

Opioid Use, Misuse, and Abuse in Patients Labeled as Fibromyalgia

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ABSTRACT

BACKGROUND: As pain is the cardinal symptom of fibromyalgia, it is logical that treatments directed toward pain relief will be commonly used. Analgesic drug therapy remains the traditional treatment intervention for most chronic pain conditions, with a progressive increased use of opioids in the past 20 years. Concerns about efficacy, risk-benefit ratio, and possible long-term effects of chronic opioid therapy have been raised. There is limited information about opioid treatment in fibromyalgia, with all current guidelines discouraging opioid use.

METHODS: A chart review of all patients referred to a tertiary care pain center clinic with a referring diagnosis of fibromyalgia was conducted to evaluate use of opioid medications.

RESULTS: We have recorded opioid use by 32% of 457 patients referred to a multidisciplinary fibromyalgia clinic, with over two thirds using strong opioids. Opioid use was more commonly associated with lower education, unemployment, disability payments, current unstable psychiatric disorder, a history of substance abuse, and previous suicide attempts.

CONCLUSION: We have observed negative health and psychosocial status in patients using opioids and labeled as fibromyalgia. Prolonged use of opioids in fibromyalgia requires evaluation.

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KEYWORDS: Abuse; Fibromyalgia; Opioid therapy

Fibromyalgia, a condition associated with nervous system dysregulation of pain processing, is recognized as a valid syndrome, with body pain as the principal symptom.¹ Fibromyalgia, however, remains a clinical challenge for 2 reasons. The absence of a confirmatory test requires that the diagnosis be made on the basis of a clinical evaluation,

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which is entirely dependent upon subjective report and response to pressure of soft tissues, that is, the tender point examination. Secondly, there is no “gold standard” of treatment, although the last decade has seen emergence of various pharmacologic treatments, with 3 recently approved by the US Food and Drug Administration.² The most rational treatment approach at present is symptom-based and addresses the major components of distress.

As pain is the most prevalent symptom in fibromyalgia, treatments directed toward pain relief will feature prominently in management.³ Traditional drugs with analgesic properties include simple analgesics such as acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), and those categorized as opioids, which have gained increased acceptance and use over the last 2 decades.⁴ There is, however, emerging concern about true efficacy, adverse effects related to long-term use, and potential for abuse for patients on opioid treatment. The short-term negative effects of opioids are well described and often lead to discontinuation; however, long-

term effects are less clear but include the potential of increased pain due to hyperalgesia, hormonal effects, and possibility for misuse and abuse.⁴

Opioids stronger than codeine had been prescribed for 37% of persons with chronic noncancer pain in a recent national Canadian survey.⁵ Patients suffering with fibromyalgia constitute a considerable component of those reporting chronic pain, with prevalence rates in the order of 2%.⁶ The prevalence of opioid use by fibromyalgia patients is unknown, although Goldenberg et al⁷ reported use of any analgesic other than NSAIDs in 52% in a cross-sectional study. Opioids are not, however, recommended by any current guidelines for the management of fibromyalgia.⁸⁻¹⁰

The primary aim of this survey was to evaluate the reported use of opioids and the associations thereof in patients referred with a diagnosis of fibromyalgia to a multidisciplinary pain center.

METHODS

From January 2005 to December 2010, all patients referred to the Alan Edwards Pain Management Unit with a referring diagnosis of fibromyalgia were evaluated in a designated fibromyalgia clinic. Patients were referred mostly by primary care physicians, with a few being referred by other specialists; the ongoing clinical care of almost all patients was the responsibility of their primary care physician. Patients were assessed individually by members of a multidisciplinary team that included a physician, psychologist, nurse-clinician, and at times, a physiotherapist. The mission of this multidisciplinary clinic is to evaluate and manage patients according to individual needs, with treatments tailored to each patient.

A chart review of all referred patients was conducted in January 2011 and data were extracted according to a predetermined protocol. At the time of intake, patients were identified as having fibromyalgia if they fulfilled 1990 American College of Rheumatology criteria for a primary diagnosis for fibromyalgia. All other patients in whom the primary cause for complaint was due to some other primary medical, psychological, or psychiatric condition were categorized as nonfibromyalgia patients.

The diagnosis of a previous or current psychological or psychiatric condition was based upon a formal psychological interview by an experienced psychologist, with diagnoses based upon the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition,¹¹ or by report from a current treating psychiatrist. The mental health status was catego-

rized as current unstable mental illness resulting in serious mental health problems, or stable mental health. Patient report of previous suicide attempts was documented. History of substance abuse was by patient report for previous or current abuse of alcohol, illicit drug use including marijuana, or prescription medications for opioids or benzodiazepines.

Demographic and symptom information was captured and included age, sex, education level, current employment status, current disability payments, pain level on a 10-cm visual analog scale (VAS), and functional measurement by Fibromyalgia Impact Questionnaire (FIQ). Current use of opioids, including name and dose, was recorded. Opioid categories were defined as “weak” for codeine and tramadol, and “strong” for all others currently available in Canada. The daily dose of opioids was converted to the equivalent dose for 10 mg morphine using the following morphine equivalent conversion factor: tramadol 100 mg, codeine 100 mg, hydromorphone 2 mg, oxycodone 5 mg, and meperidine

100 mg. The conversion for fentanyl patch was calculated as 25 $\mu\text{g}/\text{h}$ being equivalent to morphine 75 mg per day. The conversion for methadone was as follows: when the methadone dose was <30 mg/day, 1 mg of methadone was equivalent to 4 mg of morphine, and when methadone was >30 mg/day, 1 mg of methadone was equivalent to 7 mg of morphine. These conversions are due to the variable pharmacokinetics of methadone at different doses.

Patients were categorized as drug-seeking if they demonstrated “aberrant drug-related behaviors” according to a list compiled by Portenoy,¹² and any of the following: medical or pharmacy records, documented repeated inappropriate requests for opioids from multiple physicians or different pharmacies, or information obtained following an in-depth psychological evaluation wherein the patient admitted to accessing opioids by aberrant means.

Statistics

Descriptive statistics were used to categorize the sample in the following domains: demographic characteristics; psychiatric and personality features; substance abuse. We used univariate analysis of variance to compare means in normally distributed continuous data, and chi-squared tests to compare proportions for categorical data. The Kruskal-Wallis one-way analysis of variance was used to compare medians for nonparametric variables.

CLINICAL SIGNIFICANCE

- Contrary to all current recommendations, opioids were used by one third of patients diagnosed with fibromyalgia.
- Negative psychosocial associations including unemployment, unstable mental illness, and substance abuse were more commonly observed in patients using opioids.
- Active drug-seeking behavior was identified in a small number of patients in this cohort.
- Physicians choosing to prescribe opioids for patients with fibromyalgia should exercise responsible prescribing behaviors.

Table Demographic Data and Opioid use for 457 Patients Initially Labeled as Having Fibromyalgia

	All Patients n = 457	Opioids n = 144	No Opioids n = 313	P Value Opioids vs No Opioids	Strong Opioids n = 105	Weak Opioids n = 39	P Value Strong vs Weak Opioids
Age ± SD	47 ± 11	50 ± 11	47 ± 11	NS	50 ± 11	49 ± 11	NS
Sex/female, n (%)	417 (91)	132 (92)	285 (91)	NS	94 (90)	38 (97)	NS
Education (in 436)							
Schooling not completed, n (%)	50 (11)	21 (15)	29 (9)	NS	17 (16)	4 (10)	NS
High school, n (%)	132 (29)	47 (33)	85 (27)	NS	35 (33)	12 (31)	NS
College, n (%)	156 (34)	48 (33)	108 (35)	NS	33 (31)	15 (38)	NS
University, n (%)	98 (21)	19 (13)	79 (25)	.03	12 (11)	7 (18)	NS
Employed	149 (33)	23 (16)	126 (40)	<.0001	13 (12)	10 (26)	.07
Disability, n (%)	165 (36)	70 (49)	95 (30)	.0002	53 (50)	17 (44)	NS
Diagnosis							
Fibromyalgia, n (%)	302 (66)	93 (65)	209 (67)	NS	63 (60)	30 (77)	.07
Not fibromyalgia, n (%)	155 (34)	51 (35)	104 (33)	NS	42 (40)	9 (23)	.07
Current mental illness	110 (24)	52 (36)	58 (19)	.0007	43 (41)	9 (9)	.05
Cannabinoids – all, n (%)	59 (13)	28 (19)	31 (10)	.007	23 (22)	5 (13)	NS
Prescribed cannabinoids, n (%)	13 (3)	9 (6)	4 (1)	.005	7 (7)	2 (5)	NS
Marijuana	46 (10)	19 (13)	27 (9)	NS	16 (15)	3 (8)	NS
Substance abuse, n (%)	52 (11)	34 (24)	18 (6)	.0001	31 (30)	3 (8)	.0072
Suicide attempts, n (%)	28 (6)	14 (10)	14 (4)	.036	11 (10)	3 (8)	NS

Approval from the office of the Director of Professional Services of the Montreal General Hospital was obtained for chart review with extraction of data for all referred patients.

RESULTS

There were 457 patients referred to the fibromyalgia clinic during the study period. All had a referring diagnosis of fibromyalgia. After formal evaluation, 302 (66%) retained a diagnosis of fibromyalgia, whereas 155 (34%) were assigned some other primary diagnosis by the first author, a rheumatologist. Of the 302 fibromyalgia patients, 251 were eligible for entry into a prospective longitudinal cohort study, which is currently in progress. Fibromyalgia patients had a mean pain VAS of 6.4 and a FIQ score of 65.7. Patients were using an average of 1.9 prescription medications for treatment of symptoms, including NSAIDs, opioid medications, tricyclic and other antidepressants, antiepileptic agents, and tranquilizers.

Of the 155 categorized as not fibromyalgia, 140 had a valid medical diagnosis other than fibromyalgia to explain the pain, 65 had a current serious mental health/psychiatric problem (some of whom also had a valid medical cause for pain complaint), and 13 were identified as drug-seeking. Twenty-five patients (6%) of the total group (12 fibromyalgia and 13 nonfibromyalgia) were identified as drug-seeking, having demonstrated aberrant drug-related behaviors, 19 of whom also had a current unstable psychological or psychiatric condition in addition to drug-seeking behavior. Seventeen of the 25 (68%) drug-seeking patients had a

history of substance abuse, and 8 (32%) reported current use of illicit cannabinoids.

Demographic, disease, and drug-related information for all patients is shown in the Table. At entry, 144 (32%) of all patients were on daily opioid medication, with strong opioids being used by 105 and weak opioids by 39. Only 16% of those on opioids were currently employed, and almost half were receiving disability benefits. Current severe mental illness, as well as a previous history of suicide attempts and substance abuse, was more common in those on opioids. Pain duration (10.5 vs 10.9 years), pain severity VAS (6.4 vs 6.2), and functional status FIQ (65 vs 64.8) did not differ between those on opioids and those not on opioids. Five patients reported current illicit opioid use, 2 of whom also had been prescribed opioids. Three of the 25 patients who were drug-seeking denied currently using opioids.

The median daily morphine equivalent dose for all patients on opioids at the time of referral was 40 mg (interquartile range [IQR] 11-100). Patients on opioids were more likely to be unemployed ($P < .0001$), and to be receiving disability benefits ($P = .0002$). Psychological health was poorer for those on opioids with more current unstable mental illness ($P = .0007$), more report of substance abuse ($P = .0005$), and report of previous suicide attempts ($P = .036$) (Table).

Patients on opioids were grouped according to use of weak or strong opioids, with findings shown in the Table. Of the 144 patients using opioids, 73% were on strong opioids, with median morphine equivalent dose calculated

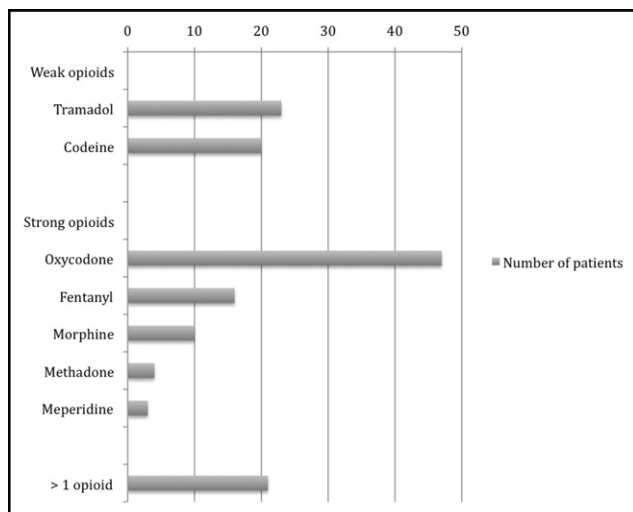


Figure Prescription opioids used by all patients referred with diagnosis of fibromyalgia (n = 144).

as 10 mg (IQR 6-20) versus 72 mg (IQR 27-120) for weak and strong opioid use, respectively ($P < .001$). Unemployment, unstable mental illness, and substance abuse was more common in those on strong opioids, although only substance abuse achieved significance ($P = .007$).

The Figure illustrates the opioid used according to type, with oxycodone identified as the most commonly used opioid. Eighteen (72%) of the patients identified as drug seekers reported current use of a strong opioid, with 4 (16%) reporting use of codeine only, and 3 reporting no current use of opioid medication, but requesting a prescription for opioids. Fifteen percent of opioid users were using more than one opioid concurrently.

DISCUSSION

Opioid use for the management of pain in fibromyalgia is strongly discouraged and is not recommended by any current guideline.⁸⁻¹⁰ The major finding of this study is that one third of those labeled as fibromyalgia patients and referred to a multidisciplinary pain center were currently using daily opioids, although duration of use is not known. Moreover, those on opioids had indications of poorer health status, with more patients being unemployed, receiving disability benefits, and presented with more unstable mental illness. Strong opioids were used by over 70% of opioid users, with a median daily morphine equivalent calculated as 72 mg morphine. Evidence for active drug-seeking was present in 6% of all patients, and similar to the findings of Turk et al,¹³ these patients had a higher rate of substance abuse and illicit drug use. This high rate of opioid use, including abuse, associated with negative psychosocial effects deserves attention and warrants further exploration, especially regarding treatment patterns and probable overuse of opioids in the primary care setting.

There is no gold standard of treatment for patients with fibromyalgia, with a recent review reporting evidence for

efficacy of over 20 treatment interventions, highlighting the uncertainty in management of these patients.^{2,14} Other than for tramadol, classified as a weak opioid, and showing a positive effect on pain in fibromyalgia in 2 studies, there have been no controlled studies that have evaluated the use of opioids in fibromyalgia.¹⁵⁻¹⁷ Conflicting evidence about the role of the endogenous opioid system in fibromyalgia adds to this quandary, with reports of down- as well as upregulation of opioid receptors, elevated levels of cerebrospinal fluid enkephalin, and variable response to naltrexone.^{18,19} Therefore, this frequent use of opioids, without evidence, requires explanation and demands further study.

The long-term effects of chronic opioid use in nonmalignant pain are not yet clear, although effects on mood, cognitive function, aggravation of pain due to hyperalgesia, and hormonal status are gaining attention.^{4,20} Moreover, patient concerns about opioid treatments have been recognized as considerable in over a third of patients and should be taken into consideration.²¹ More abuse of prescription drugs as well as an increased death rate due to drug overdosage has paralleled increased prescription of opioids.^{22,23} Although there are currently no accurate predictors for abuse of opioid medications, treatment agreements, urine drug testing, and attention to previous illicit drug or alcohol abuse may be helpful.^{12,24} Although the misuse of opioids has been associated with a subjective report of greater pain intensity,²⁵ we observed no difference in pain report in our patients stratified according to opioid use. Any prescription of opioids should take into consideration the safety of both the individual patient and the population at large.

Effective pain management should be associated with improved function. The patients in this study showed a high rate of disability, with only one third in the workforce, and a similar number receiving disability compensation. This high rate of functional impairment may indicate severity of physical symptoms, or conversely, the negative effect on health status due to factors such as mental illness or medication overuse. The associations of poorer functional status, mental illness, and substance abuse with the use of opioids in our study population are similar to those described in other chronic pain populations in North America and Europe.^{5,26,27}

It is intriguing to note that many of the negative effects of opioids, which include fatigue, sleep disturbance, increased pain due to hyperalgesia, and poor mood, are symptoms comparable with the typical symptoms of fibromyalgia. Hyperalgesia, although mostly recognized with high-dose opioids, may even occur shortly after initiating low-dose opioid treatment.²⁸ Distinguishing hyperalgesia from the pain in fibromyalgia is difficult, as both conditions may cause pain characterized as neurologic with burning and allodynia.²⁹ It is possible that the hyperalgesic effect may drive increased opioid dosing in some patients. This increased pain may even prompt aberrant drug-related behavior when not recognized by health care providers.

Similar to other reports, opioid use, especially in higher doses, was associated with a history of substance abuse.³⁰

Illicit current marijuana use was, however, not different depending on opioid use. It is not known whether active drug-seeking identified in a small subset of individuals, most of whom also had an active unstable mental illness, was for personal consumption or for diversion. However, it is notable that these persons all carried the medical diagnosis of fibromyalgia, which may have been used to validate the continued prescription of opioids by physicians.

Taking into account the new revised criteria for a diagnosis of fibromyalgia, which incorporate symptoms other than pain as components of fibromyalgia, some patients with predominant mood or psychiatric disorder and less prominent physical symptoms may be misclassified as having fibromyalgia.³¹ Even though mood disorder is the strongest associated comorbidity with fibromyalgia, prominent mental illness can masquerade as a pain syndrome and should be recognized.^{32,33} Over 20% of our patients labeled as having fibromyalgia were suffering from a primary unstable psychiatric disorder and the reported rate for previous suicide attempts was 6% for the whole group, with more attempts in opioid users. While pain and psychological illness can coexist, physicians should be cognizant that a report of pain may be a surrogate for underlying mental illness.

Referral to a pain center may be driven by a number of factors. A physician-initiated referral is likely based on challenges in management or insecurity regarding a diagnosis. We have, however, strongly advocated that ideal care for fibromyalgia patients should remain in the primary care setting, in keeping with the best standard of care in Canada.³⁴ Our study patients were referred for advice about management of fibromyalgia as our center is recognized as having an interest in this condition, and not specifically for evaluation of opioid concerns. Patients' demographic and symptom characteristics also were representative for those with fibromyalgia seen in a tertiary care setting. From the patient's perspective, a referral to a pain center may be a sincere effort to achieve well-being, may validate the severity of complaint for regulators or payers, or be used as a means to access medication with misuse of a diagnostic label of fibromyalgia.

We acknowledge a number of limitations to this study. Firstly, the diagnosis of fibromyalgia remains clinical, relies on patient report, and requires the physician to use clinical judgment about all the psychosocial issues that we have highlighted. We believe, however, that the multidisciplinary nature of our clinical setting, with input from different team members, has added strength to our findings, which may have been less obvious following a single physician-patient encounter. Secondly, our report is based upon patients seen in a tertiary care setting, which is not necessarily representative of patients seen in primary care. Although we have identified substance abuse and aberrant drug-related behaviors, as well as a report of suicide attempts within our cohort, it is possible that these numbers may be inaccurate or even underreported. Finally, we are unable to comment

on long-term safety of opioids or clinical outcome associated with opioid use.

We have documented a high rate of opioid use in a large cohort of patients carrying the diagnosis of fibromyalgia. Unemployment, disability compensation, and poorly controlled mental illness were associated with opioid use. Some active drug seekers carried the diagnosis of fibromyalgia, likely as a justification for procuring medications. This study highlights the need to assess psychosocial as well as physical aspects for patients reporting widespread pain, as well as evaluation of the risk/benefit ratio of any treatment intervention. We recommend that any physician prescribing opioids for a patient with fibromyalgia should practice responsible prescribing behaviors with attention to function and psychological status, use of screening tools or treatment agreements where appropriate, and be alert to any indication of aberrant drug behavior. The use of opioids in fibromyalgia requires further study in order to examine health outcome parameters.

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