

# Pharmacological treatment of fibromyalgia

M. Di Franco<sup>1</sup>, C. Iannuccelli<sup>1</sup>, F. Atzeni<sup>2</sup>, M. Cazzola<sup>3</sup>, F. Salaffi<sup>4</sup>, G. Valesini<sup>1</sup>,  
P. Sarzi-Puttini<sup>2</sup>

<sup>1</sup>Chair of Rheumatology, Sapienza, University of Rome, Rome, Italy;

<sup>2</sup>Rheumatology Unit, Luigi Sacco University Hospital, Milan, Italy;

<sup>3</sup>Unit of Rehabilitation Medicine, Ospedale del Circolo, Saronno, Italy;

<sup>4</sup>Department of Rheumatology, Polytechnic University of the Marche Region, Ancona, Italy.

Manuela Di Franco, MD

Cristina Iannuccelli, MD

Fabiola Atzeni, MD, PhD

Marco Cazzola, MD

Fausto Salaffi, MD, PhD

Guido Valesini, MD, Professor

Piercarlo Sarzi-Puttini, MD

Please address correspondence to:

Piercarlo Sarzi-Puttini, MD,

Rheumatology Unit,

Luigi Sacco University Hospital,

Via G.B. Grassi 74,

20127 Milano, Italy.

E-mail: sarzi@tiscali.it

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## ABSTRACT

*Fibromyalgia (FM) is a common syndrome characterised by widespread pain and at least 11/18 painful tender points that requires multimodal pharmacological treatment also combined with non-pharmacological therapy. Various drugs currently are available to control the complex and different symptoms reported by patients. Only three drugs (duloxetine, milnacipram, pregabalin) are approved by the American Food and Drug Administration (FDA) and none by the European Medicines Agency (EMA), consequently, off-label use is habitual in Europe. Most of the drugs improve only one or two symptoms; no drug capable of overall symptom control is yet available. Furthermore, different classes of drugs with different mechanisms of action are used off-label, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), opioids, non-steroidal anti-inflammatory drugs (NSAIDs), growth hormone, corticosteroids and sedative hypnotics. As no single drug fully manages FM symptoms, multicomponent therapy should be used from the beginning. Various pharmacological treatments have been used to treat FM with inconclusive results, and gradually increasing low doses is suggested in order to maximise efficacy. The best treatment should be individualised and combined with patient education and non-pharmacological therapy.*

## Introduction

Fibromyalgia (FM) is a common syndrome characterised by widespread pain and at least 11/18 painful tender points (American College of Rheumatology (ACR) 1990) (1), as well as a number of associated symptoms such as fatigue, sleep disturbance, dizziness,

headache, depression/anxiety, and irritable bowel syndrome (2). Its pathogenesis is complex and not completely understood. The disease involves central sensitisation and an amplified perception of pain in which a combination of interactions (external stressors, behavioural constructs, neurotransmitters, hormones, and the immune and sympathetic nervous system) seem to be involved (2-4).

Current research has highlighted the need for a multidisciplinary approach to symptomatic therapy that includes both pharmacological and non-pharmacological treatments but the optimal approach is very difficult to establish for various reasons. First of all, the results of randomised clinical trials are often affected by methodological limitations and, as the primary outcomes are frequently heterogeneous, they are difficult to compare. Secondly, only three drugs (duloxetine, milnacipram, pregabalin) are approved by the American Food and Drug Administration (FDA) and none by the European Medicines Agency (EMA), which means that off-label use is habitual in Europe. Thirdly, most of the drugs improve only one or two symptoms, and no drug capable of overall symptom control is yet available. Finally a wide range of different drug classes with different mechanisms of action are being used off-label, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), opioids, non-steroidal anti-inflammatory drugs (NSAIDs), growth hormone, corticosteroids, and sedative hypnotics (5).

## Antidepressants

FM is a complex syndrome in which somatic aspects such as pain and stiffness co-exist with emotional, cognitive and environmental aspects (6, 7). The

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pathogenetic hypothesis is that pain, anxiety, fatigue, chronic stress and depression may be the effect of a neuro-immunoendocrine system dysregulation that leads to unbalanced neurotransmission, hormonal alterations, and autonomic, immunological and metabolic somatic changes (3, 8). In this context, antidepressants can restore neurotransmitter levels and modulate receptor expression in the central nervous system (5).

### Serotonin norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs)

The role of norepinephrine and serotonin in pain processing has been shown by the antinociceptive effects increasing local serotonin concentrations or norepinephrine neurotransmission (9), which can enhance the analgesic action of the descending nociceptive modulatory pathways in the brain and spinal cord (10). Animal studies have shown that dual reuptake inhibitors (SNRIs), which enhance both serotonin and norepinephrine neurotransmission, are more effective in reducing pain than either norepinephrine reuptake inhibitors or selective serotonin reuptake inhibitors (SSRIs) alone (11). Furthermore, a number of large-scale clinical trials have shown that dual reuptake inhibitors of serotonin and norepinephrine, such as duloxetine and milnacipran, are effective in the treatment of FM (Table Ia, Ib) (12-19).

FDA-approved milnacipran is a serotonin-norepinephrine reuptake inhibitor with 3-fold greater selectivity for norepinephrine than serotonin. It is well absorbed (bioavailability is 85-90%), and peak concentrations are reached 2-4 hours after administration. Milnacipran does not undergo cytochrome P450 metabolism and has a half-life of 6-8 hours. Fifty-five percent of each dose is excreted unchanged in the urine. The most frequently observed adverse drug reaction is nausea, which can be reduced by slow-dose titration and administration with food (20). Discontinuation due to adverse events has been reported in 23.0% of patients receiving milnacipran 100 mg/day and 26.0% receiving 200 mg/day, compared with

12.1% of placebo-treated patients. Twice-daily dosing at 100 mg/day or 200 mg/day is superior to single daily doses (21). A recent randomised, double-blind and placebo-controlled trial involving 1,025 FM patients (22) found that milnacipran 100 mg/day improved pain, global status, fatigue, and physical and mental function.

Duloxetine is a dual serotonin and norepinephrine reuptake inhibitor that is approved by the FDA for the treatment of FM at a dose of 60 mg/day. It is also approved for major depressive disorder, diabetic peripheral neuropathic pain, and generalised anxiety disorder. More than 1600 patients have been enrolled in randomised, double-blind, placebo-controlled trials using duloxetine 60 or 120 mg/day, all of which showed a significant improvement in pain (measured using the Brief Pain Inventory [BPI]) and secondary measures such as patient-rated scales assessing mood, anxiety, pain, sleep and stiffness, the Clinical Global Impression of Severity (CGI-S), the Multidimensional Fatigue Inventory (MFI), the Cognitive and Physical Functioning Questionnaire (PFQ), Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI), the Medical Outcome Study Short-Form Health Survey (SF-36), and the Fibromyalgia Impact Questionnaire (FIQ). Treatment with duloxetine was therefore associated with feeling much better, reduced pain, being less bothered by sleeping difficulties, and improvements in mood, stiffness, fatigue and functioning. The most frequent adverse events have included nausea, headache, constipation, dry mouth, dizziness, diarrhoea, and hyperhidrosis (13, 14, 16).

Venlafaxine is another antidepressant classified as a dual serotonin and norepinephrine reuptake inhibitor that seems to inhibit both serotonin and norepinephrine reuptake at higher doses, although low doses only inhibit serotonin reuptake (23). One randomised, double-blind, placebo-controlled trial found that venlafaxine administered to FM patients at a dose of 75 mg/day for six weeks did not significantly improve the primary measures of pain (pain visual analogue scale [VAS] and McGill Pain Questionnaire [MPQ]) in

comparison with placebo; there was a significant improvement in the secondary endpoints (FIQ total and FIQ pain) but the safety profile was significantly worse than in the placebo group (24). SSRIs such as escitalopram, fluoxetine and paroxetine have mainly led to a significant reduction in the depressive symptoms of FM patients (25).

### Tricyclic antidepressants (TCAs)

Low doses of the tricyclic antidepressants (TCAs) amitriptyline and cyclobenzaprine have long been used to treat FM. They inhibit the reuptake of both serotonin and norepinephrine, and thus reduce pain. A number of trials on amitriptyline have involved patients with FM and documented a moderate improvement in sleep and pain but they were mainly small, short-term and single-centre trials.

A meta-analysis by O'Malley *et al.* (26) analysed the results of 13 trials using the TCAs amitriptyline, clomipramine and maprotiline; the SSRIs fluoxetine and citalopram; the monoamine oxidase inhibitor (MAO-I) moclobemide; and the dietary supplement S-adenosylmethionine. Sleep, overall well-being and pain severity moderately improved, whereas only slight improvements were seen in fatigue and the number of tender points. The most recent meta-analysis by Hauser *et al.* (27) found strong evidence supporting the efficacy of amitriptyline on pain, fatigue, and sleep.

The use of TCAs is limited by their relatively narrow therapeutic index and the fact that, unlike the newer dual reuptake inhibitors of serotonin and norepinephrine, they have significant affinity for histaminergic, cholinergic and adrenergic receptor systems, which contributes to the side effects of higher doses (sedation, dry mouth and constipation). The tolerability of TCAs can be improved by prescribing a very low dose before bedtime and then increasing it very gradually, while keeping it as low as possible. TCAs should be used cautiously in patients with cardiovascular, renal or hepatic disease (21).

### Analgesics

Pain is a diagnostic cornerstone of FM according to the ACR 1990 criteria.

**Table Ia.** Randomised, double-blind, placebo-controlled trials of duloxetine in fibromyalgia.

Study and refs.	No. of pts.	Treatment groups	Weeks	Outcomes
Arnold <i>et al.</i> , 2004 [12]	207	Placebo (n=103) Duloxetine 120 mg/day (n=104)	12	Pain: BPI average pain severity and interference; tender point pain threshold; tender point count; FIQ pain item
Arnold <i>et al.</i> , 2005 [13]	354	Placebo (n=120) Duloxetine 60 mg/day (n=118) Duloxetine 120 mg/day (n=116)	12	Pain: BPI average pain severity and interference (both doses); tender point pain threshold (120 mg); tender point count (120 mg); global: CGI-S (both doses); PGI-I (both doses)
Russel <i>et al.</i> , 2008 [14]	520	Placebo (n=144) Duloxetine 20/60mg/day (n=79) Duloxetine 60 mg/day (n=150) Duloxetine 120 mg/day (n=147)	12	Pain BPI average pain severity (60 and 120 mg); Global: CGI-S (60 and 120 mg); PGI-I (20/60, 60, and 120 mg); fatigue: MFI mental fatigue (60 mg)
Chappell <i>et al.</i> , 2008 [15]	330	Placebo (n=168) Duloxetine 60-120 mg/day (n=162)	24	Pain: BPI least pain and average pain interference; global: CGI-S; fatigue: MFI mental fatigue
Arnold <i>et al.</i> , 2010 [16]	530	Placebo (n=267) Duloxetine (263) 60, 90, and 120 mg/day	24	BPI average pain severity; mood (including BDI total); anxiety (patient-rated only); stiffness; CGI-S; fatigue; all SF-36 domains

BPI: Brief Pain Inventory; CGI-S: Clinical Global Impression of Severity; FIQ: Fibromyalgia Impact Questionnaire; MFI: Multidimensional Fatigue Inventory; PGI-I: Patient Global Impression of Improvement; SF-36: Short-Form 36-item Health Survey. (Modified by Mease *PJ Am J Med.* 2009).

**Table Ib.** Randomised, double-blind, placebo-controlled trials of milnacipram in fibromyalgia.

Study and refs.	No. of pts.	Treatment groups	Weeks	Outcomes*
Mease <i>et al.</i> , 2009 [17]	888	Placebo (n=223) Milnacipran 100 mg/day (n=224) Milnacipran 200 mg/day (n=441)	24	Pain: composite measures; global: PGIC (both doses); fatigue: MFI total (both doses); SF-36 physical functioning (200 mg) global: PGIC (200 mg)
Claw <i>et al.</i> , 2008 [18]	1196	Placebo (n=401). Milnacipran 100 mg/d (n=399) Milnacipran 200 mg/d (n=396)	15	Pain. Composite responders; global: PGIC (both doses); SF-36 physical functioning domain (both doses); fatigue: MFI (100 mg/d)
Branco <i>et al.</i> , 2010 [19]	884	Placebo (n=449) Milnacipran 200 mg/d (n=435)	17	Pain: composite measures; FIQ total score; Short-Form 36; fatigue: MFI
Arnold <i>et al.</i> , 2010 [22]	1025	Placebo (n=509) Milnacipran (n=516) 100 mg/day (50 mg b.i.d.)	12	Pain: composite responder criteria; FIC total score; global: PGIC score; SF-36; BPI; fatigue: MFI

BPI: Brief Pain Inventory; CGI-S: Clinical Global Impression of Severity; PGI-C: Patient's Global Impression of Change scale; FIQ: Fibromyalgia Impact Questionnaire; MFI: Multidimensional Fatigue Inventory; PGI-I: Patient Global Impression of Improvement; SF-36: Short-Form 36-item Health Survey. (Modified by Mease *PJ Am J Med.* 2009).

The usual approach to treating mild-moderate pain is to start with a non-opioid analgesic, which can also be used in FM.

A stepped care approach based on existing evidence includes simple analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), although the results of clinical trials of anti-inflammatory medications have generally been disappointing (28). NSAIDs are commonly used for arthritic conditions but may

be less effective against FM because FM-associated pain is not caused by muscle or joint inflammation. There is no scientific evidence that NSAIDs are effective in FM patients when used alone, although they may be useful to enhance analgesia when combined with TCAs. Combinations of NSAIDs and benzodiazepines have led to conflicting results (29). Although NSAIDs are statistically chosen by patients, the ACR recommends acetaminophen as the first choice analgesic for mild pain,

and it seems to be even more appropriate given its long duration of safe use (30). Acetaminophen is a centrally-acting analgesic that seems to relieve pain by means of spinal and supraspinal mechanisms (9, 10).

Alone or combined with acetaminophen, tramadol (a centrally-acting analgesic that binds mu-opioid receptors and inhibits the reuptake of norepinephrine and serotonin) has been found to be effective in FM (11). The combination may relieve pain through

multiple pathways, and a tramadol/acetaminophen combination in a ratio of approximately 1:8 has been found to be synergistic in animal models of antinociception (31). Although tramadol is considered not to be habit-forming, abstinence symptoms are likely to develop if it is abruptly discontinued, especially when it has been taken for more than one year. Patients should be told about this effect whenever they decide to stop it or their physicians plan a switch to another medication. The abstinence-like symptoms can be avoided by slowly tapering the dose.

Rational combinations of analgesic agents with different mechanisms of action can improve the efficacy and/or tolerability and safety of conventional doses of the individual drugs, and can also improve efficacy in the case of complex pain states due to multiple causes. Combinations of acetaminophen and a weak opioid agent are widely used, and the combined use of acetaminophen and tramadol exploits the well-established complementary pharmacokinetics and mechanisms of action of both as the former is characterised by a rapid onset of action, and the latter by its prolonged analgesic effect. A number of studies have confirmed the efficacy and tolerability of acetaminophen and tramadol in the long-term management of chronic pain conditions, including osteoarthritis, low back pain and FM.

Combined acetaminophen and tramadol has proved to be efficacious, safe and tolerable in treating chronic pain for up to two years without giving rise to tolerance. The efficacy of this combination has also been demonstrated in terms of reducing pain intensity and, more importantly, improving function and the quality of life, and reducing disability. Comparative trials have shown that acetaminophen plus tramadol is as efficacious as acetaminophen plus codeine but leads to greater somnolence and constipation than the codeine combination. It is also free of the organ toxicity associated with selective and non-selective NSAIDs, and therefore offers an effective and well-tolerated alternative to these or other combinations of acetaminophen and a weak opioid (28, 32).

If these combinations are inadequate, it is possible to add an opioid analgesic such as oxycodone, hydromorphone or fentanyl. Oxycodone may be administered to patients unsuccessfully treated with weak opioids (tramadol, codeine and dihydrocodeine), or as the first strong opioid to opioid-naïve patients with severe pain, or when other strong opioids lead to insufficient analgesia and/or intense adverse effects such as sedation, hallucinations and nausea/vomiting, and a switch to oxycodone may be beneficial. Oxycodone's effective analgesia can be attributed to its affinity to  $\mu$  and possibly  $\kappa$  opioid receptors, its rapid penetration through the blood/brain barrier, and its higher concentrations in the brain than in plasma. It is highly bioavailable after oral administration and, in patients with renal impairment, may be better than morphine because of its lower production of active metabolites. The adverse effects of oxycodone may be intensified by its pharmacodynamic interactions with other drugs acting on the central nerve system, such as benzodiazepines, neuroleptics and antidepressants (33).

It is essential to have a thorough understanding of the mechanisms of chronic pain and its evidence-based multi-mechanistic treatment. It is also essential to increase individualised treatment.

#### **Anticonvulsants/antiepileptic drugs**

Antiepileptic drugs such as gabapentin and pregabalin act at a number of possibly relevant sites for pain. The mechanism underlying their analgesic effect is not fully understood but it seems that they limit neuronal excitation and enhance inhibition (34). They are second-generation anticonvulsants and structural analogues of gamma-aminobutyric acid (GABA). As alpha-2-delta ligands, they modulate voltage-gated calcium channels by reducing calcium influx at nerve terminals and thus decrease the release of neurotransmitters such as glutamate, norepinephrine and substance P. It is thought that this is the mechanism underlying their analgesic, anticonvulsant and anxiolytic activity (35).

It is believed that the effects of gabapentin are mediated by the release of the

excitatory amino acids and neuropeptides that modulate calcium channels and GABA transmission (36). Animal models have shown that it is also effective in reducing allodynia and hyperalgesia (37-39). The mechanism of action of pregabalin, which is approved by the FDA for the treatment of FM, seems to be that of inhibiting calcium currents via high-voltage-activated channels containing the  $\alpha_2\delta-1$  subunit and reducing the release of neurotransmitters (noradrenaline, serotonin, dopamine and substance P) in hyper-excited neurons, thus attenuating post-synaptic excitability (40, 41).

Both drugs have a favourable safety and tolerability profile: gabapentin generally has very few side effects and non-organ toxicity; the major advantages contributing to the safety profile of pregabalin are its good bioavailability, minimal interactions with other medication, and the lack of interference with hepatic enzymes. Their most common side effects are dizziness and somnolence (42), which are also the most frequent reasons for withdrawals. Generally, all of their side effects are mild or moderate, and less severe those of TCAs, ketamine, opioids and NSAIDs (43, 44).

A recent meta-analysis by Hauser *et al.* (45) of one clinical trial of gabapentin and five of pregabalin (involving a total of more than 2000 patients treated with the drugs and more than 1000 treated with placebo) found strong evidence of reduced pain ( $p < 0.001$ ), improved sleep ( $p < 0.001$ ), and a better health-related quality of life (HRQOL) ( $p < 0.001$ ), and a non-substantial reduction in fatigue ( $p < 0.001$ ) and anxiety ( $p < 0.001$ ) but no significant changes in depressed mood. The main side effects of dizziness ( $p = 0.001$ ), somnolence ( $p = 0.04$ ), weight gain ( $p = 0.02$ ), peripheral edema ( $p = 0.03$ ), and negative neurocognitive effects ( $p = 0.003$ ) were dose-dependent. The fact that the analysis included only one trial of gabapentin precluded any comparison of the two active drugs. In conclusion, gabapentin and pregabalin can be considered for the treatment of pain and sleep disturbances in FM patients. Treatment should start at a low dose, and be increased slowly in small



steps up to 300 mg/day as both drugs have dose-dependent side effects (46).

### Other drugs

Various other drugs with different mechanisms of action are used in generally selected cases of FM.

Pramipexole (a dopamine 3 receptor agonist) has been studied in a multicentre, double-blind, placebo-controlled study involving 60 FM patients who were treated for 14 weeks (47). The primary endpoint of VAS-evaluated pain significantly improved, and there were also improvements in the measures of fatigue, global status and function; the adverse event profile was reassuring.

The efficacy of the synthetic cannabinoid nabilone has been studied in two randomised controlled trials. In the first, 44 FM patients started treatment at an oral dose of 0.5 mg at bedtime, subsequently titrated up to 1 mg b.i.d. over 4 weeks, or received a corresponding placebo; at the end of the 4-week treatment period, there were significant decreases in the pain VAS, FIQ and anxiety scale in the nabilone-treated group. The second study highlighted improvements in sleep disturbance. Both trials concluded that nabilone had a good efficacy/safety profile (48, 49).

The efficacy of low doses (4.5 mg) of naltrexone, a competitive antagonist of opioid receptors has recently been evaluated in a single-blind, placebo-controlled, cross-over pilot study as a means of reducing FM symptoms. The primary endpoint was daily self-reported symptom severity, and there was a 2.3% reduction in symptoms from during the placebo phase, and a 32.5% reduction during the active treatment phase. The study concluded that low-dose naltrexone may be an effective, highly tolerable and inexpensive treatment for FM (50).

Terguride, a partial dopamine agonist that is approved in Japan for the treatment of hyper-prolactinemia, has been used in a recent randomised, double-blind, placebo-controlled study involving patients with primary FM and no relevant concomitant medical conditions who were not receiving concurrent FM-targeted therapy. The results showed no significant between-group

differences in the pain VAS, FIQ and TP scores, except for a small sub-group of patients with cervical spine stenosis (51).

The effects of a promising drug, sodium oxybate (SXB, the sodium salt of gamma-hydroxybutyrate, which is a metabolite of the inhibitory neurotransmitter gamma-aminobutyric acid) have been investigated in four clinical trials: three single-centres, randomised, controlled and double-blind trials and one multicentre trial carried out between 1998 and 2010. In the first three trials, SXB effectively reduced the symptoms of pain and fatigue in patients with FM, and dramatically reduced the sleep abnormalities (alpha intrusion and decreased slow-wave sleep) associated with the non-restorative sleep characteristic of this disorder (52-54). The multicentre trial investigated the therapeutic efficacy and safety of two different doses of SXB over eight weeks in a large cohort of FM patients. In comparison with placebo, there were significant changes sleep disturbances, the pain VAS and fatigue VAS, the FIQ and global function, and most of the adverse events were mild or moderate. The findings of these studies suggest that SXB is effective and safe in the treatment of FM symptoms (55).

Muscle relaxants (cyclobenzaprine) and the benzodiazepines (alprazolam, bromazepam) have not shown any signs of efficacy but can be used as adjunctive therapy (56, 57).

### Conclusions

FM requires multimodal pharmacological treatment associated with non-pharmacological therapy, and a number of drugs are currently available to control the complex and different symptoms reported by patients.

Although various medications are used to manage the painful symptoms associated with FM, only pregabalin, duloxetine and milnacipram have been approved for use in the USA by the FDA over the last five years. As none of these is currently approved in Europe, the most frequently used drugs to control pain are NSAIDs or short-acting opioids alone or in combination with muscle-relaxants. Moreover, despite

the published recommendations regarding the use of strong opioids, they continue to be widely used in clinical practice (30).

Each FM patient should be individually assessed in order to establish which symptoms are prevalent and require treatment. Levels of pain control, as well as symptoms such as anxiety, depression and catastrophising, vary in different subsets of FM patients (58), and treatment should take these into account. As no single drug is capable of managing FM symptoms, multicomponent therapy should be used from the beginning. Various pharmacological treatments (including antidepressants, NSAIDs, opioids, sedatives, muscle relaxants and antiepileptic agents) have been used to treat FM but the results are inconclusive. The best way to minimise adverse side effects and maximise efficacy is to use low and gradually increasing doses of multiple drugs. Finally, the treatment needs to be individualised and associated with the patients' education and non-pharmacological therapy.

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