Fibromyalgia: a critical digest of the recent literature

L. Bazzichi[1], F. Sernissi[1], A. Consensi[1], C. Giacomelli[1], P. Sarzi-Puttini[2]

[1]*Division of Rheumatology, Department of Internal Medicine, University of Pisa, Pisa, Italy;*
[2]*Department of Rheumatology, L. Sacco University Hospital, Milan, Italy.*

Laura Bazzichi, MD
Francesca Sernissi, PhD
Aarianna Consensi, MD
Camillo Giacomelli, PhD
Piercarlo Sarzi-Puttini, MD

Please address correspondence to:
Dr L. Bazzichi,
U.O. Reumatologia,
Dipartimento di Medicina Interna,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: l.bazzichi@gmail.com

Received and accepted on December 22, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 69): S1-S11.

Key words: fibromyalgia, assessment, pathogenesis, treatment

Competing interests: none declared.

ABSTRACT

Fibromyalgia is a common syndrome characterised by widespread pain and a constellation of other symptoms and overlapping conditions that contribute to complicate the diagnosis, the assessment and the treatment.

Furthermore, the etiological causes for the moment only consist of assumptions, and the underlying pathogenetic mechanisms still remain to be clarified.

For the above-mentioned reasons, with the present review we sought to provide an overview of the literature on fibromyalgia from both the pre-clinical and clinical studies indexed in PubMed during the last year, classifying original articles and reviews into etiopathogenesis, assessment and therapy.

Introduction

Fibromyalgia (FM) is a chronic syndrome of unknown etiology, principally charactered by widespread pain, post-exertional fatigue not resolved by rest, sleep disturbances, affective and neurocognitive disorders, which can appear together with a plethora of other symptoms, particularly of neurovegetative origin.

Every year a growing number of original articles, reviews and meta-analysis are published on the principal medical journals, underlining the continuing interest towards this syndrome and its manifestations.

For that reason, the purpose of this review is to provide an overview of the literature on fibromyalgia, from both pre-clinical and clinical studies, indexed on PubMed during the last year (from November 2010 to November 2011).

Original articles and reviews included have been classified according to the aim of the research, and thus divided into etiopathogenesis, assessment and therapy.

Etiopathogenesis

What have we learned about the role of central and peripheral sensitisations in the pathogenesis of pain?

A few months ago, Kindler *et al*. (1) reviewed the scientific literature concerning the more accredited pathophysiologic mechanisms underlining chronic pain and hyperalgesia conditions.

With regard to fibromyalgia, central sensitation and impaired descending pain modulation are generally accepted as the two major underlying mechanisms causing widespread hypersensitivity to pain. According to Kindler, attributes of FM that support the role of central sensitisation include: (i) expansion of pain receptive fields, (ii) increased levels of substance P and neurotrophic factors in the cerebral spinal fluid, (iii) decreased pain thresholds, (iv) enhanced sensitivity outside of typical tender point locations, (v) abnormal windup, and (vi) prolonged pain after cessation of painful input (1).

The expansion of receptive fields (i) is an important mechanism through which central sensitation modulates the expression of hyperalgesia. This occurs as a result of prolonged excitation of wide dynamic range (WDR) neurons, which in turn activates adjacent neurons, expanding their receptive fields beyond the site of the original injury. Clinically, this results in pain being experienced by stimulation of locations that had not previously provoked a pain response (1).

As for point (ii), substance P, along with excitatory amino acids, such as glutamate and aspartate, is known to enhance the transmission of pain through the primary afferent neurons. Research demonstrates that substance P levels in FM patients are two- to three-fold that of healthy controls (1). Increased levels of substance P can induce hyperalgesia

and allodynia by lowering the firing threshold of spinal cord neurons and extend long distances from the pain locus, resulting in sensitisation at sites distant from the pain locus itself. Furthermore, the combination of elevated glutamate and substance P and reduced serotonin supports a role for central amplification in the abnormal pain transmission and perception of patients with FM. In fact, in these patients, cerebrospinal fluid (CSF) levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) were founded increased compared to healthy pain-free controls, and correlated with increased glutamate levels. The more accredited hypothesis is that NGF acts indirectly to increase BDNF expression, which then modulates N-methyl-D-aspartate (NMDA) receptor activity to increase the excitatory amino acids glutamate and aspartate, supporting the involvement of a central mechanism in the pathophysiology of FM (2, 3). As for point (iii), it has been recently reported that FM patients who underwent a cold pressor test showed lower pain threshold and tolerance, as well as higher ratings of pain intensity and unpleasantness on visual analogue scales (4). FM patients showed a reduced pain threshold also respect to patients affected by a major depressive disorder, who even did not show any deficit in pain inhibition (5). Nevertheless, hyperalgesia was not confirmed by a recent study on FM and chronic low back pain (CLBP) patients, based on exercise-provoked pain measure. In this study, women with FM showed higher repetition-induced summation activity-related pain (RISP) than those with CLBP; according to the authors, this result indicated that increased pain was not due to generalised hyperalgesia – and neither to a greater work output – but to fear of movement, which positively correlated with RISP (6).

However, local and referred pain from active myofascial trigger points (MTrPs) has been demonstrated, by another study, to fully reproduced the overall spontaneous clinical pain area in patients with FM. Hypersensitivity seemed to be related to a greater number of active MTrPs, suggesting that nociceptive inputs from active MTrPs may contribute to central sensitisation in FM (iv) (7).

Concerning Windup phenomenon (v), it is considered one major mechanism through which ongoing pain produces a hyperexcitable state within the CNS. Indeed, when the windup occurs, pain impulses originating in peripheral nerve endings – better known as nociceptors- activate both Aδ and C-nociceptive fibres; these are the nerve fibres that carry the nociceptive impulse to dorsal horn neurons in the spinal cord. FM patients demonstrate enhanced windup with a greater degree of neuronal excitability and prolonged after-sensations (1). This also means that WDR neurons have a lower firing threshold and take longer to resolve following cessation of the stimuli (vi).

In order to determine the role of peripheral sensitisations in the pathogenesis of FM, in the last year a study investigated the etiopathogenetic mechanisms of FM by comparing this syndrome to diabetic neuropathy, that is one of the most frequently observed chronic widespread pain causes of peripheral origin. It is known that both painful diabetic neuropathy (DPN) and FM patients frequently suffer from heat hyperalgesia, which is thought to be a result of peripheral sensitisation of nociceptive afferents, prickling sensations, burning pain and numbness in the affected extremities. That is the reason why clinical data and sensory symptoms of FM patients have been compared to those from DPN patients (8), finding that the combination of sensory symptoms was in most cases distinct between the two groups, although a not neglectable overlap of sensory profiles commonly characterised the 20–35% of patients (8).

Although FM has been found in a significant overlap with a chronic pain condition of peripheral origin, another study showed that FM subjects did not differ from TMD and healthy subjects in terms of adaptation – that is a phenomenon of both peripheral and central components that occurs with the first pain declines – and gradual sensitisation to thermal stimuli. This finding indicate that adaptation and gradual sensitisation are relatively undisturbed in TMD and FM and thus they may occur before the perceptual amplification of pain (9).

Nevertheless, the above-mentioned studies, globally create the impression that central sensitisation alone cannot be responsible for FM pain occurrence; indeed the involvement of peripheral tissue nociception resulted from studies analysing neural mechanisms of somatic hyperalgesia and studies showing that injection of local anesthetics into painful muscles normalises somatic hyperalgesia in FM patients. Thus "FM pain is likely to be at least partially maintained by peripheral impulse input from deep tissues", concluded Staud (10).

In conclusion, even though the etiological mechanisms underlying FM still remain almost unknown, the pathogenetic pathways of pain, investigated in 2011 by clinical and pre-clinical studies, with only few exceptions, showed how central and peripheral sensitisations are in all likelihood involved.

What have we learned about stress-induced pain?

Unfortunately, although the pathogenetic causes of FM have been at least partially clarified, the etiological mechanism by which central and peripheral sensitisations occur is less clear. Several researchers have proposed that regional or focal chronic pain, through a longstanding bombardment of spinal cord neurons by Aβ and C fibres, might produce the sustained noxious input that results in hypersensitivity of the CNS (1). Thus, it has been proposed that regional pain syndromes, such as temporomandibular disorder (TMD), irritable bowel syndrome (IBS), irritable bladder/interstitial cystitis (IC), headaches, back pain, and neck pain, may precede the development of widespread pain in most patients with FM. These peripheral pain generators could in fact provide the necessary tonic nociceptive input that leads to abnormal pain processing within the CNS (1).

Nevertheless, one of the more accredited hypothesis concerning the etiology of FM is related to physical and psychological stressors (11). Recently Green and colleagues (12) tested the hypothesis that a rat model of sound

stress-induced FM enhanced musculoskeletal and cutaneous mechanical hyperalgesia, together with IBS (as indicated by presence of gastrointestinal hypersensitivity), increased anxiety (as indicated by increased Anxiety Index in the elevated plus maze test) and comorbidity with TMD, indicated by hyperalgesia in the masseter muscle. Thus the authors concluded that an established association between stress and FM could be supported considering the following assertions: (i) acute stress can induce long-term changes in pain sensitivity with delayed onset (*e.g.* following a motor vehicle accident); (ii) response to acute stress is both the strongest predictor of maintenance of pain symptoms weeks later and increased pain symptoms at a later date in individuals with fibromyalgia and other forms of chronic widespread pain (12).

Thus, the idea that a physical or psychological stress could enhance certain neurophysiological mechanisms, consequently creating a vicious circle that contribute to pain maintenance, is widely shared. For example, atypical sensory sensitivities was found significantly increased in FM comparing with RA or controls (13). According to this study, FM and RA groups differed in both somatic (tactile) and non-somatic (taste/smell and auditory) (13). Furthermore, because RA group did not differ from the control group on any section, the presence of a chronic pain syndrome alone does not seem to increase sensitivity to sensations in daily life. Evidently, the presence of such sensory defensive behaviours in FM – as authors have speculated – may result in functional and psychologic difficulties in daily life and increased stress and anxiety-associated strong sympathetic activaton (14), contributing to decreased function and quality of life and to increased pain perception (13).

What have we learned about genetics?

Although factors such as physical and psychological stressors can reasonably represent a leading cause of FM, the genetic hypothesis is generally one of the most shared by researches from around the world. Indeed, about one-third of patients with FM have a close relative who is similarly affected and, strategically, that other person is usually a woman. A family member of a patient with FM is about 8 times more likely to develop FM than is a family member of a patient with RA. It was reasonable, therefore, to predict that genetic predisposition to or more biochemical dysfunctions may be important to the development and/or perpetuation of FM (15). Genetic associations with FM have been sought with polymorphisms of catecholamine-O-methyl transferase, monoamine oxidases, dopamine and substance P receptors, alpha1-antitrypsin (ATT), dopamine and serotonin transporters, and with the histocompatibility region locus of chromosome 6, as previously reviewed by our research team (16, 17). However, most of the identified associations have not been confirmed and few, if any, have been linked to a relevant biological function marker (18, 19).

Recently the Gly16Arg polymorphism has been seen to be associated with an altered risk of developing FM (15). Further, the authors found a genotype-related difference in ISO-induced β_2AR desensitisation in PBMC cells from patients with FM, suggesting for the first time that the agonist-induced desensitisation of cAMP production is genotype Arg16Arg-dependent. These findings imply that β_2AR polymorphism in FM may influence responses to a variety of β-adrenergic ligands. This concept may help to explain some of the differences in responsiveness of FM subgroups to the adrenergic agonist medications currently approved for FM treatment (15). β_2AR Gly16Arg-based polymorphism is not the only genetic risk factor for FM recently discovered. Indeed approximately one quarter of both FM (n=101) and control subjects (n=300) studied were found to carry at least one Apo E4 allele. The odds ratio (OR) for case subjects with FM who had ever been in a motor vehicle accident and subsequently had been diagnosed with FM was increased among those with at least one copy of the Apo E4 allele (OR 7.04) compared with those without an Apo E4 allele (OR 1.90). These data suggest that specific interactions between genetically susceptible individuals (*e.g.* those with at least one copy of the Apo E4 allele) and the environment (*e.g.* involvement in a motor vehicle accident) may contribute to the risk of being diagnosed with FMS, although Apo E4 allele status does not appear to modulate perceived FM severity.

In a recently published genetic study, a large scale candidate gene approach was used to evaluate over 350 genes known to be involved in nociception, inflammation, and affection (20). Several unsuspected genes, differed in frequency between FM patients and healthy controls, but none of the previously found gene polymorphisms have been found (16). In particular, TAAR-induced alterations in dopamine bioavailability and function may increase pain sensitivity. RGS4, expressed in several CNS regions, negatively regulates G protein signalling, and may therefore play a modulatory role in descending inhibition of pain perception. Furthermore, over-expression of RGS4 down-regulates μ-opioid receptor, and in the spinal cord RGS4 is upregulated in a rat model of neuropathic pain, resulting in a substantial attenuation of morphine analgesia.

As for variants within the CNR1 locus, that is the gene encoding for cannabinoid receptor CB-1, it have been associated with other painful chronic conditions, such as irritable bowel syndrome, migraine and post-traumatic stress disorder. In contrast to the effects of TAAR1, RGS4, and CNR1 genetic variants on analgesic mechanisms, the association of GRIA4 with FM seemed to involve central sensitisation mechanisms, providing a further proof of what have been speculated in the previous paragraphs. Indeed GRIA4 encodes the AMPA-sensitive, ionotropic glutamate receptor subunit GluR4, which mediates fast excitatory transmission of nociceptive signals in the CNS. Moreover, spinal AMPA receptors have also been implicated in the production of visceral hyperalgesia. Collectively, these observations suggest that alterations in AMPA receptors are likely to contribute to the complex signs, symptoms, and comorbidities associated with FM (20).

What have we learned from proteomic studies?

In the last few years the proteomic approach has been widely used in order to identify new diagnostic biomarkers and therapeutical targets for a plethora of diseases, including FM. In a recent original article (21), our team showed the possibility of identifying potential salivary FM biomarker through a salivary proteomic tandem analysis based on MALDI-TOF and SELDI-TOF techniques. The peaks observed were likely to belong to the calgranulin family, and they are involved in cellular proliferation and migration, calcium homeostasis, inflammation and cellular protection against oxidative stress. Another peak observed with both techniques corresponded to the protein called Rho GDP-dissociation inhibitor2. This protein is involved in the RhoGTPasi activity, which controls cellular morphology and motility. Thus the peaks observed allow the research to focus on some of the particular pathogenic aspects of FM: the oxidative stress, which contradistinguishes this condition, the involvement of proteins related to the cytoskeleton arrangements, and finally the central sensitisation. However, the proteomic approach needs further improvements before it can be provide the right answer to the "fibromyalgia question".

What have we learned about the immunity system dysregulation and inflammation in FM?

Since FM has been frequently found in association with some autoimmune diseases such as rheumatoid arthritis (22), systemic lupus erythematosus (23), etc.), also the hypothesis of autoantibody involvement in the etiopathogenesis of the syndrome has been repeatedly supported. According to our recent study investigating thyroiditis in FM patients, we have found for the first time a higher frequency of anti-thyroid antibodies, and their values seem to be correlated with the presence of certain symptoms. Thus, a subclinical thyroiditis may represents the source of many of the symptoms and of much of the disability in these patients (24).

Moreover in recent years, several morphological and immunohistochemical changes have been reported in skin biopsies of FM patients, including the presence of inflammatory cytokines, increased dermal IgG deposits, over-expression and activation of extracellular matrix mast cells (MCs), fibroblasts and mononuclear resident cells, abnormal quantitative and morphological patterns of dermal collagen, increased expression of nociceptive glutamate N methyl-D-aspartate subtype 2D (NMDA 2D) receptors, and morphological changes of nociceptive C fibres. Concerning the analysis of inflammation-related markers, an increased numbers of mastocytes in skin biopsies have recently been observed (18), thus supposing that mastocyte degranulation-related can be associated with symptoms frequently present in FM patients (such as fatigue, headache, flushing, abdominal discomfort, hypotension, and tachycardia). Moreover, the authors found decreased expression of the proinflammatory cytokines monocyte chemoattractant protein (MCP-1) and the vascular endothelial growth factor (VEGF) in blood and skin, indicating a possible dysregulation of the immune system in FM patients (18). However, serum VEGF alterations with respect to healthy pain-free volunteers have not been confirmed by another study (25), which instead found elevated IL-8 serum levels and presence of arterial stiffness. Since both studies are limited by the small sample size, the inconsistency of the results do not surprise us.

In conclusion, some evidences support the presence of immune dysregulation and inflammation associated with FM, but further studies on larger populations are essential so that these are confirmed.

Table I. Studies and findings that support or confute the hypothesis of central and peripheral sensitisation mechanisms involved in the etiopathogenesis of FM.

	Central sensitisation	Peripheral sensitisation
Pros	Expansion of pain receptive fields (1)	• Overlap with diabetic pain nephropathy (8)
	• Increased levels of substance P and neurotrophic factors (2, 3)	• Injection of local anaesthetics into painful muscles normalises somatic hyperalgesia (10)
	• Decreased pain thresholds (4, 5) • Enhanced sensitivity outside of typical tender point locations (7) • Abnormal windup (1) • Prolonged pain after cessation of painful input (1) • Stress-induced hyperalgesia animal model (12) • Association of FM with a polymorphism of the gene encoding for AMPA receptor (20)	
Cons	• Increased pain not due to hyperalgesia but to fear of movement (6) • Phenomenon of adaptation not involved in the pathogenesis (9)	• Phenomenon of adaptation not involved in the pathogenesis (9)

Assessment

Is there any news about classification criteria?

The American College of Rheumatology (ACR) classification, criteria drawn up in 1990, required tenderness on pressure in at least 11 of 18 specified sites and the presence of widespread pain for diagnosis, defined as axial pain, left and right-sided pain, and upper and lower segment pain. In the last years, many objections have been expressed in relation to these criteria (26), particularly because they stipulated that, in order to make a diagnosis of fibromyalgia, chronic widespread pain should be present for at least 3 months, without specifying that any other disease, accounting for the chronic widespread pain, had to be excluded by the examiner. Furthermore, tender point count was rarely or incorrectly performed in primary care and the symptoms were not given the right consideration. Indeed patients whose symptoms and tender points decreased often failed to satisfy these criteria: approximately 25% of FM patients did not satisfy the ACR 1990 classification criteria even though they were considered to have fibromyalgia by their physicians.

However, the 1990 criteria performed well in specialty clinics and were very useful in providing some patient homogeneity for clinical trials.
The previous objections, together with the real need to find a common definition and classification for FM, led Wolfe *et al*. (27) in 2010 to develop simple, practical criteria for a clinical diagnosis of fibromyalgia. These new criteria had been thought to be suitable for use in primary and specialty care and did not require a tender point examination, providing instead a severity scale for characteristic fibromyalgia symptoms.
The authors identified two variables that best defined fibromyalgia and its symptom spectrum: the widespread pain index and the composite symptom severity scale, a composite variable composed of physician-rated cognitive problems, unrefreshing sleep, fatigue and somatic symptoms.
Furthermore, in 2011, Wolfe published a modification of the ACR preliminary Diagnostic Criteria for Fibromyalgia that allowed their use in epidemiologic and clinical studies without the requirement for an examiner. Practically, the author modified the symptom severity scale by substituting the somatic symptoms item with a 0–3 item that represented the sum of 3 items: headaches, pain or cramps in liver, abdomen or depression symptoms during the previous 6 months. However, it is important to remark that, although simple to use, the new criteria are not thought to be used for self-diagnosis (28).

Is there any news about symptom evaluation and monitoring?
FM is a generalised pain condition accompanied by a number symptoms such as fatigue, sleep disturbance, headache, cramps, irritable bowel syndrome, temporomandibular joint disorder, restless leg syndrome and mood disorder. Articles published in the last year have evaluated some of these symptoms, as listed below.

– Fatigue
Fatigue may represent, after chronic pain, the most common and invalidating problem. A definition of the "fatigue" is not an easy one and it involves both physical and mental features. It is associated with a range of chronic disease, in particularly rheumatic disease as Sjögren's syndrome (SS). In SS, fatigue is one of the most common symptoms, although it is not included in the current classification criteria. In a study of Priori *et al*. the authors evaluated the relationship between fatigue and SS and the overlapping FM. An overlapping FM can contribute to, but does not entirely account, for fatigue in Italian patients with primary SS (29).

– Sleep disturbance
Although not included in the standard diagnostic criteria for FMS, sleep disturbances, such as difficulty falling asleep, frequent awakening during the night, and early awakening with difficulty returning to sleep, are very commonly reported by persons with FM.
In 2011 two studies evaluated the concordance between the subjective and objective methods of sleep assessment and found that women with objective sleep deficits had significantly higher pain scores on the tender point index, perceived their sleep as significantly worse, and reported significantly more depressive symptoms and more negative impact of FM on functioning than those without deficits (30, 31).
Misestimation of sleep seems to be common in FM patients, particularly when their sleep quality is poor. That is the reason why Crawford and colleagues developed a new scoring algorithm of the Jenkins Sleep Scale (JSS), a self-completed instrument assessing sleep symptoms, and support its use in research to document treatment benefit with regard to sleep problems in FM patients (32, 33). Improvement in quality of sleep, as measured by the JSS, has been shown to correlate with improved FM pain symptoms.
What other leading causes could there be, excluding pain, for poor sleep quality in FM? The literature suggests that obesity, that is common in FM, supports a positive relationship between obesity and shorter sleep duration in the general population. Moreover, sleep quality is a significant contributor both for fatigue and pain in FM, as reported by a study by Okifuji *et al*. that evaluated the relationship between FM and obesity in the multiple domains relevant to FM, including pain, hyperalgesic response, sleep, physical abilities, and mood, with a larger sample of FM patients. Obesity in FM was in fact associated with greater pain sensitivity, poorer sleep quality, and reduced physical strength and flexibility. Moreover, the results of this study suggest that obesity may aggregate FM and weight management may need to be incorporated into treatments (34).
Another factor that can influence and disrupts sleep is the presence of restless legs syndrome (RLS), a sensorimotor disorder characterised by an urge for leg movement, often accompanied by an uncomfortable sensation deep within the legs. RLS can be an idiopathic condition, or occur secondary to iron deficiency, peripheral neuropathy, uraemia, pregnancy, medication side-effects, and other conditions. The clinical overlap between RLS and FM has motivated researchers to search for a link between these disorders. The relationship between RLS and FM was evaluated in a recent cross-sectional study analysing the influence on sleep. This study demonstrates that FM is strongly associated with RLS, which was about 10 times more prevalent in the FM group than among the control group; FM patients have higher insomnia and daytime sleepiness ratings than controls.
In conclusion a substantial portion of sleep disturbance in FM may be RLS-related and because RLS is a treatable cause of sleep disruption and insomnia, it is prudent to routinely evaluate patients with FM for RLS (35).

– Muscle stiffness and cramps
Cramps and muscle stiffness are very common in FM particularly in patients with spasmophilia. The literature shows that FM is often accompanied by the presence of latent tetany or spasmophilia (SP) that requires provocative tests to be highlighted and that could be secondary to hypomagnesaemia.
There are no relevant data in the literature that analyse the characteristics of patients with spasmophilia. In a study published in 2011 (36), 314 patients affected by FM and FM in overlap with

SP (FM+SP) in a single centre, were evaluated by our team. No differences were found regarding the quality of life, fatigue, pain and other evaluated symptoms, while a lower mean tender points (TP) number and a higher frequency of restless leg syndrome and tachycardia were found in the FM+SP group.
Moreover, the presence of SP seems to influence psychiatric comorbidity, which was less prevalent in FM+SP patients. In FM+SP patients, panic disorder unexpectedly was not representative, as panic disorder and latent tetany appear to occur concomitantly (36).

– Pain
As previously described concerning the etiopathogenesis, pain is the principal symptom of FM. It is known that many factors can influence pain perception. During the last years a particular attention has been focused on vitamin D levels, which seem to influence non-specific bone pain. The role of vitamin D was studied in many diseases and deficiency of vitamin D has been reported in patients with many types of musculoskeletal pain. Thus, the involvement of 1,25-OH D in immune system regulation could represent a link between muscle pain and vitamin D deficiency. Nevertheless, it is not possible to exclude that, alternatively, patients with musculoskeletal pain could be vitamin D deficient due to pain itself, poor mobility or associated depression, potentially leading to less time spent outdoors, or high rates of adiposity leading to decreased synthesis of vitamin D.
In the past, some studies investigating vitamin D levels in FM and other non-specific skeletal pain conditions were published, highlighting a vitamin D deficiency and a positive association of vitamin D deficiency and pain, particularly in women. However these correlations were not confirmed by more recent studies, which were not able to find statistically significant differences between FM patients and controls, either with respect to the mean serum concentration of 1,25-OH D or to the classification of levels as deficient, insufficient, or sufficient. Moreover, there was no correlation between 1,25-OH D levels and pain intensity (37-39).

What about psychiatric comorbidity?
It is well known that FM is frequently associated with psychiatric symptoms such as anxiety and depression; indeed some authors have argued about the possibility of classifying this syndrome into affective spectrum disorders.
Like other chronic pain conditions, FM is thought to involve psychological and social factors. The basis of this hypothesis is that pre-existing personality and psychological characteristics of the individual are mainly responsible for a variety of emotional reactions following a painful event. In the past year, many studies have reported a familial aggregation in FM. However, no differences between FM patients and their relatives with and without FM were found regarding psychological distress symptoms (40). Glazer *et al*. wanted to supply additional support by investigating whether patients with FM differ from their first-degree relatives with and without FM regarding the four personality traits, known as novelty seeking, harm avoidance, reward dependence, and persistence. This study suggests that relatives with FM show personality resemblance to FM patients especially in the personality trait harm avoidance. It appears that there are factors in this personality trait that are hereditary and that may contribute to the development of FM (41).
However, the most problematic aspect of FM and overlapping psychiatric disorders is represented by an increased risk of death from suicide and accidents. The causes of a markedly increased rate of suicide among female patients with FM are at present unknown but may be related to increased rates of lifetime depression, anxiety, and other psychiatric disorders (42). Furthermore, mortality directly due to the disease and to the resulting disability has not increased. Thus, risk factors for suicide should be sought at the time of the diagnosis of FM and carefully evaluated during the follow-up (43, 44).

Is there any news about the social costs of FM?
FM affects a population mostly of a productive age and is thus associated with significant lost of productivity and disability, in addition to healthcare costs for medications and physician visits. Winkelmann *et al*. have recently examined health resource utilisation and costs associated with FM in routine clinical practice in France and Germany. FM imposes a significant economic burden on society. Consistent with other studies, FM subjects were found to have substantial costs, over 75% of which were driven by indirect costs from lost productivity (45). These costs increased as FM severity increased, resulting in a more than 200% difference in cost between mild and severe FM (46).

Therapy
A broad range of drugs has been traditionally used to treat FM (47). Pharmacological therapies which are effective in most patients do not already exist. Indeed the response to therapy is characterised by a wide variability among patients, due to the nature of the disease itself, which includes several different subtypes. These subtypes share, as previously explained, a common pathogenetic mechanism involving central sensitisation, but we cannot exclude that they could follow different effector mechanisms.
Moreover Mitsikostas *et al*., in a meta-analysis of placebo-controlled clinical trials on 2026 placebo-treated patients, highlighted that nocebo dropouts in FM trials were four-fold and two-fold higher than in randomised controlled trials (RCTs) for multiple sclerosis treatment and migraine. Thus, since nocebo is known to contribute to drug intolerance and treatment failure in clinical practice, identification of predisposing factors and efforts to prevent nocebo by educating these patients appropriately may be important for FM outcome (48).
In order to develop responder definitions for fibromyalgia clinical trials using key symptom and functional domains, a meta-analysis of the pooled results for four of the most commonly used medications established risk ratios to determine the definitions that best favoured medication over placebo. Two definitions performed best in the analyses. Both definitions included ≥30% reduction in pain and ≥10% improvement in physical function. They differed in that one (FM30 short version) included

≥30% improvement in sleep or fatigue, and the other (FM30 long version) required ≥30% improvement in two of the following symptoms: sleep, fatigue, depression, anxiety, or cognition. The identification of these two definitions may improve the sensitivity of clinical trials to identify meaningful improvements, leading to improved management of fibromyalgia (49).

Therefore, symptoms, comorbidities, adverse effects, and, of course, patient preference are important considerations in drug selection. That is the reason why we have planned to provide a useful review of old and new drugs for the treatment of FM, underlining what emerged during the last year from meta-analysis, new RTCs and head-to-head trials.

What is new about old drugs?

– Amitriptyline

Amitriptyline is the most common drug prescribed for the treatment of fibromyalgia. In the recent past, amitriptyline was known to influence the autonomic nervous system and that seemed to contrast the associated disautonomia which is very frequently reported in FM patients. However, Kulshreshtha *et al*. have recently demonstrated that amitriptyline therapy (10 mg for 3 months increases blood flow to the affected sites. Moreover, when prescribed for 3 months to 21 female patients with fibromyalgia, it did not affect autonomic tone and reactivity (50).

Head-to-head trials including amitriptyline are few, and provided low-strength evidence that short-term treatment with amitriptyline is inferior to immediate-release paroxetine in reducing pain and sleep disturbance. Nevertheless amitriptyline did not result to be statistically different as compared with nortriptyline (one of its active metabolites) and cyclobenzaprine, both in terms of efficacy and safety, and in particular it was similar to duloxetine, milnacipran, and pregabalin on outcomes of pain and fatigue (51).

– Cyclobenzaprine

Another commonly prescribed drug is cyclobenzaprine, a muscle relaxant agent marketed for decades. A recent study evaluated cyclobenzaprine efficacy on 36 randomised patients treated with low dose cyclobenzaprine (1–4 mg) administered at bedtime. Changes in subjective symptoms including pain, tenderness, fatigue, mood and objective electroencephalogramme (EEG)-assessed sleep physiology were also evaluated. The authors concluded that bedtime-low doses of the drug improved core FM symptoms associated to positive changes of EEG (52).

– Opioids

There is limited information on opioid treatment in fibromyalgia, with all current guidelines discouraging opioid use. In this regard, Fitzcharles *et al*. have recently conducted a chart review of all FM patients referred to a tertiary care pain centre clinic in order to evaluate use of opioid medications. Opioids were used by 32% of 457 patients, with over two thirds using strong opioids. The authors observed negative health and psychosocial status in FM patients using opioids. Thus a prolonged use of opioids in fibromyalgia requires evaluation (53).

What about more recently used drugs?

– Milnacipran

Milnacipran is a serotonin-noradrenalin reuptake inhibitor (SRNI), also active in rodent models of irritable bowel syndrome and abdominal visceral pain. Indeed, pre-clinical studies suggested that milnacipran has potential clinical application in the treatment of visceral pain, *i.e*. irritable bowel syndrome-which is known to frequently appear in comorbidity with FM (54).

Concerning the FM symptoms control, milnacipran seemed instead to be more effective in non-depressed patients (55). The incidence rates of serious cardiovascular between large cohorts receiving milnacipran *versus* venlafaxine, and amitriptyline were not different, thus confirming the safety profile of the drug (56).

– Duloxetine

During the last year several studies concerning duloxetine have been published. Duloxetine is another potent SRNI, effective for the treatment generalised anxiety disorder and fibromyalgia. It recommended at doses of 60, 90 and 120 mg/day (51), though which the patient can achieve a pain reduction, be less bothered by sleep difficulties, and improve mood, stiffness, fatigue and functioning (56). Although well tolerated, it is important to be knowledgeable about the potential for pharmacokinetic interactions. According to a review by Knadler *et al*., only impaired hepatic function or severely impaired renal function warrant specific warnings or dose recommendations. Pharmacokinetic results from drug interaction studies show that activated charcoal decreases duloxetine exposure. In addition, smoking is associated with a 30% decrease in duloxetine concentration. The exposure of duloxetine with CYP2D6 inhibitors or in CYP2D6 poor metabolisers is increased to a lesser extent than that observed with CYP1A2 inhibition and does not require a dose adjustment. Pharmacodynamic study results indicate that duloxetine may enhance the effects of benzodiazepines, but not alcohol or warfarin. An increase in gastric pH produced by histamine H2-receptor antagonists or antacids did not impact the absorption of duloxetine (57).

Moreover, Wang *et al*. have recently ventured into the research of early indicators of response to duloxetine treatment for fibromyalgia pain. To achieve this purpose, pooled data from four double-blind, placebo-controlled trials in duloxetine-treated patients (n=797) with fibromyalgia were analysed. Classification and Regression Tree (CART) analysis was used to determine what level of early pain improvement – as measured by the 24-hour average pain severity question on the Brief Pain Inventory (BPI) – best predicted later response. The results of the CART analysis showed that, for patients with ≥15% improvement in pain at week 1 and ≥30% improvement at week 2, the probability of response at 3 months was 75%. For patients with <15% improvement at both week 1 and week 2, the probability of not responding at 3 months was 86%. These results may aid clinicians to predict the likelihood of response at 3 months within the first 2 weeks of duloxetine treatment (58).

Another study evaluated the improvement of fatigue in FM patients treated with duloxetine. In fact, fatigue represents one of the most disabling symptoms associated with FM, greatly impacting patients' quality of life. Patients were randomised to duloxetine 60–120 mg/day (n=263) or placebo (n=267) for the 12-week acute phase. At week 12, all placebo-treated patients were switched to double-blind treatment with duloxetine for the extension phase. Fatigue was assessed at baseline and every 4 weeks with the Multidimensional Fatigue Inventory (MFI) scales. Treatment with duloxetine significantly improved multiple dimensions of fatigue in patients with fibromyalgia, and improvement was maintained for up to 24 weeks. Also placebo-treated patients who switched to duloxetine (n=187) had significant within-group improvement in Physical, General, and Mental Fatigue (59).

– Pregabalin

Pregabalin is an anticonvulsant drug indicated in the treatment of neuropathic pain. In a recently published international, double-blind, placebo-controlled trial, the efficacy and safety of pregabalin monotherapy (300, 450 or 600 mg twice a day) were evaluated. Pregabalin demonstrated modest efficacy in pain, global assessment, and function in FM at 450 mg/day, and improved sleep across all dose levels, but it did not provide consistent evidence of benefit at 300 and 600 mg/day. Indeed, a indirect comparison meta-analysis suggests that pregabalin at a dose of 450 mg per day could result in more responders than at 300 mg, but this result needs to be interpreted with caution as there were no significant differences between 600 and 300 mg or between 600 and 450 mg (60). Nevertheless pregabalin was generally well tolerated (61). Furthermore, results from another study published in the last year confirmed that licensed doses of pregabalin produced significantly greater improvements in sleep, when compared with milnacipran (as measured by Medical Outcomes Study Sleep Scale) (62). Finally, the comorbid conditions (*e.g.* irritable bowel syndrome, neurological disorders, concomitant headache, allergies, gastroesophageal, and/or psychiatric disorders) presence in FM patients are not associated with altered pregabalin efficacy (63).

– Sodium oxybate

Concerning treatments for which indication for FM has been supported, sodium oxybate (SXB) represents a novelty of the last years. Indeed, several randomised, controlled trials, among which one was published in May 2011 (64), demonstrated significantly improved FM symptoms with SXB. Last summer, Professor Staub, gave his opinion on the use of SXB in FM patients and on the reaction of the Food and Drug Administration (FDA) towards the possibility to prescribe it for FM.

As seen in narcolepsy trials, sodium oxybate improved sleep of FM patients, increased slow-wave sleep duration as well as delta power, and reduced frequent night-time awakenings. Furthermore, FM pain and fatigue was consistently reduced with nightly administrations over time. Commonly reported adverse events, including headache, nausea, dizziness and somnolence, showed an incidence twice than that of placebo. Despite its proven efficacy and safety, SXB did not receive FDA approval for the management of FM in 2010, mostly because of concerns about abuse. According to Staub, insomnia, fatigue and pain are important clinical FM symptoms that showed moderate improvements with SXB in several large, well-designed clinical trials. Because of the limited efficacy of currently available FM drugs, additional treatment options are needed. In particular, Staub strongly affirmed that drugs like SXB, which belong to a different drug class than other FDA-approved FM medications (*i.e.* pregabalin, duloxetine and milnacipran), would provide a much-needed addition to presently available treatment options. However, the FDA has set the bar high for future SXB re-submissions, with requirements of superior efficacy and improved risk mitigation strategies. At this time, no future FDA submission of SXB for the FM indication is planned (65).

Is there any new drug candidate for FM treatment?

– Dolasetron

Dolasetron is a 5-hydroxytryptamine 3 receptor antagonist, recently proposed for the treatment of FM. A randomised placebo-controlled trial, aimed to evaluate the efficacy and safety of dolasetron, intravenously administered at the dose of 12.5 mg/day, was conducted in few patients, but with promising results. Reduction in pain intensity at the third month (M3) of treatment was significantly greater in dolasetron-treated patients (p=0.04, -21.3 on a 0–100 visual analogue scale) compared with placebo controls (-5.9). The "patient global impression of change" was significantly greater in the dolasetron group at M3 (p=0.02). Unfortunately, the other secondary outcomes FM impact questionnaire, assessment of quality of life (SF-36), the hospital anxiety and depression scale, the manual tender point count, and functional symptoms associated with FM) failed to reach statistical significance. Nevertheless, the most common adverse events – constipation, nausea, dizziness and headache – did not statistically differ between the two groups (66). Finally, with this clinical trial the role of 5-HT3 receptor in the pathogenesis of FM was confirmed.

– Melatonin

Melatonin, the major hormone produced by the pineal gland under the influence of the dark/light cycle, has been shown to have a large number of therapeutic effects. As well as its chronobiological role, several pharmacological effects of melatonin have been reported including anxiolytic, antidepressant, sedative, antioxidant and analgesic activities. It is known that melatonin may be effective in treating the pain associated with FMS, however, few data support this claim. The recent study using different doses of melatonin alone or in combination with fluoxetine administration showed that this was effective in the treatment of patients with FMS (67).

What about complementary therapies?

In order to improve quality of life of FM patients, exercise has been suggested as the main non pharmacologi-

cal strategy in the management this complex syndrome (68).

In the past year, Cazzola *et al*. (69) examined the effectiveness of different kinds of physical exercise in FM patients. Twenty-seven randomised controlled trials published between 1985 and August 2010, were selected, considering: land-based physical aerobic exercises, water exercises and muscle strengthening exercises. Although it was not easy to highlight differences coming from clinical trials evaluating various types of physical exercises – which were in fact characterised by different workloads and rehabilitation settings – the authors agreed on the effectiveness of landed-based physical aerobic activity in improving physical function. Nevertheless, there was no evidence to suggest any improvement in pain and other extra-skeletal symptoms. Only water-based exercises showed some advantages in reducing pain and improving depressive symptoms, but the data were insufficient to establish its superiority with respect to land-based exercises. In conclusion, the authors underlined the importance of monitoring post-exercise pain in order to assess whether the programme fits the requirements of actual and possible patient performance (69).

A new physical therapy proposed for the treatment of FM is the Whole Body Vibration (WBV), an exercise programme that uses a vibration platform generating a mechanical stimulus that increases the muscles gravitational load. WBV has been used with success in sports training and in the rehabilitation of different diseases A clinical trial evaluated the efficacy of WBV in a 6-week exercise programme, in which patients were randomised to two different arms of treatments, so that physical exercises with or without the addition of WBV. Although the study was carried on a small number of patients, this new treatment seemed to improve muscular function and to provide additional health benefits (70).

Concerning complementary alternative medicine (CAM), acupuncture is one of the most frequently used intervention, even if the most recent qualitative systematic reviews on the efficacy of acupuncture in FM did not provide consistent conclusions. The difficulty in demonstrating the efficacy of such a treatment is obviously complicated by the impossibility to perform double-blind trials, as reported by a recent study (71). In 2010, Langhors *et al*. published a systematic review about the efficacy of acupuncture in FM analysing seven RCTs that included 385 patients. Strong evidence was found for the reduction of pain at post-treatment, while there was no evidence for a positive effect on other main symptoms of FM. The authors concluded that acupuncture was not associated with serious harmful events and that it is a good acceptance treatment but it cannot be recommended for the management of FM (72).

What can we conclude?

During the last year, no significant novelty was introduced concerning the therapeutic approach of fibromyalgia. Indeed, the state of the art remains more or less the same as published in the Fibromyalgia Supplement of 2010: "Although various medications are used to manage the painful symptoms associated with FM, only pregabalin, duloxetine and milnacipran have been approved for use in the USA by the FDA over the last five years. However treatment with sodium oxybate appears to be promising. 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" (73).

Fibromyalgia is a disease that affects the quality of life as is the case with arthritis, however, more FM patients see the disease as having more detrimental effects on their health than RA patients and the general population (74).

Therefore, the new issues raised from clinical studies and reviews published during the last year, here reported, are predominantly linked to the utilisation of the described treatments in real practise. Thus, the multimodal approach of FM (which includes pharmacological and complementary therapies, and patients' education) still remains the most effective and safe, and the choice of treatments should be individualised based on patients' symptoms (75) and comorbidities.

References

1. KINDLER LL, BENNETT RM, JONES KD: Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Manag Nurs* 2011; 12: 15-24.
2. PETERSEL DL, DROR V, CHEUNG R: Central amplification and fibromyalgia: disorder of pain processing. *J Neurosci Res* 2011; 89: 29-34.
3. HARRIS RE: Elevated excitatory neurotransmitter levels in the fibromyalgia brain. *Arthritis Res Ther* 2010; 12: 141.
4. REYES DEL PASO GA, GARRIDO S, PULGAR Á, DUSCHEK S: Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *J Psychosom Res* 2011; 70: 125-34.
5. NORMAND E, POTVIN S, GAUMOND I, CLOUTIER G, CORBIN JF, MARCHAND S: Pain inhibition is deficient in chronic widespread pain but normal in major depressive disorder. *J Clin Psychiatry* 2011; 72: 219-24.
6. LAMBIN DI, THIBAULT P, SIMMONDS M, LARIVIERE C, SULLIVAN MJ: Repetition-induced activity-related summation of pain in patients with fibromyalgia. *Pain* 2011; 152: 1424-30.
7. ALONSO-BLANCO C, FERNÁNDEZ-DE-LAS-PEÑAS C, MORALES-CABEZAS M, ZARCO-MORENO P, GE HY, FLOREZ-GARCÍA M: Multiple active myofascial trigger points reproduce the overall spontaneous pain pattern in women with fibromyalgia and are related to widespread mechanical hypersensitivity. *J Clin Pain* 2011; 27: 405-13.
8. KOROSCHETZ J, REHM SE, GOCKEL U *et al*.: Fibromyalgia and neuropathic pain--differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. *BMC Neurol* 2011; 11: 55.
9. HOLLINS M, HARPER D, MAIXNER W: Changes in pain from a repetitive thermal stimulus: the roles of adaptation and sensitization. *Pain* 2011; 152: 1583-90.
10. STAUD R: Is it all central sensitization? Role of peripheral tissue nociception in chronic musculoskeletal pain. *Curr Rheumatol Rep* 2010; 12: 448-54.
11. BUSKILA D, ABLIN JN, BEN-ZION I *et al*.: A painful train of events: increased prevalence of fibromyalgia in survivors of a major train crash. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S79-85.
12. GREEN PG, ALVAREZ P, GEAR RW, MENDOZA D, LEVINE JD: Further validation of a model of fibromyalgia syndrome in the rat. *J Pain* 2011; 12: 811-8.
13. WILBARGER JL, COOK DB: Multisensory hypersensitivity in women with fibromyalgia: implications for well being and intervention. *Arch Phys Med Rehabil* 2011; 92: 653-6.
14. DI FRANCO, IANNUCCELLI C, ALESSANDRINI C *et al*.: Autonomic dysfunction and neuropeptide Y in fibromyalgia. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S75-8.
15. XIAO Y, HE W, RUSSELL IJ: Genetic polymorphisms of the beta2-adrenergic receptor relate to guanosine protein-coupled stimulator receptor dysfunction in fibromyalgia syndrome. *J Rheumatol* 2011; 38: 1095-103.

16. BAZZICHI L, ROSSI A, GIACOMELLI C, BOMBARDIERI S: Exploring the abyss of fibromyalgia biomarkers. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S125-30.
17. COHEN H, NEUMANN L, GLAZER Y, EBSTEIN RP, BUSKILA D: The relationship between a common catechol-O-methyltransferase (COMT) polymorhism val(158) met and fibromyalgia. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S51-6.
18. BLANCO I, BÉRITZE N, ARGÜELLES M *et al*.: Abnormal overexpression of mastocytes in skin biopsies of fibromyalgia patients. *Clin Rheumatol* 2010; 29: 1403-12.
19. ABLIN JN, BAR-SHIRA A, YARON M, ORR-URTREGER A: Candidate-gene approach in fibromyalgia syndrome: association analysis of the genes encoding substance P receptor, dopamine transporter and alpha1-antitrypsin. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S33-8.
20. SMITH SB, MAIXNER DW, FILLINGIM RB *et al*.: Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. *Arthritis Rheum* 2011 Sep 8 [Epub].
21. GIACOMELLI C, BAZZICHI L, GIUSTI L *et al*.: MALDI-TOF and SELDI-TOF analysis: "tandem" techniques to identify potential biomarker in fibromyalgia *Reumatismo* 2011; 63: 165-170.
22. AKAR S, CAN G, SOYSAL O *et al*.: Fibromyalgia syndrome in patients with rheumatoid arthritis: which criteria is appropriate to define the condition. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S106.
23. TORRENTE-SEGARRA V, CARBONELL-ABELLÓ J, CASTRO-OREIRO S, MANRESA DOMÍNGUEZ JM: Association between fibromyalgia and psychiatric disorders in systemic lupus erythematosus. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S22-6.
24. BAZZICHI L, ROSSI A, ZIRAFA C *et al*.: Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia? *Rheumatol Int* 2010 Nov 18 [Epub] .
25. KIM SK, KIM KS, LEE YS, PARK SH, CHOE JY: Arterial stiffness and proinflammatory cytokines in fibromyalgia syndrome. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S71-7.
26. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Conmittee. *Arthritis Rheum* 1990; 33: 160-72.
27. WOLFE F, CLAWN D, FITZCHARLES MA *et al*.: The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care Res* 2010; 62: 600-10.
28. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011; 38: 1113-22.
29. PRIORI R, IANNUCCELLI C, ALESSANDRI C *et al*.: Fatigue in Sjögren's syndrome: relationship with fibromyalgia, clinical and biologic features. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S82-6.
30. STUIFBERGEN AK, PHILLIPS L, CARTER P, MORRISON J, TODD A: Subjective and objective sleep difficulties in women with fibromyalgia syndrome. *J Am Acad Nurse Pract* 2010; 22: 548-56.
31. OKIFUJI A, HARE BD: Nightly analyses of subjective and objective (actigraphy) measures of sleep in fibromyalgia syndrome: what accounts for the discrepancy? *Clin J Pain* 2011; 27: 289-96.
32. JENKINS CD, STANTON BA, NIEMCRYK SJ, ROSE RM: A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol* 1988; 41: 313-21.
33. CRAWFORD BK, PIAULT EC, LAI C, SARZI-PUTTINI P: Assessing sleep in fibromyalgia: investigation of an alternative scoring method for the Jenkins Sleep Scale based on data from rendomised controlled stidies. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S100-9.
34. OKIFUJI A, DONALDSON GW, BARCK L, FINE PG: Relationship between fibromyalgia and obesity in pain, function, mood, and sleep. *J Pain* 2010; 11: 1329-37.
35. VIOLA-SALTZMAN M, WATSON NF, BOGART A, GOLDBERG J, BUCHWALD D: High prevalence of restless legs syndrome among patients with fibromyalgia: a controlled cross-sectional study. *J Clin Sleep Med* 2010 15; 6: 423-7.
36. BAZZICHI L, CONSENSI A, ROSSI A *et al*.: Spasmophilia comorbidity in fibromyalgia syndrome. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S94-9.
37. BHATTY SA, SHAIKH NA, IRFAN M, KASHIF SM, VASWANI AS, SUMBHAI A, GUNPAT: Vitamin D deficiency in fibromyalgia. *J Pak Med Assoc* 2010; 60: 949-51.
38. HEIDARI B, SHIRVANI JS, FIROUZJAHI A, HEIDARI P, HAJIAN-TILAKI KO: Association between nonspecific skeletal pain and vitamin D deficiency. *Int J Rheum Dis* 2010; 13: 340-6.
39. DE REZENDE PENA C, GRILLO LP, DAS CHAGAS MEDEIROS MM: Evaluation of 25-hydroxyvitamin D serum levels in patients with fibromyalgia. *J Clin Rheumatol* 2010; 16: 365-9.
40. GLAZER Y, CHOEN H, BUSKILA D, EBSTEIN RP, GLOSTER L, NEUMANN L: Are psychological distress symptoms different in fibromyalgia patients compared to relatives with and without fibromyalgia? *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S11-S15.
41. GLAZER Y, BUSKILA D, COHEN H, EBSTEIN RP, NEUMANN L: Differences in the personality profile of fibromyalgia patients and their relatives with and without fibromyalgia. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S27-32.
42. DELL'OSSO L, BAZZICHI L, CONSOLI G *et al*.: Manic spectrum symptoms are correlated to the severity of pain and the health-related quality of life in patients with fibromyalgia. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S57-61.
43. WOLFE F, HASSETT AL, WALITT B, MICHAUD K: Mortality in fibromyalgia: a study of 8,186 patients over thirty-five years. *Arthritis Care Res* 2011; 63: 94-101.
44. DREYER L, KENDALL S, DANNESKIOLD-SAMSØE B, BARTELS EM, BLIDDAL H: Mortality in a cohort of Danish patients with fibromyalgia: increased frequency of suicide. *Arthritis Rheum* 2010; 62: 3101-8.
45. RIVERA J, REJAS J, ESTEVE-VIVES J; GROUPO ICAF: Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56): S39-45.
46. WINKELMANN A, PERROT S, SCHAEFER C *et al*.: Impact of fibromyalgia severity on health economic costs: results from a European cross-sectional study. *Appl Health Econ Health Policy* 2011; 9: 125-36.
47. MALMUD CJ: Focus on pain mechanisms and pharmacotherapy in the treatment of fibromyalgia syndrome. *Clin Exp Rheumatol*. 2009; 27 (Suppl. 56): S86-91.
48. MITSIKOSTAS DD, CHALARAKIS NG, MANTONAKIS LI, DELICHA EM, SFIKAKIS PP: Nocebo in fibromyalgia: meta-analysis of placebo-controlled clinical trials and implications for practice. *Eur J Neurol* 2011 Oct 4 [Epub] .
49. ARNOLD LM, WILLIAMS DA, HUDSON JI *et al*.: Development of responder definitions for fibromyalgia clinical trials. *Arthritis Rheum* 2011 Sep 27 [Epub] .
50. KULSHRESHTHA P, GUPTA R, YADAV RK, BIJLANI RL, DEEPAK KK: Effect of low-dose amitriptyline on autonomic functions and peripheral blood flow in fibromyalgia: a pilot study. *Pain Med* 2011 Dec 5 [Epub] .
51. SMITH B, PETERSON K, FU R, MCDONAGH M, THAKURTA S, PORTLAND OR: Drug Class Reviews. Oregon Health & Science University, 2011.
52. MOLDOFSKY H, HARRIS HW, ARCHAMBAULT WT, KW ONG T, LEDERMAN S: Placebo-controlled Study. *J Rheumatol* 2011; 38: 2653-63.
53. FITZCHARLES MA, STE-MARIE PA, GAMSA A, WARE MA, SHIR Y: Opioid use, misuse, and abuse in patients labeled as fibromyalgia *Am J Med* 2011; 124: 955-60.
54. DEPOORTÈRE R, MELEINE M, BARDIN L *et al*.: Milnacipran is active in models of irritable bowel syndrome and abdominal visceral pain in rodents. *Eur J Pharmacol* 2011; 672: 83-7.
55. MEASE PJ, ZIMETBAUM PJ, DUH MS *et al*.: Epidemiologic Evaluation of Cardiovascular Risk in Patients Receiving Milnacipran, Venlafaxine, or Amitriptyline: Evidence from French Health Data (February). *Ann Pharmacother* 2011 Feb 8 [Epub] .
56. ARNOLD LM, CLAUW D, WANG F, AHL J, GAYNOR PJ, WOHLREICH MM: Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2010; 37: 2578-86.
57. KNADLER MP, LOBO E, CHAPPELL J, BERGSTROM R: Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2011; 50: 281-94.
58. WANG F, RUBERG SJ, GAYNOR PJ, HEINLOTH AN, ARNOLD LM: Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia. *J Pain* 2011; 12: 1088-94.
59. ARNOLD LM, WANG F, AHL J, GAYNOR PJ, WOHLREICH MM: Improvement in multiple dimensions of fatigue in patients with fibro-

myalgia treated with duloxetine: secondary analysis of a randomized, placebo-controlled trial. *Arthritis Res Ther* 2011; 13: R86.

60. TZELLOS TG, TOULIS KA, GOULIS DG *et al*.: Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic reviewand a meta-analysis. *J Clin Pharm Ther* 2010; 35: 639-56.
61. PAUER L, WINKELMANN A, ARSENAULT P *et al*.: An International, Randomized, Double-blind, Placebo-controlled, Phase III Trial of Pregabalin Monotherapy in Treatment of Patients with Fibromyalgia. *J Rheumatol* 2011; 38: 2643-52.
62. CHOY E, MARSHALL D, GABRIEL ZL, MITCHELL SA, GYLEE E, DAKIN HA: A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. *Semin Arthritis Rheum* 2011; 41: 335-45.
63. BHADRA P, PETERSEL D: Medical conditions in fibromyalgia patients and their relationship to pregabalin efficacy: pooled analysis of Phase III clinical trials. *Expert Opin Pharmacother* 2010; 11: 2805-12.
64. RUSSELL IJ, HOLMAN AJ, SWICK TJ *et al*.: Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. 2011; 152: 1007-17.
65. STAUD R: Sodium oxybate for the treatment of fibromyalgia. *Expert Opin Pharmacother* 2011; 12: 1789-98.
66. VERGNE-SALLE P, DUFAURET-LOMBARD C *et al*.: A randomised, double-blind, placebo-controlled trial of dolasetron, a 5-hydroxytryptamine 3 receptor antagonist, in patients with fibromyalgia. *Eur J Pain* 2011; 15: 509-14.
67. HUSSAIN SA, AL-KHALIFA II, JASIM NA, GORIAL FI: Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res* 2011; 50: 267-71.
68. SUMAN AL, BIAGI B, BIASI G *et al*.: One-year efficacy of a 3-week intensive multidisciplinary non-pharmacological treatment program for fibromyalgia patients. *Clin Exp Rheumatol* 2009; 27: 7-14.
69. CAZZOLA M, ATZENI F, SALAFFI F, STISI S, CASSISI G, SARZI-PUTTINI P: Which kind of exercise is best in fibromyalgia therapeutic programmes? A practical review *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S117-24.
70. SAÑUDO B, DE HOYO M, CARRASCO L *et al*.: The effect of 6-week exercise programme and whole body vibration on strength and quality of life in women with fibromyalgia: a randomised study. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S40-5.
71. VAS J, MODESTO M, AGUILAR I, SANTOS-REY K, BENÍTEZ-PAREJO N, RIVAS-RUIZ F: Effects of acupuncture on patients with fibromyalgia: study protocol of a multicentre randomized controlled trial. *Trials* 2011; 12: 59.
72. LANGHORST J, KLOSE P, MUSIAL F, IRNICH D, HÄUSER W: Efficacy of acupuncture in fibromyalgia syndrome – a systematic review with a meta-analysis of controlled clinical trials. *Rheumatology* 2010; 49: 778-88.
73. DI FRANCO M, IANNUCCELLI C, ATZENI F *et al*.: Pharmacological treatment of fibromyalgia. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S110-6.
74. SALAFFI F, SARZI-PUTTINI P, GIROLIMETTI R, ATZENI F, GASPARINI S, GRASSI W: Health-related quality of life in fibromyalgia patients: a comparison with rheumatoid arthritis patients and the general population using the SF-36 health survey. *Clin Exp Rheumatol* 2009; 27 (Suppl. 56):S67-74.
75. SALAFFI F, SARZI-PUTTINI P, CIAPETTI A, ATZENI F: Assessment instruments for patients with fibromyalgia: properties, applications and interpretation. *Clin Exp Rheumatol* 2009; 27 (Suppl 56): S92-105.