Fibromyalgia
Review

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Fibromyalgia: do I tackle you with pharmacological treatments?

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Abstract

Pharmacological approaches are frequently proposed in fibromyalgia, based on different rationale. Some treatments are proposed to alleviate symptoms, mainly pain, fatigue, and sleep disorder. Other treatments are proposed according to pathophysiological mechanisms, especially central sensitization and abnormal pain modulation. Globally, pharmacological approaches are weakly effective but market authorization differs between Europe and United States. Food and Drug Administration–approved medications for fibromyalgia treatment include serotonin and noradrenaline reuptake inhibitors, such as duloxetine, and pregabalin (an anticonvulsant), which target neurotransmitter modulation and central sensitization. Effect of analgesics, especially tramadol, on pain is weak, mainly on short term. Low-dose naltrexone and ketamine are gaining attention due their action on neuroinflammation and depression modulation, but treatment protocols have not been validated. Moreover, some treatments should be avoided due to the high risk of abuse and severe side effects, especially opioids, steroids, and hormonal replacement.

Keywords: Fibromyalgia, Pharmacological treatments, Drugs, Opioids

1. Introduction

Management of fibromyalgia includes patient education, non-pharmacological strategies such as exercise or cognitive behavioral therapy (CBT), pharmacological, and complementary treatments.[27] In this multimodal management, it is important to analyze the efficacy of pharmacological approaches and if this is relevant to prescribe drugs in this context. Fibromyalgia is a complex disorder with a poorly defined pathophysiology, and pharmacological treatments may be proposed according to different targets and rationale: pharmacological treatments may act on pain, on other symptoms, and also on the pathophysiological mechanisms. In the United States, only 3 treatments have received market authorization for fibromyalgia, pregabalin, duloxetine, and milnacipran, and in Europe, currently there is no pharmacological treatment officially dedicated to fibromyalgia. It must be acknowledged that pharmacological treatment has been met, in general, with rather modest rates of success. Real-life data[32] indicate that only a minority of fibromyalgia patients continue taking medications for more than a short period of time due to either lack of efficacy, side effects, or both. Current guidelines published regarding the treatment of fibromyalgia advocate a multidisciplinary approach, combining pharmacological treatment with complimentary modalities, including CBT, aerobic and strengthening physical training, and even meditative movement therapies.[3,23]

2. Pharmacological approaches to treat pain

2.1. Opioids

Evidence of the effectiveness of opioid therapy to treat fibromyalgia pain has been discussed for many years[15,17]: there have been very weak efficacy on nociplastic pain and their use is associated with important risks related to long-term opioid treatment. For that reason, leading pain specialty societies advise that opioids should be avoided for treating fibromyalgia.[23] Moreover, opioids may induce hyperalgesia that may increase allodynia,[4] and prolonged exposure to opioids can cause tolerance and provoke distressing withdrawal symptoms when the drug is necessarily discontinued or the dosage reduced. There is also some potential risk for opioid use disorder, but despite these known risks, opioids are frequently prescribed to this population and are associated with a greater burden of illness.[6]

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2.2. Tramadol

Tramadol, considered a weak opioid agonist, is the exception to the rule of avoiding opioid in fibromyalgia. Tramadol has a mechanism of action related to serotonin reuptake inhibition, clearly demonstrated in rats.[16] In a 91-day study of fibromyalgia patients taking a fixed-dose combination product of 37.5 mg tramadol and 325 mg of paracetamol (acetaminophen), the tramadol–paracetamol patients had significantly less pain and better function than control patients, and no serious adverse events were reported,[5] but very few clinical trials have been performed and results are inconclusive.[10] In daily practice, tramadol is frequently prescribed in fibromyalgia, but there are increasing reports on the tramadol-related risks, especially increase of insomnia and other symptoms.[19] Warnings on drug dependence and withdrawal syndromes are increasing[7] that should make this prescription more guided.

2.3. Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered not really effective in treating fibromyalgia pain.[11] In fact, this is probably true for background chronic pain, but NSAIDs can be proposed for breakthrough pain or exercise-related pain for short-term effects. Since many NSAIDs are available over-the-counter, they are frequently used by the patients, without physicians' prescriptions for acute flares.

3. Pharmacological approaches to treat the disease and different symptoms?

Advances in fibromyalgia studies have caused the European League Against Rheumatism to issue 2017 recommendations that shift away from reliance expert opinion to more evidence-based recommendations.[23] Despite a limited number of studies, low-dose amitriptyline, duloxetine or milnacipran, tramadol, pregabalin, and cyclobenzaprine are considered supported by high-quality evidence in these recommendations while their effect is modest in different dimensions of fibromyalgia[26] (**Table 1**).

3.1. Gabapentinoids

Gabapentinoids (pregabalin and gabapentin) are anticonvulsants that act by reducing the calcium-dependent release of glutamate, norepinephrine, calcitonin gene–related peptide, and substance P. As such, they treat neuropathic pain as well but with some well-known limitations. Their analgesic benefit may be modest, there are potentially treatment-limiting side effects, and not all patients respond to them.[30] There is mixed evidence in the literature about the effectiveness of gabapentinoids against painful symptoms of fibromyalgia. The most frequently reported side effects with pregabalin and gabapentin are dizziness, somnolence, headache, and edema, with recent alert from the Food and Drug Administration (FDA) about respiratory depression. Overall, gabapentin and pregabalin offer greater pain control for fibromyalgia patients than placebo, the response appears to be somewhat dose dependent, and they are not durable since about a third of patients losing response at around 6 months.[8,30] An important gap in our understanding of fibromyalgia treatments is the absence of head-to-head studies of various agents in this population.

3.2. Mixed antidepressants

Amitriptyline is a tricyclic antidepressant that is often recommended as monotherapy or part of a combination regimen to treat fibromyalgia pain. One of the first tricyclic antidepressants to be approved to market, amitriptyline inhibits serotonin and norepinephrine reuptake and may be active at histaminergic, muscarinic, and norepinephrine receptors. Amitriptyline is effective against 6 of the main domains of fibromyalgia: pain, sleep disturbances, fatigue, affective symptoms, functional deficits, and cognitive impairment and has a ubiquitous action. Although there is a paucity of studies, amitriptyline at low doses in the range of 10 to 75 mg/d is considered effective in managing fibromyalgia pain.[28] Concerns with amitriptyline in this population are tachyphylaxis and cardiotoxic effects. Cyclobenzaprine is also proposed for many years in some countries (United States) where is it available, and new sublingual tablets formulation has been recently proposed in fibromyalgia with a request of specific indication from the FDA, after a positive clinical trial.[21]

Serotonin and norepinephrine reuptake inhibitors have been shown to be effective in decreasing pain intensity in patients with fibromyalgia.[2] Duloxetine is described as a balanced serotonin and noradrenaline reuptake inhibitor and is indicated to treat diabetic peripheral neuropathy, major depressive disorder, and urinary stress incontinence.[22] It has been used to manage fibromyalgia pain both alone or in combination with other drugs. The typical dose range is 60 to 120 mg per day. The FDA has issued a black box warning about suicidality associated with duloxetine, and its other potentially serious side effects include tachycardia and hypertension.[13]

Table 1

Efficacy (Effect-size) of pharmacological treatments on Fibromyalgia core domains.

Treatment	Pain	Sleep disturbance	Fatigue	Affective symptoms	Functional deficit	Cognitive impairment
	Effect size (95% CI)	Effect size (95% CI)	Effect size (95% CI)	Effect size (95% CI)	Effect size (95% CI)	Effect size (95% CI)
Amitriptyline	**0.82** (0.36,1.28)	**0.69** (0.41 to 0.96)	**0.58** (0.05 to 1.11)	0.08 (−0.27 to 0.43)	0.37 (−0.01 to 0.74)	—
Citalopram	0.12 (−0.49 to 0.72)	0.29 (−0.16 to 0.74)	−0.03 (−0.48 to 0.41)	0.15 (−0.30 to 0.60)	—	—
Duloxetine	0.36 (0.19 to 0.53)	0.24 (0.06 to 0.43)	0.22 (0.07 to 0.36)	0.23 (0.10 to 0.35)	0.34 (0.18 to 0.49)	0.37 (0.22–0.51)
Fluoxetine	**0.67** (0.01 to 1.34)	0.28 (−0.09 to 0.65)	0.30 (−0.07 to 0.67)	0.48 (0.10 to 0.85)	0.31 (−0.06 to 0.69)	—
Growth hormone	**1.35** (0.50 to 2.20)	—	—	—	**1.24** (−0.36 to 2.84)	—
Milnacipran	0.22 (0.15 to 0.30)	0.11 (0.00 to 0.21)	0.13 (0.06 to 0.21)	0.12 (0.04 to 0.19)	0.15 (0.08 to 0.23)	0.17 (0.09–0.24)
Pregabalin	0.31 (−0.06 to 0.67)	0.57 (0.42 to 0.71)	—	—	0.19 (−0.02 to 0.39)	—
Sodium oxybate	0.44 (0.31 to 0.58)	**0.47** (0.28 to 0.66)	**0.48** (0.35 to 0.60)	*	*	*

— The domain was not measured in the study or not enough information was provided to calculate effect size.
Bolded values indicate effect sizes >0.5.
Data from meta-analysis from Perrot and Russel, *Eur J Pain* 2014.[26]
* The effect size for the domain was not calculated, data available from only one study.

Milnacipran, at doses of 100 to 200 mg/d, is a serotonin–norepinephrine reuptake inhibitor and is one of only a handful of agents expressly developed to treat fibromyalgia.[18] While it reduces pain and fatigue, its benefits may be modest and side effects include sleep-related disturbances and depression.[9]

There are few head-to-head studies of fibromyalgia agents. A meta-analysis of various fibromyalgia treatments indirectly compared pregabalin, amitriptyline, and duloxetine at various dosages and reported that amitriptyline 25 mg had superior results, followed next by pregabalin 450 mg.[2]

4. Recent approaches

4.1. Ketamine

Ketamine has been proposed in chronic pain states and especially in fibromyalgia since it may act on nociception-dependent central sensitization via N-Methyl-D-Aspartate Receptor blockade. Clinical studies revealed a short-term reduction—only for a few hours after the infusions—in self-reported pain intensity with single, low-dose, intravenous ketamine infusions. Case studies suggest that increases in the total dose of ketamine and longer, more frequent infusions may be associated with more effective pain relief and longer-lasting analgesia. Another neurotransmitter release may be contributing to this outcome. A systematic review suggests a dose response, indicating potential efficacy of intravenous ketamine in the treatment of fibromyalgia.[25] In their double blind study, Noppers et al.[24] have demonstrated that efficacy of ketamine was limited and restricted in duration to its pharmacokinetics. The authors argue that a short-term infusion of ketamine is insufficient to induce long-term analgesic effects in patients with fibromyalgia.

4.2. Ozone

A recent study in 65 patients with fibromyalgia treated with a novel form of ozone therapy found >50% symptomatic relief in 70% of the patients with no side effects reported.[31] Ozone therapy is being used to treat a number of chronic conditions and appears to exert a mild state of controlled oxidative stress that upregulates the antioxidant system and modulates the immune system.[31]

4.3. Cannabinoids

Despite legalization efforts and a wealth of new research, clinicians are still not confident about how to prescribe cannabinoids, what forms of cannabinoids and routes of administration to recommend, or how well cannabinoids will work for fibromyalgia symptoms.[1] Cannabinoid receptors, known as CB1 and CB2, are part of the body's endocannabinoid system. CB1 receptors are mostly centrally located and mediate euphoric and analgesic effects. CB1 can also reduce inflammation and blood pressure. CB2 receptors, on the other hand, are mainly located in the periphery and have immunomodulatory and anti-inflammatory effects. The endocannabinoid system is active in both central and peripheral nervous systems and modulates pain at the spinal, supraspinal, and peripheral levels.[29] Cannabinoids may be effective in addressing nociplastic pain.[16] While there is promising evidence that cannabinoids may indeed be a safe and effective treatment for fibromyalgia symptoms, there are limitations with their use, particularly the most appropriate form to use, dosing, and potential adverse effects particularly with long-term exposure.[20] While the general public is increasingly interested in cannabis as an analgesic alternative, there is evidence of cannabis use disorder and comorbid mental health conditions associated with prolonged exposure. There are no guidelines for their use, and there is also a concern about recreational use and abuse.

It should be noted that cannabinoids are relatively contraindicated for those under the age of 21 years and in people with a history or active substance use disorder, mental health condition, congestive heart failure or cardiovascular disease/risk factors, and people suffering palpitations and/or chest pain. Cannabinoids may be associated with mild to severe adverse events, such as dizziness, drowsiness, hypotension, hypoglycemia, disturbed sleep, tachycardia, cardiac palpitations, anxiety, sweating, and psychosis.

On balance, cannabinoids may rightly be considered for managing fibromyalgia symptoms despite the lack of evidence, particularly for patients suffering chronic painful symptoms for which there is little other source of relief. When effective, cannabinoids may be opioid-sparing pain relievers.

4.4. Low-dose naltrexone

At doses of 50 to 100 mg, naltrexone is approved in the United States to treat opioid or alcohol use disorder and opioid dependence, but at very low doses of 2.5 to 4.5 mg, the agent may have analgesic and anti-inflammatory properties. In a systematic review of studies of low-dose naltrexone in patients with fibromyalgia, the regimen was found to be effective in controlling fibromyalgia symptoms with no severe adverse events reported.[33] A recent study did not confirm this efficacy[12] This off-label use of low-dose naltrexone is not widely prescribed or well known among clinicians and is currently limited to US prescribers.

5. Drugs that we should not use

According to side effects, to the risk of misuse and abuse, some treatments are not recommended. In this context, we may emphasize that opioids and steroids are not treatments that should be prescribed in fibromyalgia, even if they may demonstrate some effects, especially in the short term.[14] Long-term side effects are deleterious, both for opioids and steroids. This has already been discussed in the text.

6. Future pharmacological approaches

New potential treatments being explored, such as fremanezumab already registered for migraine, rozanolixizumab proposed in myasthenia, ASP8062, and ASP0819, are currently in phase 2 trials. Studies with esketamine are also developed. Research has shown that there is a link between chronic pain conditions, such as fibromyalgia, with low-grade intestinal inflammation and an imbalance in the bacterial composition and activity in the gut, known as dysbiosis; thus, some treatments acting on microbiota are also considered.

In conclusion, pharmacological approaches have limited efficacy in fibromyalgia. Effect on pain is weak, and mainly on short term. Global effect is also weak. In fact, there is a need to change the views on fibromyalgia; pain is not the unique symptom, and fatigue and cognitive disorders have also an important impact on quality of life of patients.

(1) Clinical trials to demonstrate some efficacy in fibromyalgia should be adapted to the disease and demonstrate a significant impact on quality of life rather than on single symptoms like pain, sleep, cognitive disorders, and associated symptoms.

(2) More importantly, clinical trials should demonstrate that pharmacological approaches are useful, in combination with other approaches, like exercise or CBT. They should demonstrate that there is a synergistic effect of the combination within pharmacological approaches but also with non-pharmacological therapies, and which synergistic effect is more effective.

Disclosures

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