MAYO CLINIC

REVIEW

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

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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.

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, 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.

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