

ORIGINAL ARTICLE

Fibromyalgia syndrome: the pharmacological treatment options

Il trattamento farmacologico della sindrome fibromialgica

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RIASSUNTO

Il trattamento farmacologico della sindrome fibromialgica (FM) si è gradualmente arricchito di nuove molecole; tuttavia, nessun farmaco da solo è in grado di controllare completamente la costellazione dei sintomi che caratterizzano tale sindrome. Attualmente non è possibile trarre conclusioni definitive sul migliore approccio farmacologico per trattare la FM, poiché i risultati degli studi clinici controllati presentano limitazioni metodologiche e vi è una consistente eterogeneità nelle strategie terapeutiche, che rendono gli studi di difficile confronto. Una varietà di trattamenti farmacologici, che comprendono antidepressivi, farmaci antiinfiammatori non steroidei (FANS), oppioidi, sedativi, rilassanti muscolari e anti-epilettici vengono utilizzati per trattare la FM con risultati contrastanti. In questa review, si parlerà principalmente dei farmaci che hanno mostrato i risultati clinici più significativi. La natura della FM suggerisce che un approccio terapeutico a più livelli, sia farmacologico che non farmacologico, sembra costituire attualmente la decisione terapeutica più appropriata.

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INTRODUCTION

Fibromyalgia (FM), also known as fibromyalgia syndrome (FMS), is a frequently observed systemic disorder characterized by widespread musculoskeletal pain (1, 2). Its prevalence in the general

population is 1-3%, and it is more common among females than males. The American College of Rheumatology (ACR) classification criteria defines it as widespread pain with patients endorsing at least 11 of 18 tender points as painful (3). Although its defining feature is chronic, widespread pain, FM patients may also have a number of other symptoms including sleep disturbance, fatigue, irritable bowel syndrome, headache and mood disorders (1).

Current evidence advocates a multifaceted program emphasizing patient education, medications for im-

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proving symptoms, and aggressive use of exercise and cognitive-behavioural approaches to retain or restore function (4-6). Physicians and patients should be educated about current theories regarding the underlying pathophysiologic mechanisms of FM, and then set realistic goals for all modalities of treatment.

However, it is not possible to draw definite conclusions concerning the best approach to managing FM because results of randomized clinical trials present methodological limitations, and therapeutic programs are consistently heterogeneous, which renders them difficult to compare (7,8). However, a variety of pharmacological treatments, including analgesics, antidepressants, antiepileptics and many other drugs have been used to treat symptoms of FM with mixed results (8). In this review, we will discuss those drugs that have produced the most significant clinical results in treating FM patients.

Analgesics

The use of steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) in FM has had disappointing outcomes (1, 8). NSAIDs, which are commonly used for arthritic conditions, may be less effective for FM because pain associated with FM is not caused by muscle or joint inflammation. There is no scientific evidence that NSAIDs are effective when used alone in FM patients, although they may be useful adjuncts for analgesia when combined with tricyclic medications (1); the combination of NSAIDs with benzodiazepines, however, gave inconsistent results (1, 7-9).

The central nervous system (CNS) mechanisms for the disorder, specifically, central sensitization, central disinhibition and a dysfunctional hypothalamic-pituitary-adrenal axis, could justify the relatively reduced efficacy of NSAIDs and opioids, the latter being more effective for "peripheral" pain (7). However, NSAIDs can be helpful in reducing pain that flares with excessive physical activity, tendinitis or bursitis; but they should be used only as needed to avoid side effects. COX₂ inhibitors have much fewer side effects, but have less efficacy in pain.

Acetaminophen acts differently for FM patients; it has a degree of strength for FM and is safe for use over long periods (9). Wolfe et al. surveyed rheumatic disease patients about their preferences for NSAIDs versus acetaminophen in terms of efficacy and side effects (10). There was a considerable and statistically significant preference for

NSAIDs among patients; but the authors stress that if safety and costs are issues, then the recommendation of the American College of Rheumatology that acetaminophen be the first choice, primarily for mild pain, seems appropriate given the long duration of safe use (11).

The use of NSAIDs or acetaminophen, with or without opioids, is always justified when patients who already suffer from FM have other peripheral sources of pain (osteoarthritis, inflammatory arthritis, degenerative disk disease) (11).

Opioids are meant to improve function in FM patients who are impaired by pain, even though there is an open debate about their usefulness and safety as a "specific" medication for fibromyalgia patients (12-14).

Few clinical trials exist that address the use of opioids to treat persistent pain in FM patients, but those trials show that these drugs are helpful for relieving FM pain; moreover, opioids can help to reduce *sleep disturbances*, anxiety and *depression* and to increase mobility and enjoyment of life (13, 15).

Potential side effects tend to decline over time, and addiction has been disproven by the scientific literature.

Opioids that are available on the Italian market include codeine, tramadol, oxycodone, hydromorphone, morphine, buprenorphine and fentanyl.

Furlan et al. (15) conducted a meta-analysis of 41 randomized trials (6019 patients, 7% affected by FM) to evaluate the efficacy of opioids ranging in duration from 1-16 weeks. They found that opioids were more effective than placebo for both pain and functional outcomes; and strong opioids were significantly superior to naproxen and nortriptyline, but only for pain relief. Despite the relative brevity of the trials, more than 1/3 of the participants abandoned treatment (15).

Tramadol, in particular, was beneficial for FM patients (8, 9, 12-14). It is an atypical pain reliever that differs from other narcotics in its action on the central nervous system, specifically, on reuptake of serotonin and norepinephrine. Its most common side effects are drowsiness, dizziness, constipation and nausea, and it should not be given in combination with tricyclic antidepressants.

Tramadol, used alone or in combination with acetaminophen, is commonly prescribed for relief of fibromyalgia pain (16-18) in a dose of 200-300 mg/d. A small double-blind, placebo-controlled trial initially suggested that tramadol was effective and well-tolerated in patients with FM (16).

A larger RCT (n=69) reported decreased visual analogue pain scores, improved pain relief and decreased pain threshold after tramadol treatment. Another study compared a combination of 37.5 mg tramadol/325 mg acetaminophen tablets with placebo in 315 patients with FM. Pain and physical functioning improved significantly in the tramadol/acetaminophen-treated subjects. The average dose of tramadol/acetaminophen was 4.0 ± 1.8 tablets per day with an attrition rate of 19% (n=29) due to adverse events. The attrition rate in the placebo-treated subjects was 12% (n=18). This study suggested that the combination of tramadol/acetaminophen was effective in treating FM patients' pain without causing serious adverse events (17).

Bennett et al. (18) examined efficacy data to compare the impact of tramadol/acetaminophen versus placebo on quality of life; the authors concluded that moderate-to-severe fibromyalgia pain significantly impairs health-related quality of life (HRQOL) in placebo-treated patients.

A recent study has demonstrated that transdermal buprenorphine, a strong opioid, has beneficial effects on severe widespread pain (VAS >6/10), but it is less effective on other symptoms that are typical of the disease (19).

FM that is diagnosed according to the ACR criteria seems to include patients with different pain processing mechanisms. Screening for disorders that may initiate or exacerbate symptoms of FM is critical; if comorbid disorders are not identified early and treated appropriately, therapies that target FM, only, may be ineffective.

In fact, there is a subset of FM patients that do not respond to opioids, while other patients, who may have overlapping conditions such as diabetes, chronic myofascial pain, temporomandibular joint disorder, arthritis, degenerative disc disease and other diseases, may benefit quite significantly from opioids (8, 18).

Physicians should obtain a careful medical and psychological profile of the patient before prescribing opioids (17, 18). Therapy with these drugs should be initiated after an adequate trial of acetaminophen for nociceptive pain and of tricyclic antidepressants or anticonvulsants.

To obtain a synergistic effect on analgesia, some patients may be prescribed combinations of different pain relievers (multimodal analgesia) with different effects on pain pathways, but not for managing side effects. Patients should be asked to give informed consent for treatment; even though it is

not necessary for legal purposes, it would help to educate patients and give them a sense of responsibility (18).

It is appropriate to increase doses of immediate-release opioids slowly until pain reduction is achieved and then switch patients to controlled-release opioids, considering that most patients with chronic, non-malignant pain can be managed with <200-300 mg/d of morphine (or equivalent).

When opioids prove to be necessary, they must, of course, be used with extreme caution. Patients should be evaluated periodically for continuing pain relief, side effects and indications of dependence. They must be closely monitored, must agree to seek psychotherapy and must complete a signed agreement to communicate with a single prescribing physician and a single dispensing pharmacy.

As with any chronic pain syndromes, patients should be carefully selected for opioid therapy, and a plan for appropriate follow-up and monitoring for pain reduction, outcome improvement, side effects and misuse should be clearly outlined. The interdiction of all opioid medications is inappropriate because some patients cannot achieve a reasonable quality of life and daily functioning with any other treatment.

Harris, et al. (20) have tried to investigate the apparent insensitivity of FM patients to opioids. Using positron emission tomography (PET), they found that FM patients, compared to healthy, matched controls, had reduced μ -opioid-receptor (MOR)-binding potential (BP) in the nucleus accumbens, the anterior cingulate and the amygdala. These areas of the brain are known to play a role in pain modulation (14).

These findings indicate altered endogenous opioid analgesic activity in FM and suggest a possible explanation for the reduced efficacy of exogenous opioids in this population.

Antidepressants

The treatment of pain requires a multimodal approach that has to consider not only somatic aspects (i.e., pain onset, location, quality, quantity, duration, aggravating and alleviating factors), but also emotional aspects (i.e., mood and anxiety), cognitive aspects (i.e., coping styles, beliefs about pain), and environmental aspects (i.e., social context and patients' relationships) (1, 2, 8). The hypothesis that pain, anxiety, chronic stress and depression share common pathogenetic backgrounds which are represented by neurotransmitters and immune response is noteworthy. As such, depression must

be considered as a systemic disease that is related not only to neurotransmission imbalance, but also to other neurotrophic, neurosteroidal, CNS hormonal modifications and diffuse, autonomic, immunologic, and metabolic somatic changes (8, 21). According to this hypothesis, antidepressants restore neurotransmitter levels and modulate receptor expression in the hypothalamus, which normalizes hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (18, 1). An over-activation of the HPA axis is observed in depression and in chronic stress, both of which are frequently present in patients with long-term pain disorders. Conversely, the response to stress is considered to play a crucial role in the pathogenesis of several syndromes, such as FM, chronic fatigue syndrome and irritable bowel syndrome (22, 23). Similarly, autonomic system alterations, such as sympathetic overactivity, are present in both depression and FM (21). Finally, pro-inflammatory cytokines within the CNS play a role in the pathophysiology of mood disorders (and pain), and modulating these cytokines via chronic antidepressant treatment contribute to improve depression (and pain) (24).

Several studies reported high frequency of mood disorders in FM patients (25, 26) compared to controls (27). Short-term clinical studies have shown efficacy for antidepressants in the treatment of FM (28).

Abnormalities in central monoaminergic neurotransmission that are observed in depression might play a role in FM pathophysiology because dysfunction of 5-HT- and NE-mediated descending pain-inhibitory pathways is an important mechanism related to the pain experienced by FM patients. Antidepressants that increase 5-HT and NE-mediated neurotransmission are commonly used to treat FM and other chronic pain conditions, particularly neuropathic pain. Inhibition of both the 5-HT and NE reuptake transporters using tricyclic anti-

depressants (TCA) or SNRIs (serotonergic and noradrenergic reuptake inhibitors), seems more effective in treating pain, and FM, in general, than inhibition of either transporter alone using selective serotonergic (SSRIs) or noradrenergic (NARIs) reuptake inhibitors (29-31).

However, the efficacy of TCAs is counterbalanced by side effects (32, 33), while the better-tolerated SSRIs demonstrate less effectiveness in treating fibromyalgia (34-37).

Antidepressants acting both on NE and 5HT induce a contextual increase of the endogenous opioid system response that raises the pain threshold at the periaqueductal level and increases the gate control of nociception at the spinal cord level (38). Antidepressants usually produce a fast, direct analgesic effect (on opioid, enkephalinergic, substance P) that is independent of mood state; it first appears after a few hours and can be achieved with low doses.

After a longer period of 2-3 weeks, a more robust analgesic effect develops when antidepressants have a more profound influence on mood and anxiety, and the affective and cognitive components of pain become regulated. This effect can only be produced with full doses that are easier to achieve with the new generation of antidepressants, such as SSRIs and SNRIs (39, 40).

Concerning the use of antidepressants in fibromyalgia, Perrot and colleagues (41) identified forty-nine publications on the use of antidepressants to treat painful rheumatologic conditions (including 37 studies and 12 meta-analyses) that were considered valid and used to develop the following considerations: the analgesic effect is higher for TCAs than SSRIs; clear evidence concerning dose-response does not exist; the onset of action occurs within a week; the route of administration is oral; and side effects are more prevalent in TCAs than SSRIs. Unfortunately, this review included studies

Table 1 - Summary of the controlled studies of dual reuptake inhibitors (SNRI).

Authors	References	Drug	N. Pts	Weeks	Dose	Outc.	Results
Arnold, 2004	43	DUL vs PLA	207	12	120	FIQ	DUL > PLA
Russell, 2008	44	DUL vs PLA	520	24	20-120	BPI PGI	DUL > PLA
Vitton et al., 2005	45	MIL vs PLA	125	4	200	PGI FIQ	MIL > PLA
Arnold, 2005	46	DUL > PLA	354	12	60-120	BPI	DUL > PLA

VLF = venlafaxine; DUL = duloxetine; MIL = milnacipran; dose in mg/day; outc. = outcome measures: VAS = Visual Analog Scale; FIQ = Fibromyalgia Impact Questionnaire;

from 1966 to 2003 and did not consider new antidepressants such as SNRIs that are less effective than TCAs but remarkably more tolerated, particularly in long-term treatment (42).

Antidepressants that act on both NE and 5HT, i.e., SNRIs (Serotonergic and Noradrenergic Reuptake Inhibitors), are venlafaxine, duloxetine and milnacipran (milnacipran is not marketed in Italy).

Only a few controlled studies are available to date; these are summarized in Table I (43-46). All of these controlled studies demonstrated a significant superiority of the SNRI over placebo, and reported few and mild side effects (more frequent nausea, dry mouth and constipation in the first two weeks of treatment) (47).

Cyclobenzaprine, a tricyclic muscle relaxant, has also proven to be moderately effective in FM patients at a dose of 10-40 mg/day (48). This has recently been confirmed by a meta-analysis of five randomised, placebo-controlled trials (49), which showed that patients treated with cyclobenzaprine were approximately three times as likely to report symptom improvement, but there was a high dropout rate and the duration of the studies was short (49).

In our experience treating cancer pain with antidepressants, we have found that the impact of antidepressants on emotion and cognition is quite interesting: after a month of treatment, especially when brief psychotherapy is also included, patients who have pain as well as maladaptive coping styles (such as despair or hopelessness) begin to adopt positive coping styles (such as fighting spirit). This change is obtained by improving mood and reshaping beliefs about pain, both of which are extremely important in malignant pain diseases (50). A final consideration involves the placebo effect in pain treatment.

In a medical model placebo is mainly considered an inert substance, and at present, it is well known that the placebo effect on pain is mediated by an opioid mechanism (51).

In clinical practice, however, we consider that a placebo effect is also an adjunct response to an active drug: the individual expectation of a positive response will increase the pharmacological action of the drug, while a negative expectation will reduce the effectiveness of the therapy (nocebo effect).

The placebo effect is highly related to the relationship between patient and physician (52), a relationship that is also important in affecting pharmacological treatments as well.

Anticonvulsants/antiepileptic drugs

Antiepileptic drugs (i.e., gabapentin and pregabalin) act at a number of sites that may be relevant to pain. The precise mechanism of their analgesic effect remains unclear, but it is thought that they limit neuronal excitation and enhance inhibition (53). The relevant sites of action include voltage-gated ion channels (i.e., sodium and calcium channels), ligand-gated ion channels, excitatory receptors for glutamate and N-methyl-D-aspartate, the inhibitory receptors for gamma-aminobutyric acid (GABA) and glycine (54).

In preclinical pain models, gabapentin is a structural analogue of the neurotransmitter GABA; it exerts robust analgesic and anti-allodynic effects in syndromes that are secondary to sensitization of pain responses but has minimal effects in models of acute, transient pain (55). Taylor, et al. (56) suggested that gabapentin did not appear to reduce acute pain from injury, but appeared to be effective in reducing abnormal hypersensitivity (allodynia and hyperalgesia) induced by inflammatory responses or nerve injury. The antinociceptive effects of gabapentin are hypothesized to be mediated by modulation of calcium channels via α_2 binding, modulation of transmission of GABA, and possibly other additional unidentified mechanisms.

Arnold, et al. (57) conducted a 12-week, randomized, double-blind study that was designed to compare gabapentin (1,200-2,400 mg/day; n=75 patients) versus placebo (n=75 patients) for efficacy and safety in treating pain associated with FM. Patients who were treated with gabapentin displayed significantly greater improvements in the Brief Pain Inventory (BPI) average pain interference score, the Fibromyalgia Impact Questionnaire (FIQ) total score, the Clinical Global Impression of Severity, the Patient Global Impression of Improvement, the Medical Outcomes Study (MOS) Sleep Problems Index, and the MOS Short Form 36 vitality score; but they did not show improvements in the mean tender point pain threshold or the Montgomery Asberg Depression Rating Scale. Gabapentin was generally well tolerated by these FM patients.

Pregabalin is an α_2 - δ ligand that has analgesic, anxiolytic-like, and anticonvulsant activity in animal models. Biochemical studies identified α_2 - δ (type 1) as the primary binding site for both pregabalin and the related compound, gabapentin (57). α_2 - δ is an auxiliary protein associated with voltage-gated calcium channels. Potent binding of pregabalin at the α_2 - δ site reduces calcium influx

at nerve terminals (58) and, therefore, reduces the release of several neurochemicals, including glutamate, noradrenaline, and substance P (58, 59). The reduced neurotransmitter release caused by drug binding at the α_2 - δ site is presumed to account for the analgesic, anticonvulsant, and anxiolytic-like actions of pregabalin in animal models. Reduction of neurotransmitter release from neurons in the spinal cord and brain is also proposed as the mechanism of action that may result in clinical benefit for patients with FM. In an 8-week, multicentre, double-blind, randomised, placebo-controlled clinical trial, Crofford, et al. (61) compared the effects of pregabalin (150, 300 and 450 mg/day) on pain, sleep, fatigue and health-related quality of life in 529 FM patients, and found that it was superior to placebo in reducing the scores for pain, SF-MPQ, sleep index, fatigue, patient and clinician global impression of change, and four of the eight SF-36 domains. The most frequent adverse events were dizziness and somnolence.

Arnold, et al. (62) conducted a study to assess symptoms of anxiety and depression in a large cohort of FM patients to determine the impact of these symptoms on pain during a course of pregabalin treatment. The results indicated that anxiety symptoms were more common than depressive symptoms in this cohort, and that the pain treatment effect of pregabalin did not depend on baseline anxiety or depressive symptoms, which suggests that pregabalin improves pain in patients with or without these symptoms. Finally, much of the pain reduction appears to be independent of improvements in anxiety or mood symptoms.

In a multicenter, double-blind, placebo-controlled trial, Mease, et al. (63) randomly assigned 748 FM patients to receive placebo or pregabalin (300, 450, or 600 mg/day, dosed twice daily) for 13 weeks. The pregabalin groups showed statistically significant improvements in mean pain score and in Patient Global Impression of Change (PGIC) compared to the placebo group. Improvements in FIQ-Total Score for the pregabalin groups were numerically but not significantly greater than those for the placebo group. Compared with placebo, all pregabalin treatment groups showed statistically significant improvement in assessments of sleep and in patients' impressions of their global improvement. Dizziness and somnolence were the most frequently reported adverse events. The study concluded that pregabalin monotherapy provides clinically meaningful benefit to patients with FM.

Other drugs

Serotonergic receptors have been implicated in processing information and in the development of pain in FM, and randomised, controlled trials have found that tropisetron, a 5-hydroxytryptophan intermediate metabolite of L-tryptophan, is more effective than placebo (64, 65)

In a pilot study, Papadopoulos, et al. (66) found that tropisetron might be effective in treating pain in FM patients, but Koeppe, et al. (67) did not observe any significant change in the intensity of habitual pain following local injection of tropisetron in FM patients who took part in a pre- and post-treatment, double-blind study of pain perception and central processing.

In an open trial of pindolol, a mixed serotonin (5-HT)(1A) presynaptic autoreceptor/beta-adrenergic receptor antagonist, at a dose of 7.5 mg/day (titrated to a maximum of 15 mg/day) for a total of 90 days in 20 female FM patients, Wood, et al. (68) demonstrated a significant improvement in primary tender point counts ($p < 0.001$), tender point scores ($p < 0.001$), and FIQ ($p < 0.005$). The depression and anxiety scores did not significantly change among the women who completed the study, and the impact on cardiovascular parameters was clinically insignificant (68).

Despite the suggestion of relative growth hormone (GH) deficiency in FM patients and reports of improvements after the administration of GH injections, the enthusiasm for this approach has been dampened by the appearance of adverse effects, the need for frequent injections, and its high cost (69).

Low doses of a β -blocker have been tried in selected cases with prominent autonomic symptoms, such as palpitations and orthostatic tachycardia; however, the effects are not known (68).

Lidocaine hydrochloride injections, botulinum toxin injections, are sometimes offered to patients with FM (1, 8, 70, 71).

CONCLUSIONS

The success of the current treatments for FM is still limited, and there is a need for the development of new drugs that are targeted at the CNS, and that undergo efficacy and toxicity testing in long-term, comparative trials involving large numbers of patients. Recent data concerning polymorphisms of the genes in the serotonergic and dopaminergic systems may facilitate the development of a more

rational, genotype-based, pharmacological approach (72). Subjects with the short 5HTTLPR allele in the serotonergic system may be more suitable candidates for antidepressant treatment (73), whereas subjects with polymorphisms in the dopaminergic system, such as the dopamine D4 receptor exon III repeat polymorphism, may be

candidates for dopaminergic medications (73). Certainly, further randomized, controlled clinical trials that are conducted with subgroups of patients using standardized outcome measurements and sufficient length of follow-up are necessary to observe and document changes in patient symptoms and behaviors over time.

SUMMARY

Pharmacological treatment has been gradually enriched by a variety of compounds; however, no single drug is capable of fully managing the constellation of fibromyalgia (FM) symptoms. Currently, it is not possible to draw definite conclusions concerning the best pharmacological approach to managing FM because results of randomized clinical trials present methodological limitations and therapeutic programs are too heterogeneous for adequate comparison. However, a variety of pharmacological treatments including antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, sedatives, muscle relaxants and antiepileptics have been used to treat FM with varying results. In this review, we will evaluate those pharmacological therapies that have produced the most significant clinical results in treating FM patients.

The nature of FM suggests that an individualized, multimodal approach that includes both pharmacologic and non-pharmacologic therapies seems to be the most appropriate treatment strategy to date.

Key words - Pharmacologic approach, non-pharmacologic approach, opioids, antiepileptics, nonsteroidal anti-inflammatory drugs.

Parole chiave - *Terapia farmacologica, terapia non-farmacologica, oppioidi, antiepilettici, anti-infiammatori non steroidei.*

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