 35(2), 359–372 (2009).

3. Moore RA. What works for whom? Determining the efficacy and harm of treatments for pain. *Pain*. 154(Suppl 1), S77–86 (2013).

4. Plazier M, Ost J, Stassijns G *et al.* Pain characteristics in fibromyalgia: understanding the multiple dimensions of pain. *Clin. Rheumatol.* 34(4), 775–783 (2015).

5. Lumley MA, Cohen JL, Borszcz GS *et al.* Pain and emotion: a biopsychosocial review of recent research. *J. Clin. Psychol.* 67(9), 942–968 (2011).

6. Volkow ND, McLellan TA, Cotto JH *et al.* Characteristics of opioid prescriptions in 2009. *JAMA*. 305(13), 1299–1301 (2011).

7. Goldenberg DL, Clauw DJ, Palmer RE *et al.* Opioid Use in Fibromyalgia: A Cautionary Tale. *Mayo. Clin. Proc.* 91(5), 640–648 (2016).

8. McNett M, Goldenberg D, Schaefer C *et al.* Treatment patterns among physician specialties in the management of fibromyalgia: results of a cross-sectional study in the United States. *Curr. Med. Res. Opin*. 27(3), 673–683 (2015).

9. Macfarlane GJ, Kronisch C, Dean LE *et al.* EULAR revised recommendations for the management of fibromyalgia. *Ann. Rheum. Dis*. 76(2), 318–328 (2017).

10. Wolfe F, Walitt BT, Katz RS *et al*. Longitudinal patterns of analgesic and central acting drug use and associated effectiveness in fibromyalgia. *Eur. J. Pain*. 17(4), 581–586 (2013).

11. Bennett RM, Jones J, Turk DC *et al*. An internet survey of 2,596 people with fibromyalgia. *BMC. Musculoskelet. Disord*. 8, 27 (2007).

12. Gaskell H, Moore RA, Derry S *et al*. Oxycodone for pain in fibromyalgia in adults. *Cochrane. Database. Syst. Rev*. 9, CD012329 (2016).

13. Gaskell H, Derry S, Stannard C *et al*. Oxycodone for neuropathic pain in adults. *Cochrane. Database. Syst. Rev*. 7, CD010692 (2016).

14. Carville SF, Arendt-Nielsen S, Bliddal H *et al*. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann. Rheum. Dis*. 67(4), 536–541 (2008).

15. Painter JT, Crofford LJ. Chronic opioid use in fibromyalgia syndrome: a clinical review. *J. Clin. Rheumatol*. 19(2), 72–77 (2013).

16. Chou R, Fanciullo GJ, Fine PG *et al*. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J. Pain*. 10(2), 113–130 (2009).

17. Chou R. Long-Term Opioid Therapy for Chronic Pain. In Response. *Ann. Intern. Med*. 163(2), 148 (2015).

18. Wand G. The influence of stress on the transition from drug use to addiction. *Alcohol. Res. Health*. 31(2), 119–136 (2008).

19. Gota CE, Kaouk S, Wilke WS. Fibromyalgia and Obesity: The Association between Body Mass Index and Disability, Depression, History of Abuse, Medications, and Comorbidities. *J. Clin. Rheumatol*. 21(6), 289–295 (2015).

20. Witkin JM, Statnick MA, Rorick-Kehn LM *et al*. The biology of Nociceptin/Orphanin FQ (N/OFQ) related to obesity, stress, anxiety, mood, and drug dependence. *Pharmacol. Ther*. 141(3), 283–299 (2014).

21. Sinha R, Jastreboff AM. Stress as a common risk factor for obesity and addiction. *Biol. Psychiatry*. 73(9), 827–835 (2013).

22. Halpern R, Shah SN, Cappelleri JC *et al*. Evaluating Guideline-recommended Pain Medication Use among Patients with Newly Diagnosed Fibromyalgia. *Pain. Pract*. (2015).

23. Wolfe F, Smythe HA, Yunus MB *et al*. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis. Rheum*. 33(2), 160–172 (1990).

24. Wolfe F, Rasker JJ. The Symptom Intensity Scale, fibromyalgia, and the meaning of fibromyalgia-like symptoms. *J. Rheumatol*. 33(11), 2291–2299 (2006).

25. Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. *Arthritis. Rheum*. 54(1), 169–176 (2006).

26. Williams JW, Jr., Pignone M, Ramirez G *et al*. Identifying depression in primary care: a literature synthesis of case-finding instruments. *Gen. Hosp. Psychiatry*. 24(4), 225–237 (2012).

27. Kroenke K, Spitzer RL, Williams JB *et al*. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen. Hosp. Psychiatry*. 32(4), 345–359 (2010).

28. Hirschfeld RMA, Williams JBW, Spitzer RL *et al*. Development and validation of a screeing instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire *Am. J. Psychiatry*. 157, 1873–1875 (2000).

29. Kim B, Wang HR, Son JI *et al*. Bipolarity in depressive patients without histories of diagnosis of bipolar disorder and the use of the Mood Disorder Questionnaire for detecting bipolarity. *Compr. Psychiatry*. 49, 469–475 (2008).

30. Miller CJ, Klugman J, Berv DA *et al*. Sensitivity and specificity of the Mood Disoder Questionnaire for detecting bipolar disorder. *J. Affect. Disord*. 81, 167–171 (2004).

31. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. *Chest*. 103, 30–36 (1993).

32. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health. Qual. Life. Outcomes*. 1, 20 (2003).

33. Robinson RL, Kroenke K, Williams DA *et al*. Longitudinal Observation of Treatment Patterns and Outcomes for Patients with Fibromyalgia: 12-Month Findings from the REFLECTIONS Study. *Pain. Med*. 2013.

34. Painter JT, Crofford LJ, Talbert J. Geographic variation of chronic opioid use in fibromyalgia. *Clin. Ther*. 35(3), 303–311 (2013).

35. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J. Bone. Joint. Surg. Am*. 91(4), 919–927 (2009).

36. Kidner CL, Gatchel RJ, Mayer TG. MMPI disability profile is associated with degree of opioid use in chronic work-related musculoskeletal disorders. *Clin. J. Pain*. 26(1), 9–15 (2010).

37. Peng X, Robinson RL, Mease P *et al*. Long-term evaluation of opioid treatment in fibromyalgia. *Clin. J. Pain*. 31(1), 7–13 (2015).

38. Wolfe F. The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. *Ann. Rheum. Dis*. 56(4), 268–271 (1997).

39. Gota CE, Kaouk S, Wilke WS. The impact of depressive and bipolar symptoms on socioeconomic status, core symptoms, function and severity of fibromyalgia. *Int. J. Rheum. Dis.* (2015).

40. Wasserman RA, Brummett CM, Goesling J *et al*. Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Reg. Anesth. Pain. Med*. 39(1), 13–17 (2014).

41. Fitzcharles MA, Faregh N, Ste-Marie PA *et al*. Opioid use in fibromyalgia is associated with negative health related measures in a prospective cohort study. *Pain. Res. Treat*. 898493 (2013).

42. Eriksen J, Sjogren P, Bruera E *et al*. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 125(1–2), 172–179 (2006).

43. Darnall BD, Stacey BR, Chou R. Medical and psychological risks and consequences of long-term opioid therapy in women. *Pain. Med*. 13(9), 1181–1211 (2012).

44. O'Connell C, Azad TD, Mittal V *et al*. Preoperative depression, lumbar fusion, and opioid use: an assessment of postoperative prescription, quality, and economic outcomes. *Neurosurg. Focus*. 44(1), E5 (2018).

45. Etcheson JI, Gwam CU, George NE *et al*. Patients With Major Depressive Disorder Experience Increased Perception of Pain and Opioid Consumption Following Total Joint Arthroplasty. *J. Arthroplasty*. (2017).

46. Lutz PE, Kieffer BL. Opioid receptors: distinct roles in mood disorders. *Trends. Neurosci*. 36(3), 195–206.

47. Martikainen IK, Pecina M, Love TM *et al*. Alterations in endogenous opioid functional measures in chronic back pain. *J. Neurosci*. 33(37), 14729–14737 (2013).

48. Panerai AE, Vecchiet J, Panzeri P *et al*. Peripheral blood mononuclear cell beta-endorphin concentration is decreased in chronic fatigue syndrome and fibromyalgia but not in depression: preliminary report. *Clin. J. Pain*. 18(4), 270–273 (2002).

49. Harris RE, Clauw DJ, Scott DJ *et al*. Decreased central mu-opioid receptor availability in fibromyalgia. *J. Neurosci*. 27(37), 10000-10006 (2007).

50. Schrepf A, Harper DE, Harte SE *et al*. Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study. *Pain*. 157(10), 2217–2225 (2016).

51. Kennedy SE, Koeppe RA, Young EA *et al*. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. *Arch. Gen. Psychiatry*. 63(11), 1199–1208 (2006).