Management of fibromyalgia: Current pharmacologic therapies & recommendations for therapeutic optimisation

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Abstract

Introduction
Fibromyalgia is a chronic musculoskeletal pain disorder characterised by complex underlying pathophysiological mechanisms, a complexity that requires careful adjustment of treatment tailored to patient’s needs. This article reviews the various pharmacologic options currently used or are under investigation for the treatment of fibromyalgia.

Discussion
Drugs currently used in clinical practice for the treatment of fibromyalgia possess varying degrees of evidence for efficacy. Antidepressants and calcium alfa2delta blockers (mainly pregabalin) are the agents with the highest level of evidence in fibromyalgia. Drugs whose evidence of efficacy that is less pronounced include sodium oxybate, 5-HT3 antagonists (tropisetron and dolasetron), and pramipexole. On the other hand, analgesics (excluding the combination of tramadol and paracetamol), antipsychotics and sedative-hypnotics had less or no benefit in fibromyalgia. The combination of two or more drugs with different mechanisms of action and non-overlapping side-effects profile can be necessary in the most severely affected patients.

Conclusion
As the benefits of the pharmacologic agents for the treatment of fibromyalgia are limited, a multidisciplinary treatment plan that includes a combination of pharmacologic and non-pharmacologic therapies is recommended in the management of the disease. Adequate communication techniques should be adopted to potentiate placebo and minimize nocebo effects in clinical practice.

Introduction
Fibromyalgia syndrome is a musculoskeletal pain disorder characterised by chronic generalised pain and several other somatic and psychological symptoms, such as fatigue, stiffness, sleep disturbances, depression, anxiety, and cognitive dysfunction. It is a prevalent syndrome affecting 2% to 5% of the general population, with higher prevalence among females although the exact female/male ratio has been recently questioned. The prevalence rates are influenced by the diagnostic criteria of fibromyalgia, which were first formulated in 1990 by the American College of Rheumatology (ACR), requiring the presence of tenderness in at least 11 out of 18 musculoskeletal tender points lasting a minimum of 3 months. These criteria were modified by the ACR in 2010 to assess pain with the Widespread Pain Index (WPI) without the requirement to explore tender points, and add a Symptom Severity (SS) Scale that evaluates the intensity of fatigue, sleep problems, and cognitive dysfunction, and also takes into consideration the presence of other somatic symptoms.

Fibromyalgia is classified as a central sensitization syndrome, which is associated with abnormal pain processing manifested in the presence of hyperalgesia, allodynia and referred pain. However, the exact pathophysiological mechanisms underlying the disease are not fully understood yet, despite the recognition of several genetic and environmental factors involved in fibromyalgia development.

The complex clinical presentation of patients with fibromyalgia and the unclear pathophysiological mechanisms underlying the disease complicate the attempts toward formulating a clear treatment plan in the management of this syndrome. However, several treatment guideline recommendations for the management of fibromyalgia are currently available and a consensus exists about the competence of a multimodal approach in the treatment of fibromyalgia, through the combination of both pharmacologic and non-pharmacologic therapies. This article reviews the different pharmacological treatment options available for the management of fibromyalgia syndrome.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in the studies.

The use of medications on “off-label” basis for the management of fibromyalgia is frequent due to the limited number of drugs approved by the drug regulatory authorities. Only three drugs have been authorised by the U.S. Food and Drug Administration (FDA) for their use in fibromyalgia: pregabalin, duloxetine, and milnacipran and none by the European Medicines Agency (EMA). A focus on the major classes of drugs currently used in the management of fibromyalgia is discussed below.

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Antidepressants

Antidepressants have been shown to be effective in the treatment of different chronic pain conditions such as neuropathic pain, headaches, cancer pain, lower back pain, or irritable bowel syndrome in addition to fibromyalgia. Antidepressants of various classes such as tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs) have been extensively studied in the treatment of fibromyalgia.

TCAs, the oldest class of antidepressants used in the treatment of fibromyalgia, have been shown to be effective in fibromyalgia treatment used at low doses (<75 mg/day). In a meta-analysis, they were associated with significant improvement in pain, sleep disturbances, fatigue and health-related quality of life in patients with fibromyalgia, and their effect sizes in improving pain and sleep were larger compared with other classes of antidepressants. The superiority of the TCA amitriptyline was also evident in another meta-analysis that compared it with duloxetine and milnacipran; however, the methodological limitations of amitriptyline studies prevented the authors from acknowledging it as the gold standard in the treatment of fibromyalgia. Cyclobenzaprine, a centrally acting muscle relaxant structurally related to TCAs, has also demonstrated effectiveness in reducing pain and improving sleep in patients with fibromyalgia.

SNRIs are characterised by their selective inhibition of serotonin and norepinephrine reuptake, a characteristic that confers them better tolerability and side-effects profile compared with the non-selective TCAs. Duloxetine and milnacipran are the SNRIs most frequently used in the treatment of fibromyalgia. Although venlafaxine was the first SNRI studied in fibromyalgia, it is not usually used in clinical practice for the management of this condition given that only two uncontrolled studies investigating its use in fibromyalgia have been published in contrast with the large amount of evidence available for duloxetine and milnacipran. Duloxetine (60-120 mg/day) and milnacipran (100-200 mg/day) have been linked to beneficial outcomes in the treatment of fibromyalgia, improving pain, sleep, fatigue, depression, and health-related quality of life. In another meta-analysis that studied the effects of each SNRI separately, duloxetine and milnacipran were shown to significantly reduce pain, depressive symptoms and improved quality of life; however, only duloxetine resulted in significant improvements in sleep disturbances, and fatigue was significantly reduced by milnacipran exclusively.

Data concerning the effectiveness of SSRIs in the treatment of fibromyalgia confirm previous findings of their limited role in the treatment of other chronic pain conditions. They have been shown to improve pain, sleep, fatigue, depression, and quality of life, although with small and non-substantial effect sizes. Their limited side-effects profile consequent to their selectivity to serotonin receptors designates them as an alternative in case of non-tolerability to other antidepressants.

Trazodone, an old second-generation antidepressant, is characterised by a sedative hypnotic activity at low doses. It has been shown, in two uncontrolled studies, to improve sleep quality, anxiety, and depression but to lack efficacy in relieving pain.

Anti-epileptics

Anti-epileptics are widely used in the treatment of chronic pain, namely neuropathic pain conditions such as post-herpetic neuralgia, diabetic peripheral neuropathy, and trigeminal neuralgia. Evidence of efficacy in the treatment of fibromyalgia is exclusively limited to the calcium channel modulators class of anti-epileptics, pregabalin, and gabapentin. Their effect in pain modulation is mediated through the inhibition of α2δ voltage-gated calcium channel, leading to a blockade in the release of excitatory neurotransmitters involved in the process of pain perception. In a meta-analysis studying the effect of gabapentin and pregabalin in fibromyalgia, a strong evidence for their efficacy in improving pain, sleep disturbances and health-related quality of life was found, but with small effect sizes; on the other hand, they were associated with a non-substantial effect on fatigue and anxiety, and lacked effect on depression. Pregabalin was the first drug to be approved by the FDA in the treatment of fibromyalgia in 2007. Pregabalin’s stronger evidence for efficacy in fibromyalgia and its surpassing pharmacokinetic and pharmacodynamic profiles designate it as the more desirable anti-epileptic agent in fibromyalgia compared with gabapentin except in cases of non-tolerability, a condition that advocates gabapentin use.

Analgesics

Non-steroidal Anti-inflammatory Drugs

Although NSAIDs are widely used among patients with fibromyalgia, limited evidence exists about their efficacy in this condition. This can be explained by the non-inflammatory nature of the disease that eliminates a direct potential benefit of these compounds on the pathogenesis of fibromyalgia. Subsequently, NSAIDs are not widely examined in fibromyalgia and investigations concerning their use in fibromyalgia were limited to a small number of controlled clinical trials that have demonstrated little or no efficacy in the long-term treatment of the disease.

Opioids

Opioids are widely used in the treatment of fibromyalgia despite the lack of evidence for efficacy. On the contrary, a general impression that they are not effective in fibromyalgia exists in clinical practice. On that
basis, besides their side effect profile and concerns about potential abuse, it is advised to avoid opioids’ use in fibromyalgia. Interestingly, opioid antagonists have produced beneficial effects when used in fibromyalgia, where low-dose naltrexone, a competitive opioid receptor antagonist has been associated with significant reduction of pain, improved general satisfaction with life and improved mood, however, neither fatigue nor sleep were improved.

Other Analgesics

Tramadol and tapentadol are two structurally related centrally acting analgesics that combine an agonistic action on μ opioid receptors with monoamines uptake inhibition. Compared with tramadol, tapentadol has higher affinity toward μ opioid receptors and a selective inhibition of noradrenaline reuptake with minimal effect on serotonergic reuptake. In a double-blind placebo controlled trial, the combination of tramadol-acetaminophen led to a significant reduction in pain among patients with fibromyalgia, in addition to a significant improvement in sleep, depressed mood, and health-related quality of life. However, it remains preferable to avoid the chronic use of tramadol sparing it to the periods of flare-ups. On the other hand, tapentadol has not been studied in fibromyalgia; yet, its efficacy results in the management of other chronic pain conditions are encouraging and point toward a potential promising role in fibromyalgia treatment.

Antipsychotics

Considering their analgesic effect and their role in improving sleep problems, a postulation of a possible role for antipsychotics in fibromyalgia has been suggested. However, most of the studies investigating the role of first or second generation antipsychotics such as olanzapine, quetiapine, amisulpride, and levomepromazine in fibromyalgia have been uncontrolled. To date, only quetiapine has been evaluated in randomised controlled trials and only preliminary results have been published; additional information is needed before concluding if this drug can be considered as a useful therapeutic alternative for the treatment of fibromyalgia.

Other Drugs

Sodium Oxybate

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate, is an endogenous metabolite of the inhibitory neurotransmitter gamma-aminobutyric acid. It gained an FDA orphan drug status for the treatment of cataplexy and daytime sleepiness in patients suffering from narcolepsy. The use of sodium oxybate in fibromyalgia has been investigated in four randomised clinical trials. It has improved scores of the different pain scales, fatigue, sleep disturbances, fibromyalgia impact questionnaire and the patient global impression of change. However, and due to the concerns of potential abuse, it failed to gain the FDA approval in the treatment of fibromyalgia.

Sedative-hypnotics

Clinical trials conducted to investigate the role of sedative hypnotics in fibromyalgia point toward a limited role of these agents in the treatment of fibromyalgia. Benzodiazepines such as alprazolam, bromazepam, and temazepam as well as two non-benzodiazepines GABA-A agonists zolpidem and zopiclone only improved sleep without significant improvement of other symptoms such as pain or fatigue.

Dopamine Agonists

In view of the analgesic effects of dopamine, a suggestion of beneficial outcomes that could be attained from the use of dopamine agonists in fibromyalgia was considered. However, only pramipexole has induced, in a randomised clinical trial, improvements in pain, fatigue and global well-being, whereas, neither ropinirole nor the novel extended-release formulation of ropinirole were capable of significantly reducing pain among patients with fibromyalgia compared to placebo.

5-HT3 Antagonists

Considering the analgesic effects of 5-HT3 antagonists, several clinical trials investigated the role of tropisetron orally and intravenously for the treatment of fibromyalgia, where both routes of administration have been linked to a significant reduction of pain. Similarly, intravenous dolasetron significantly reduced pain in a 12-month randomised clinical trial in patients with fibromyalgia. These agents have been recommended primarily to patients presenting with substantial pain levels but lacking psychological distress.

Designing the Treatment Plan in Fibromyalgia: Mono or Polytherapy?

The broad range of symptomatology spectrum in fibromyalgia complicates the attempts of finding a gold standard agent capable of alleviating the various symptoms of this syndrome. As commented above, the efficacy of pharmacologic agents in fibromyalgia is limited. In a meta-analysis that compared the three drugs approved by the FDA in fibromyalgia (pregabalin, duloxetine, and milnacipran), only small effect sizes (<0.40) were obtained in alleviating the various symptoms assessed (pain, fatigue, sleep, depressed mood, and health-related quality of life) with each of the three drugs considered. These facts easily explain that in clinical practice, polytherapy is seen in a considerable proportion of patients with fibromyalgia, although a very limited number of clinical trials have investigated the efficacy and safety of drug combinations in fibromyalgia. This constitutes a challenging issue for healthcare professionals, who need to take their decisions about drug combinations.
based on solid pharmacological knowledge of each agent, so that efficacy is maximized and overlapping side effects are minimized.\(^3\)

Placebo and "Nocebo" effects: Potential Influence in Fibromyalgia

Placebo effect is defined as the beneficial outcome(s) experienced by a patient following a nonspecific treatment, while nocebo refers to the negative outcome(s) experienced and they are both caused by cognitive factors relating to the patient’s perception of the particular intervention rather than the intervention itself. In fibromyalgia, substantial magnitudes of placebo and nocebo responses were seen in a meta-analysis of 18 trials of drugs applying for approval for fibromyalgia (duloxetine, milnacipran, pregabalin, and sodium oxybate), with a pooled estimate of 50% pain reduction by placebo reaching 18.6% (95% CI 17.4% to 19.9%) and a pooled estimate of drop out due to adverse events in placebo reaching 10.9% (95% CI 9.9% to 11.9%)\(^3\). In another meta-analysis, 67.2% (95% CI 51% to 81.5%) of 2,026 placebo treated patients with fibromyalgia reported at least one adverse event, and 9.5% (95% CI 8.3% to 10.9%) discontinued placebo treatment because of intolerance, where nocebo dropouts in fibromyalgia were fourfold and two-fold higher than those seen in multiple sclerosis treatment and migraine preventive treatment, respectively.\(^3\)

Consequently, a considerable bias to the results of trials in fibromyalgia could be attributed to placebo and nocebo effects, which suggests the need for optimizing clinical trial designs and employing adequate methodology to minimize the confounding impact of such effects. In contrast to clinical investigators, placebo effect constitutes a potential add-on therapeutic tool for clinicians who try to maximize it through warm and empathic interactions with patients. On the other hand, nocebo effects are undesirable for both clinicians and clinical investigators who aim to reduce them through authorized patient concealment of side effects, educating patients about the possibility of nocebo responses, in addition to reassuring, empathetic and supportive communication.\(^3\)

Conclusion

Fibromyalgia is a complex musculoskeletal syndrome whose clinical management represents a challenging and difficult task for healthcare professionals. Pharmacologic therapy should be tailored based on the individual patients’ symptoms using one or several drugs simultaneously. However, drugs alone only induce a limited benefit in fibromyalgia. A multidisciplinary treatment plan, including a combination of pharmacologic and non-pharmacologic therapies has shown to be effective and therefore should be adopted. The relevance of placebo and nocebo effects in fibromyalgia requires the use of adequate communication techniques to potentiate placebo and minimize nocebo effects in clinical practice.

References

Critical review