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Opioid Use in Fibromyalgia: A Cautionary Tale

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Abstract

Multiple pharmacotherapies are available for the treatment of fibromyalgia (FM), including opioid analgesics. We postulate that the mechanism of action of traditional opioids predicts their lack of efficacy in FM. Literature searches of the MEDLINE and Cochrane Library databases were conducted using the search term *opioid AND fibromyalgia* to identify relevant articles, with no date limitations set. Citation lists in returned articles and personal archives of references were also examined for additional relevant items, and articles were selected based on the expert opinions of the authors. We found no evidence from clinical trials that opioids are effective for the treatment of FM. Observational studies have found that patients with FM receiving opioids have poorer outcomes than patients receiving nonopioids, and FM guidelines recommend against the use of opioid analgesics. Despite this, and despite the availability of alternative Food and Drug Administration–approved pharmacotherapies and the efficacy of nonpharmacologic therapies, opioids are commonly used in the treatment of FM. Factors associated with opioid use include female sex; geographic variation; psychological factors; a history of opioid use, misuse, or abuse; and patient or physician preference. The long-term use of opioid analgesics is of particular concern in the United States given the ongoing public health emergency relating to excess prescription opioid consumption. The continued use of opioids to treat FM despite a proven lack of efficacy, lack of support from treatment guidelines, and the availability of approved pharmacotherapy options provides a cautionary tale for their use in other chronic pain conditions.

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The cardinal symptom of fibromyalgia (FM) is chronic widespread pain.[1-4] Fibromyalgia is a prototypical central pain disorder, and it has been used as a model to study related chronic pain disorders. It is also associated with multiple somatic symptoms, including fatigue, sleep disturbances, mood and cognitive disturbances, and headache, as well as bowel and bladder irritability.[1-4] It has an estimated prevalence of approximately 1.1% to 5.4% in the general population,[1,5-7] and it often coexists with other pain conditions. Of patients with rheumatic diseases, including osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus, 10% to 20% have FM, as do 30% to 70% of individuals with chronic pain disorders, such as irritable bowel syndrome and temporomandibular joint disorder.[4]

There is strong evidence for the efficacy of nonpharmacologic therapies, including patient education, cognitive behavior therapy, and exercise, in FM.[8] Pharmacologic treatments with demonstrable efficacy in FM include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (eg, duloxetine and milnacipran), and alpha-2-delta ligands (gabapentin and pregabalin).[9] Duloxetine, milnacipran, and pregabalin are approved by the US Food and Drug Administration (FDA) for the treatment of FM. Opioid analgesics continue to be commonly used for the treatment of FM.[10,11] However, medical guidelines, including those of the American Pain Society and the American Academy of Pain Medicine,[12] the American Academy of Neurology,[13] the European League Against Rheumatism,[14] the Canadian Pain Society and the Canadian Rheumatology Association,[15] and the British Pain Society,[16] recommend against the use of long-term opioids in FM. There is evidence that tramadol may be effective in the treatment of FM,[17-19] but it is considered a weak opioid receptor agonist, and its efficacy in FM is likely related to its other mechanism of action as a serotonin-norepinephrine reuptake inhibitor.[20,21] This review is, therefore, limited to traditional opioid analgesics, and tramadol is not included. Moreover, use of the

terms *strong* and *weak* opioids can be misleading because definitions are inconsistent and it is the duration of opioid treatment that is key. We deliberately do not use these terms unless individual studies have given specific definitions.

The widespread use of opioid analgesics for chronic pain disorders is of particular concern given the ongoing public health emergency in the United States relating to prescription opioid use.[22] This review examines the place of opioids in the treatment of FM by assessing the physiologic and clinical evidence supporting opioid use, their use and outcomes in real-world FM populations, and factors that may influence their use in FM. Because FM is considered the prototypical centralized pain state,[8] this information has implications for other chronic pain disorders, in particular those with a centralized component.

METHODS

Literature searches of the MEDLINE and Cochrane Library databases were conducted using the search term *opioid AND fibromyalgia* to identify relevant articles. No date limitations were set, and no other filters were applied. As of September 4, 2015, 190 articles were returned from MEDLINE and 2 from the Cochrane Library. Citation lists in returned articles and personal archives of references were also examined for additional relevant items. The selection of articles for inclusion in this review was based on the expert opinions of the authors.

EVIDENCE OF ALTERED OPIOID ACTIVITY IN FM

Many studies have suggested altered baseline opioidergic activity in FM. Although the peripheral actions of opioids are poorly understood and are unlikely to directly reflect central activity, nearly all studies examining peripheral opioid activity to date show fairly striking differences between patients with FM and controls. Reduced concentrations of endogenous opioids in peripheral blood mononuclear cells were found in patients with both FM and chronic fatigue syndrome but not in depressed individuals.[23] Another study demonstrated markedly increased μ- and δ-opioid receptor expression in the skin of patients with FM.[24] Using radioimmunoassay,

ARTICLE HIGHLIGHTS

- There is no clinical or real-world evidence demonstrating the efficacy or effectiveness of opioids in the treatment of fibromyalgia (FM).

- Despite this, and despite treatment guidelines recommending against the use of long-term opioids for FM, opioid use is very common in patients with FM.

- The rate of opioid prescribing is high in FM despite the availability of guideline-recommended and Food and Drug Administration—approved medications for FM.

- Excess opioid prescription by physicians and opioid consumption by patients with FM may be contributing to the ongoing opioid epidemic in the United States and provides a valuable lesson for other chronic pain disorders.

Vaeroy et al[25,26] examined levels of several endogenous opioids, including β-endorphin and Met-enkephalin, in the cerebrospinal fluid of patients with FM and found these to be normal. However, early radioimmunoassay investigations showed extensive cross-reactivity between endogenous opioids and other ligands. A more recent radioimmunoassay study demonstrated increased endogenous opioid levels in the cerebrospinal fluid of patients with FM vs controls.[27] In a subsequent positron emission tomography imaging study, [^{11}C]-carfentail, a μ-opioid receptor selective tracer, was used to quantify μ-opioid receptor availability in patients with FM.[28] Receptor availability was reduced in several pain-processing and modulatory regions, including the dorsal cingulate, amygdala, and nucleus accumbens, compared with controls. Moreover, reduced receptor availability was associated with greater clinical pain in the FM group, as reported at the time of the positron emission tomography experiment.

There are 2 possible interpretations of these data that are not mutually exclusive. First, individuals with FM may have a more activated opioid system at rest, reflecting increased release of endogenous opioids and reduced receptor availability. Second, patients with FM may have fewer opioid receptors, which could lead to elevated pain. Regardless of the operative mechanism, both outcomes would predict that individuals with lowered receptor availability have a diminished response to opioid analgesics.

Perhaps the strongest data supporting a state of excess endogenous opioid activity in FM comes from studies that showed that low doses of naltrexone, an opioid receptor antagonist, may be effective in FM.[29,30] Although the use of opioid antagonists requires further study, these data emphasize the notion that opioid analgesics are not likely to be effective in FM.

The hypothesis of aberrant endogenous opioid-related pain processing is supported by indirect evidence from patient phenotypic characteristics and opioid analgesic consumption. In a prospective, observational cohort study in 519 patients who underwent lower-extremity joint arthroplasty, those with higher preoperative FM survey scores used more opioid medication and reported higher pain severity.[31] Moreover, FM survey score and preoperative opioid use were highly predictive of postoperative opioid consumption. For each 1-point increase in FM survey score, patients used 9 mg more of oral morphine equivalents in the perioperative period. The authors concluded that the higher pain sensitivity, preoperative opioid use, and postoperative opioid consumption in patients with higher FM survey scores may reflect aberrant opioid-related central pain processing. These findings have been replicated in a different surgical cohort of women undergoing hysterectomy.[32] In this study, each 1-point increase in FM survey score was associated with the use of 7 mg more of oral morphine equivalents. In a separate study of 582 patients taking opioid medication for pain relief, 49% continued to report severe pain.[33] Among phenotypic characteristics, higher FM survey scores and more neuropathic pain symptoms were associated with higher levels of pain, suggesting that patients with persistently high pain scores despite opioid therapy were more likely to present with characteristics of centralized pain, typified by FM.

Further supporting evidence for involvement of the central opioid system in FM is the phenomenon known as opioid-induced hyperalgesia (OIH), identified as a paradoxical increase in pain sensitivity on exposure to opioids.[34-37] The exact mechanisms are unknown, but multiple hypotheses have been suggested that lead to sensitization of central pronociceptive pathways.[37] Opioid-induced hyperalgesia has yet to be directly demonstrated in patients with FM but has been suggested in patients with other chronic pain conditions.[38,39] In addition, OIH has been reported in healthy volunteers receiving opioid infusions,[34,40] and there is also good evidence of OIH from a variety of animal studies.[36] Therefore, OIH may be an iatrogenic phenomenon that leads to a centralized pain state, analogous to the centralized pain in patients with FM that is caused by an aberrant endogenous central opioid system, both of which result in elevated pain.

CURRENT USE OF OPIOID ANALGESICS FOR FM

Clinical Trials of Opioid Analgesics for FM

There is no evidence from clinical trials to support the efficacy and safety of opioids in FM. Two pilot studies evaluating a single morphine infusion in patients with FM reported mixed results.[41,42] The lack of supporting data on the use of opioids in FM is reflected by a Cochrane systematic review of oxycodone for the treatment of neuropathic pain or FM.[43] This review was unable to identify any relevant studies for FM. Moreover, a recent systematic review found insufficient evidence to support the use of long-term (>1 year) opioid therapy for the treatment of any form of chronic pain.[44]

Real-world Data on the Use of Opioid Analgesics for FM

Opioid Analgesic Use Is Common in Real-world Studies. The widespread, real-world use of opioids in patients with FM has been comprehensively demonstrated in several large retrospective health claims database studies (Table 1). These studies documented opioid use in large numbers of patients with FM.[45-51] Rates of opioid use ranged from 11.3% to 69%, including short- and long-acting opioids. Two recent studies assessed opioid use in relation to the use of approved or recommended nonopioid treatment options. In patients with FM who had been newly prescribed amitriptyline, duloxetine, pregabalin, or gabapentin, opioid use was greater than 50% during the baseline period and significantly decreased during the 3 years after treatment initiation, but opioids were still being used by more than 45% of patients in each cohort.[50] In the second study, opioid use decreased in the first year of treatment in patients prescribed opioids alone or with an approved FM treatment, but

TABLE 1. Rates of Opioid Analgesic Use in Patients With FM From Retrospective Health Claims Database Studies[a]

Database	Sample (No.)	Study duration (y)	Rate of opioid use (%)	Reference, year
PharMetrics Patient-Centric Database, a US health insurance database of >85 health plans covering ∼11 million persons	33,176 newly diagnosed as having FM	3	37.8 (37.1 short acting, 6.8 long acting)	Berger et al,[45] 2007
Ingenix employer database, a large administrative claims database of 31 self-insured US companies	27,947 newly diagnosed as having FM; 13,588 with established FM	2 (newly diagnosed) and 1 (established)	39.5[b] 43.5[c] 43.9[d]	White et al,[46] 2009
Humana's commercial and Medicare populations	9988	2	40.8[e] 46.7[f]	Palacio et al,[47] 2010
Medstat MarketScan Health and Productivity Management Database, a large health insurance claims database of 80 US health plans covering ∼28 million persons	1803 newly diagnosed as having FM	2	51.3 (51.1 short acting, 5.5 long acting)[e] 55.9 (55.5 short acting, 7.7 long acting)[f]	Berger et al,[48] 2010
Nationally representative US data set of 15 million commercially insured individuals	245,758 across 48 states	3	11.3 (range, 4.0-20.2)	Painter et al,[49] 2013
Innovus InVision Data Mart, a commercial US health plan of 14 million subscribers	74,378 newly prescribed amitriptyline, duloxetine, pregabalin, or gabapentin for FM	3	54-69[g] >45[h]	Kim et al,[50] 2013
Large US health plan	96,175	1	55.4[i] 38.5[j]	Halpern et al,[51] 2015

[a]FM = fibromyalgia.
[b]In the 1 year before diagnosis in newly diagnosed patients.
[c]In the 1 year after diagnosis in newly diagnosed patients.
[d]In the 1 year after the most recent FM diagnosis in established patients.
[e]In the 12 months before diagnosis.
[f]In the 12 months after diagnosis.
[g]At baseline. The rate of opioid use depended on which approved FM-related medication (amitriptyline, duloxetine, pregabalin, or gabapentin) was newly prescribed.
[h]In the 3 years after the study index date.
[i]In the first quarter after FM diagnosis. Includes patients prescribed opioids alone or opioids plus an approved FM treatment.
[j]In the fourth quarter after FM diagnosis. Includes patients prescribed opioids alone or opioids plus an approved FM treatment.

38.5% were still using an opioid in the fourth quarter after diagnosis.[51] Once patients received opioids after the diagnosis of FM, the likelihood of receiving guideline-recommended medications was small.[51] The availability and use of FDA-approved and guideline-recommended nonopioid treatment options, therefore, does not eliminate the widespread use of opioid analgesics.

In addition to data from health claims databases, other studies have examined the prevalence of opioid use in patients with FM in a real-world setting. A 7-year prospective study of 538 patients from 6 rheumatology centers with an interest and expertise in FM identified opioid use in 7% of patients,[52] whereas in an 11-year longitudinal study of 3123 US adult patients, 46.7% of patients were using opioids at the end of the study.[53] During the 11-year study period, severity-adjusted use of any opioid increased from 40.0% to 46.6%. It is notable that opioid use increased during this period even though use of the FDA-approved FM treatments duloxetine, milnacipran, and pregabalin increased from less than 10% to 39% during the same period.

In a separate 12-month, prospective, observational study of 1700 participants, opioid use was 24.2% at baseline.[54] At any time during the 12 months of follow-up, opioids were used by 36.5% of patients.[55] A total of 61.4% of patients used an opioid at any time during the study.

Impact of Opioid Analgesic Use in FM. There is evidence that the use of opioids in FM may have a negative effect on patient outcomes

TABLE 2. Outcome Data on the Use of Opioid Analgesics in Fibromyalgia

Study design	Sample (No.)	Regimen, type of opioid(s), and number of patients	Study duration (y)	Main outcomes	Reference, year
Single center, prospective, longitudinal	131	43 opioid users and 88 nonopioid users	2	Pain severity scores at 2 y were significantly better in nonopioid vs opioid users, as measured by VAS (P<.05) and MPQ (P<.01) Scores for measures of patient function, including PGA, FIQ, and HAQ, were all significantly better (P<.05) in nonopioid vs opioid users at 2 y	Fitzcharles et al,[56] 2013
Multicenter, prospective, observational	1700	412 opioid users (including concurrent tramadol) and 1056 nonopioid users	1	Improvements in BPI-S scores not significantly different between cohorts Significant improvements in scores for BPI-I, FIQ, ISI, SDS, and PHQ-8 (all P<.05) for nonopioid vs opioid cohorts	Peng et al,[57] 2015

BPI-I = Brief Pain Inventory-Interference; BPI-S = Brief Pain Inventory-Severity; FIQ = Fibromyalgia Impact Questionnaire; HAQ = Health Assessment Questionnaire; ISI = Insomnia Sleep Index; MPQ = McGill Pain Questionnaire; PGA = patient global assessment; PHQ-8 = 8-item Patient Health Questionnaire; SDS = Sheehan Disability Scale; VAS = visual analog scale.

compared with other therapies (Table 2), extending findings from clinical studies that demonstrate a lack of proven efficacy. A 2-year longitudinal analysis of 43 opioid and 88 nonopioid users documented improved pain severity scores and patient function in both groups but significantly greater improvement in nonopioid users.[56] Similarly, in a 12-month observational study, improvements in pain severity scores were not statistically different between 412 opioid users (concurrent use of tramadol was permitted) and 1056 patients not taking opioids.[57] However, patients not taking opioids showed statistically significant improvements in scores for pain interference and patient function, as well as measures of insomnia, disability severity, and depression severity, vs the opioid cohort. The authors concluded that the results showed little support for the long-term use of opioids in patients with FM.[57]

Factors Associated With the Use of Opioids in FM. A retrospective medical record review of 457 patients referred to a Canadian tertiary care pain center clinic with a diagnosis of FM found opioid use by 31.5%.[58] Use of weak opioids, ie, codeine and tramadol, occurred in 8.5% of patients, whereas 23.0% used strong opioids, ie, all other opioids available in Canada at that time. Use of opioids was associated with lower educational status, unemployment, disability, unstable mental illness, a history of substance abuse, and previous suicide attempts. Unemployment, unstable mental illness, and substance abuse were more common in patients using strong opioids than in those using weak opioids.

Patient preference for opioids has varied. An Internet survey conducted before the FDA approvals of duloxetine, milnacipran, and pregabalin asked 2569 patients which different medications they had tried for relief of FM symptoms and whether they considered each to be helpful.[59] A total of 44% of patients had ever used hydrocodone plus acetaminophen, and 32% had used oxycodone plus acetaminophen. Of the patients who had used each treatment, 75% considered hydrocodone plus acetaminophen to be helpful, and 67%

considered oxycodone plus acetaminophen to be helpful. Of all the medications used, including nonopioids, hydrocodone preparations were considered to be the most helpful. The duration of opioid therapy was not noted. In contrast, results from a German consumer survey of 1661 patients demonstrated that patients considered treatment with strong opioids to be the most harmful management strategy in terms of adverse effects, and the use of strong opioids did not feature in the top 10 most effective management strategies.[60] This study did not report which opioids were classified as strong or weak.

Physiologic and psychological factors seem to be important in the use of opioids in FM. In a cohort of women undergoing hysterectomy, higher FM survey scores were associated with higher levels of pain in patients taking opioids who continued to report severe pain.[33] In a comparison of patients with FM who were either taking (n=19) or not taking (n=25) opioids, those taking opioids had significantly lower self-efficacy ratings, a measure of patients' confidence in accomplishing specific tasks despite concurrent pain, and significantly higher pain catastrophizing scores, a measure of negative thoughts experienced during pain, with no apparent difference in pain severity between groups.[61] In a large health database study that reported chronic opioid use in 11.3% of 245,758 patients with FM in the United States, demographic and geographic factors were important determinants of opioid use.[49] The authors identified a 5-fold difference in long-term opioid use in the 48 different states assessed, ranging from approximately 4% to approximately 20%. Female sex and previous illicit opioid use were associated with higher rates of use, whereas physician prevalence and FM prevalence were associated with lower rates of use. There was also a significantly negative association between opioid use and the prevalence of the use of code 729.1 of the *International Classification of Diseases, Ninth Revision, Clinical Modification*, the code used to identify FM, in a given geographic area.

McNett et al,[62] in a cross-sectional study of treatment patterns among physician specialties in the management of FM, reported different rates of opioid prescription across different specialties. In a sample of 203 patients, the rate of opioid prescription was 54.4% by primary care physicians, 44.0% by psychiatrists, 39.1% by rheumatologists, and 36.8% by neurologists.

DISCUSSION

These findings suggest that the use of long-term opioid therapy in FM should be discouraged and that it is the duration of opioid treatment rather than the use of strong or weak opioids that is important. There are no randomized clinical trials of opioids in FM, but large population-based surveys and results from tertiary pain clinics have shown no evidence that long-term opioid treatment is effective for FM. Indeed, long-term opioid use in FM has been associated with poorer outcomes than in individuals who are not receiving opioids.[56,57] Furthermore, mechanisms of altered pain processing in FM are not likely to be improved with opioids. In fact, the aggregate studies suggest that the endogenous opioid system may contribute to the hyperalgesia seen in FM, akin to OIH.

Despite these facts, opioids have been prescribed for 10% to 60% of patients with FM in large database sets (Table 1). It might be expected that the more recent availability of 3 FDA-approved medications for FM would diminish earlier reliance on opioids. However, in reports of patients with FM receiving the FDA-approved medications duloxetine, milnacipran, or pregabalin, more than 45% of these patients were still taking opioids.[50] Furthermore, after opioids are prescribed, the likelihood of a patient receiving one of the FDA-approved medications is small.[51] These findings suggest that although the use of FDA-approved medications is increasing, there is sustained or even increasing use of opioids. This may be due to several factors, such as patient demand because they believe that opioids are a stronger or better analgesic[59] or because the FDA-approved medications are not effective for many patients.[9,63] There has also been suboptimal use of effective nonpharmacologic therapies.[8] Opioids, especially for short-term use, may be recommended for carefully selected patients with FM, particularly those with severe FM. The use of opioids in these circumstances is broadly supported by current medical guidelines.[12,14,15]

Fibromyalgia is the prototype for most chronic pain conditions, typically accompanied by sleep disturbances, depression and anxiety,

and catastrophizing.[4] Higher scores on FM criteria surveys characterize a central pain phenotype and have been associated with adverse analgesic outcomes. For example, higher FM scores were associated with increased postoperative opioid consumption and poorer long-term pain reduction after total hip or knee replacement.[31,64]

Physicians in the United States frequently prescribe opioids as part of chronic pain management. In 2012, 82.5 opioid analgesic prescriptions per 100 people were written in the United States.[65] The apparent overreliance on opioids as part of the armamentarium for chronic pain disorders, such as FM, may, in part, be due to the complexity of managing chronic pain conditions[66] and the limited education available to health care professionals.[67-69]

The FM phenotype is prominent in most chronic pain disorders, including low back pain and chronic headaches.[4,70] Psychiatric comorbidity, an important factor in FM and in most chronic pain disorders, predicts the risk of opioid use and misuse.[71] For example, depression was associated with chronic opioid use irrespective of pain severity or physical function.[72] Cautioning health care providers about the misuse of opioids in FM may be the best approach to changing current practice habits. The study by Painter et al[49] reporting significant geographic variation in opioid prescribing for FM suggests an important role for physician education. This study also found a negative correlation of opioid use with a greater regional *International Classification of Diseases* FM diagnosis. The lessons learned from FM suggest that health care providers should stratify patients at risk for chronic pain and avoid opioids in those high-risk individuals.

CONCLUSION

The mechanism of action of traditional opioids predicts their lack of efficacy in FM, and there is no evidence from clinical trials that opioids are effective for the treatment of FM. Moreover, FM guidelines recommend against the use of opioid analgesics. Observational studies indicate that patients who receive opioids have poorer outcomes than those who do not. Nonopioid pharmacologic and nonpharmacologic therapies with demonstrable efficacy are available. In addition, the United States is in the grip of an ongoing public health emergency relating to excess and long-term opioid analgesic use. Despite these issues, opioids are still commonly used to treat FM. Targeting health care providers to change their current practice habits regarding FM may be the best approach to reduce the overuse of opioids, suggesting an important role for physician education. Educating patients about the lack of benefit and potential risks associated with opioid use would also be beneficial. The example of FM provides a cautionary tale for the use of opioids in other chronic pain conditions.

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