Review

Fibromyalgia: a critical digest of the recent literature

C. Giacomelli[1], F. Sernissi[1], P. Sarzi-Puttini[2], M. Di Franco[3], F. Atzeni[2], L. Bazzichi[1]

[1]*Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy;*
[2]*Rheumatology Unit, Luigi Sacco University Hospital, Milan, Italy;*
[3]*Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome, Italy.*

Camillo Giacomelli, PhD
Francesca Sernissi, PhD
Piercarlo Sarzi-Puttini, MD
Manuela Di Franco, MD
Fabiola Atzeni, MD, PhD
Laura Bazzichi, MD

Please address correspondence to:
Camillo Giacomelli,
Dipartimento di Medicina Interna,
U.O. di Reumatologia,
Ospedale S. Chiara,
via Roma 67,
56126 Pisa, Italy.
E-mail: camillo.giacomelli@for.unipi.it

Received and accepted on December 5, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 79): S153-S157.

Key words: fibromyalgia, recent literature

Competing interests: none declared.

ABSTRACT

Fibromyalgia (FM) syndrome is a chronic disease with unknown etiology, characterised by widespread pain and fatigue. Moreover, several patients manifest non-specific symptoms such as sleep disturbances, mood disorders, and neurocognitive impairment. We have reviewed the literature of the past year to underline the progress of research in the fields of etiopathogenesis, therapies and assessment, considering articles published between November 2012 and November 2013.

Introduction

Fibromyalgia (FM) syndrome is a chronic disease with unknown etiology, characterised by widespread pain and fatigue. Moreover, several patients manifest non-specific symptoms such as sleep disturbances, mood disorders, and neurocognitive impairment. In the wake of the previous editions, we decided to review the literature of this last year to underline the progress of research in the fields of etiopathogenesis, therapies and assessment. For this reason, we propose an overview of the articles published between November 2012 and November 2013.

Ethiopathogenesis

With regard to the pathogenesis of FM some hypotheses have been formulated. Menzies *et al*. studied the epigenetic alteration to determine whether spontaneously occurring micronuclei and genome-wide methylation patterns could be related to FM (1). They found significant differences in methylation patterns in FM with respect to the control subjects and the majority of diferentially mehilated sites occurred in neuron differentiation and in the skeletal system. The genetic basis of FM emerged from a work published by Feng *et al*. (2). They performed a complete exome sequencing in a large cohort of FM patients and found a close relationship between C11orf40 mutation and plasma levels of cytokines, MCP-1 and IP-40. Other genetic alterations were found by a Turkish group who studied the polymorphism of the IL4 gene in a large cohort of 300 FM patients (3). They found a significant difference in the genome of IL4 in patients compared to the controls, and they suggested an association of IL-4 gene 70 bp VNTR polymorphism with susceptibility to develop FM. Some other polymorphisms were found in guanosine triphosphate cyclohydrolase 1 (4), the catechol-O-methyltrasferase (5), and alpha-1-antitrypsin polymorphisms (6); the related studies confirmed the previous findings, and underlined the familiar aggregation for FM.

Muscular pain is the main symptom of FM and among several authors searching for possible alterations in muscular fibres in FM patients, Klaver-Krol and colleagues measured the conduction velocity in FM patients and controls using surface electromyography (7). These authors found higher values of CV in FM patients and a correlation between CV scores and tender point scores.

An interesting point of view on pathogenesis is the one that takes into account the frequent diagnosis of FM in other rheumatic diseases. In fact several patients who suffer from rheumatic disease, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), were found to be in comorbidity with FM. Donmez *et al*. investigated this interesting observation, reporting that a concomitant FM was associated with depression and somatisation, rather than with the presence of autoantibodies (8). Another study that underlined the relationship between FM and other rheumatic diseases was published by Roussou and Ciurtin. In particular they observed an increase

of FM diagnosis in patients with spondyloarthritis (SPA); with one third of patients with inflammatory back pain belonging to their cohort who fulfilled the criteria for FM (9). In addition, it is noteworthy that fatigue and pain, two of the main symptoms of FM, are debilitating symptoms that negatively impact the quality of life in patients with SLE and primary Sjögren's syndrome (pSS). Indeed Iannuccelli *et al*. found a high percentage of FM in these diseases and speculated that FM seems to contribute to constitutional symptoms in SLE and pSS by the evaluation of tender points, the Health Assessment Questionnaire, the Fibromyalgia Impact Questionnaire and Zung Depression and Anxiety Scales (10).

The hypothesis that FM is a central sensitisation and dysregulation emerge from a large study performed on 11,288 patients with FM, RA and osteoarthritis (OA) (11). The authors observed in FM more sensory and non-sensory symptoms than in other patients with rheumatic disease. In particular, FM patients showed an increased hearing loss frequency than other patients, and this finding may support the central sensitisation of FM.

Despite the non-inflammatory origin of FM, several studies have reported the alteration of several cytokines in FM. Garcia *et al*. evaluated serum concentration of various chemokines (12), such as thymus and activation-regulated chemokine (TARC)/(CCL17), monokine induced by gamma-interferon (MIG)/(CXCL9), macrophage-derived chemokine (MDC)/(CCL22), interferon-inducible T-cell alpha chemoattractant (I-TAC)/(CXCL11), eotaxin (CCL11), pulmonary and activation-regulated chemokine (PARC)/(CCL18) and haemofiltrate CC-chemokine-4 (HCC-4)/(CCL16) in a small cohort of FM patients. They observed elevated serum levels of TARC, MIG, MED, I-TAC and eotaxin, and these results could be useful to characterise a subgroup of patients. Cytokine pattern was also studied by Oktayoglu *et al*. by the detection of high mobility group box 1 protein (HMGB1), a proinflammatory cytokine, in 29 FM patients. The researcher found higher levels of HMGB1 in FM patients and a positive correlation between this cytokine and FIQ score (13). Cordero *et al*. in a study of coenzyme Q10 reported the deficiency and mtochondrial dysfunction in FM. Mitochondrial dysfunction was accompanied by increased levels of interleukin-1 and interleukin-18, and the concept of inflammasome, therefore, seemed to play a central role in FM (14).

Assessment

The controversy between new and old diagnostic criteria remains open, and in a recent editorial, Professors Salaffi and Sarzi-Puttini were keen to point out that the results of the validation are currently still ongoing. Moreover, they reported that as many as 25% of patients diagnosed according new proposed criteria do not meet the older ones (15).

Another important aspect of FM evaluation is the focus on treatment satisfaction. A German group recently published an interesting cross sectional study, that evaluated putative patients-related predictors of treatment satisfaction in 1651 FM patients by means of a self reported questionnaire (16). They concluded that starting with the treatment of comorbidities such as depression could be an effective strategy to actively cope with the disease, and that this approach might prove to be successful in improving overall treatment satisfaction of FM-patients.

A common challenge in the assessment of fibromyalgia is represented by the psychiatric comorbidity. Veltri and colleagues recently evaluated a number of tools potentially able to evaluate the depressive comorbidy in FM, and they concluded that the mood spectrum self-report (MOOD-SR) is particularly appropriate for screening FM patients (17). In addition, Alciati and colleagues (18) studied the presence of bipolarspectrum disorders using both a categorical and a dimensional approach. The first one was based on a version of the DSM-IV SCID-CV interview, modified to improve the detection of bipolar spectrum disorders; the second one was based on the hypomania symptom checklist HCL-32, which adopts a dimensional perspective of the manic/hypomanic component of mood, by including sub-syndromal hypomania. The results showed an higher frequency of bipolar spectrum in FM with both approaches, suggesting that fibromyalgia may be related to bipolar spectrum disorders, and in particular to the hypomania/overactivity components.

Therapies

During the last year, researchers from all around the globe have published a number of papers concerning the therapy for the treatment of FM and its symptoms. In particular, many of these were focused on physical activities, rehabilitation and alternative medicine and, with respect to previous years, a lower number were related to pharmacological therapies.

Baptista *et al*. investigated the role of belly dance in FM patients (19). They studied 80 FM patients and showed a significant improvement of pain in the dance group, as well as higher Fibromyalgia Impact questionnaire (FIQ) scores and lower mental and emotional activity scores evaluated by SF-36 questionnaire. The authors point out the improvement of self-image as an improvement of quality of life in FM patients.

Another paper investigating the role of physical activity was published by Maddali-Bongi *et al*. (20). They evaluated the application of the Resseguier Method and Qi Gong in FM patients. The Resseguier Method is classified as a mind-body therapy aiming to obtain greater control of body perception, while Qi Gong is an ancient oriental method based on respiratory and mental training. The patients treated with both methods showed a significant improvement of pain, disability, and quality of life (QoL) at the and of the treatment protocol (15 weeks). The physical role and pain improvement was also studied by Bertan-Carrillo *et al*. (21). In a small cohort of patients, they evaluated the role of a nine-month physical exercise programme on FM symptoms, highlighting the usefulness of physical activity not only for pain but also for-social interaction, mood and cognitive impairment. A different opinion is instead found by the authors of a review on yoga and rheumatic disease (22)

who came to the conclusion that yoga may have only a weak recommendation for the ancillary management of FM. Another study investigating the impact of physical therapy on FM patients was published by Liptan G *et al*. who evaluated two techniques of body massage – myofascial relase therapy versus Swedish massage – in 12 FM patients (23). In particular, 8 patients received the myofascial release therapy and 4 the Swedish approach, and the authors observed an improvement of symptoms in both groups. Obviously, as admitted by the authors, it is necessary to extend the number of patients to support these data. An alternative treatment was studied also by Iannuccelli *et al*. (24), who evaluated acupuncture practice in 30 FM patients, with good results in terms of pain relief.

As for pharmacological therapies, an important therapeutic option for FM is still represented by serotonin/noradrenaline reuptake inhibitor (SNRI). Bateman *et al*. (25) evaluated the switch to milnacipran in patients with inadequate response to duloxetin, suggesting that this approach may have a beneficial effect in many patients with FM. The drug Milnacipran was the object of another study published by Bernstein *et al*. (26) who underlined the modest activity of milnacipran in pain relief, especially when used alone. Nonetheless, milnacipran has been confirmed to be effective for the treatment of some symptoms associated with FM, such as fatigue and cognitive impairment.

Also Ang *et al*. (27) investigated the effect of milnacipran in combination with cognitive-behavioural therapy. Fifty-eight FM patients were randomised in three study arms: combination therapy, milnacipran plus education programme, and cognitive-behavioural therapy plus placebo. They observed a moderate effect of combination therapy in physical function domain and a small effect on pain reduction. The limit of the study was the small number of patients, however, it confirmed the importance of a multidimensional approach for the treatment of FM. New promising therapies for FM are the agonists of 5-HT(2C) receptor. Three 5-HT(2C) receptor agonists (lorcaserin, vabicaserin and YM348), which were found to be useful in the treatment of several central nervous system diseases, including obesity and schizophrenia, were evaluated. Ogino *et al*. studied the effects of these molecules in a animal model of FM (28). The effect of systemic administration of these agents on the muscular hyperalgesia developed by reserpine-induced myalgia rats – a putative model of FM – generates a decrease in muscle pain threshold. These results, in addition to the possibility to develop new drugs for FM, are also of great interest for studies on serotonin as a central neurotransmitter with a role in muscular hyperalgesia.

Another drug studied in a randomised double blind trial was naltrexone (29). In this small size study the researchers evaluated the effectiveness of a low dosage of naltrexone (4.5 mg/day) in pain reduction. The small cohort of patients treated with the drug reported a specific and clinically beneficial impact on fibromyalgia pain without safety concerns. The authors suggested a large clinical trial to investigate the real efficacy of this drug.

A meta-analysis on the FM management evaluated the pharmacological and non-pharmacological approach in FM (30). By analysing the literature the authors speculated that the most relevant benefit for FM derived from pregabalin and SNRI as pharmacological interventions, together with multicomponent therapy, aerobic exercise and cognitive behavioural therapy as non-pharmacological interventions.

The multidisciplinary approach seem to be very useful in FM management. In a randomised trial published by Matin *et al*., the authors evaluated the approach based on psychological, medical, educational, and physiotherapeuticcomponents over time, compared to standard pharmacological care (31). They observed a significant improvement in quality of life, physical function and pain in patients treated using the multidisciplinary programme with respect to the group of patients treated with a traditional approach.

In a review recently published, Bernardy *et al*. studied the importance of cognitive behavioural therapy in FM (32). The authors underlined the low grade of accuracy of studies performed, which can only suggest a small incremental benefit in the reduction of pain, negative mood and disability.

Another non-traditional technique recently evaluated for FM was the transcutaneous electrical nerve stimulation (TENS). Carbonario *et al*. (33)evaluated the TENS results in a small cohort of FM patients, by an assessment of QoL, pain and tender points pain threshold. The patients treated by TENS reached a pain decrease higher than the control group, as well as an improvement of QoL and a reduction of anxiety. In conclusion, they reported an effective role of TENS in pain relief and FM symptoms control with short- term FM management.

Moreover, for studies investigated the effectiveness of transcranial direct current stimulation in FM patients (tDCS). The tDCS induces changes in neuronal activity that may affect cognition and analgesia. Villamar *et al*. evaluated the effects of tDCS in 18 FM patients, with interesting results in term of perceived pain (34). The same results, evaluated by the functional magnetic resonance, were proposed by Taylor *et al*. (35), who observed a decreased activation in pain processing regions. Another small trial on tDCS was proposed by Lee *et al*., who observed a significant reduction in Beck Depression Questionnaire scores and FIQ scores by the application of a repetitive transcranial magnetic stimulation (36). Using the same technique, Baudic *et al*. obtained an improvement of cognitive aspect in FM patients (37). Although all studies were performed on a few patients, the randomisation with a sham treatment was always performed, and the results seem to be interesting especially with respect to pain and cognitive disorders.

In recent years also nutritional aspects and the use of appropriated supplementation for the treatment of FM have been the objects of extensive research activities. For instance, Cordero *et al*. proposed a small double blind, placebo controlled, clinical trial on the effectiveness of coenzyme Q10 in FM patients (38). They underlined the clinical improvement in terms of FIQ reduc-

tion, pain, fatigue and morning tiredness, after CoQ10 supplementation

In addition, a dietary approach was evaluated by Holton *et al*. (39), who recruited 57 FM patients with an irritable bowel syndrome as comorbidity, placing them on a 4-week monosodium glutamate-free diet, which seemed to be effective in improving FM symptoms.

A few months later, Bagis *et al*. published the results of a study in which they had evaluated the magnesium-based treatment in a small cohort of FM patients (40). They had divided the enrolled FM patients into three groups: the first one treated with 300 mg/day of magnesium citrate, the second one on amitriptyline 10 mg/day, and the third one with the combination therapy based on magnesium and amitriptyline. The combination therapy proved to be effective for all investigated parameters with the exception of numbness.

A singular approach in FM management was proposed by Hidalgo-Tallon *et al*. (41). In an open-label study, they evaluated the effectiveness and tolerability of rectal insufflations of ozone. They observed a reduction of FIQ total scores and a significant improvement was also seen both in depression scores and in the Physical Summary Score of the SF-12. As one can easily suppose, meteorism was the most frequently reported side effect.

Some limitations of clinical trials carried with FM patients derive from the study design, in particular for placebo-controlled studies. An interesting meta-analysis that evaluated 18 studies for a total of 3546 patients enrolled (42), asserted that the placebo and nocebo response in FM clinical trials is a crucial issue, with a pooled estimated at 50% in pain reduction which is 18.6%, as well as a drop out rate of 10.9% in placebo groups. These findings impose a critical observation of clinical trials on FM.

Conclusion

During last year, no significant novelty was introduced in FM concerning ethiopathogenesis, therapeutic approach or assessment.

As far as FM treatment is concerned, complementary and alternative medicine seem to dominate the scene, especially if we consider the number of papers on physical therapies. The criticism of most of these studies is related to the number of patients treated and the presence of control groups. None of the traditional drugs has been developed for FM, and the few studies published last year involved SNRI. The same negative observation is related to pathogensis; in fact none of the recent papers seems to represent a milestone for scientific research in the field of FM. Over the years many hypotheses on the onset of disease have been formulated, and the most accredited ones remain those involving cytokines, inflammation and oxidative stress. Nevertheless, some original and innovative papers have been submitted in the last year; one of these is probably the one evaluating FM comorbidity in other rheumatic diseases (37). Indeed the presence of FM could aggravate the symptoms of other rheumatic diseases, also leading to misdiagnosis and overtreatment of patients; this finding certainly plays a crucial role in terms of socioeconomic burden, both for FM and the other rheumatic diseases.

References

1. MENZIES V, LYON DE, ARCHER KJ *et al*.: Epigenetic alterations and an increased frequency of micronuclei in women with fibromyalgia. *Nurs Res Pract* 2013; 2013: 795784.
2. FENG J, ZHANG Z, WU X *et al*.: Discovery of potential new gene variants and inflammatory cytokine associations with fibromyalgia syndrome by whole exome sequencing. *PLoS One* 2013; 8: e65033.
3. YIGIT S, INANIR A, TEKCAN A, INANIR S, TURAL S, ATES O: Association between fibromyalgia syndrome and polymorphism of the IL-4 gene in a Turkish population. *Gene* 2013; 527: 62-4.
4. KIM SK, KIM SH, NAH SS *et al*.: Association of guanosine triphosphate cyclohydrolase 1 gene polymorphisms with fibromyalgia syndrome in a Korean population. *J Rheumatol* 2013; 40: 316-22.
5. MARTÍNEZ-JAUAND M, SITGES C, RODRÍGUEZ V *et al*.: Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene. *Eur J Pain* 2013; 17: 16-27.
6. SCHMECHEL DE, EDWARDS CL: Fibromyalgia, mood disorders, and intense creative energy: A1AT polymorphisms are not always silent. *Neurotoxicology* 2012; 33: 1454-72.
7. KLAVER-KRÓL EG, ZWARTS MJ, TEN KLOOSTER PM, RASKER JJ: Abnormal muscle membrane function in fibromyalgia patients and its relationship to the number of tender points. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S44-50.
8. DÖNMEZ S, PAMUK ÖN, ÜMIT EG, TOP MŞ: Autoimmune rheumatic disease associated symptoms in fibromyalgia patients and their influence on anxiety, depression and somatisation: a comparative study. *Clin Exp Rheumatol* 2012; 30 (Suppl 74): S65-69.
9. ROUSSOU E, CIURTIN C: Clinical overlap between fibromyalgia tender points and enthesitis sites in patients with spondyloarthritis who present with inflammatory back pain. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S24-30.
10. IANNUCCELLI C, SPINELLI FR, GUZZO MP *et al*.: Fatigue and widespread pain in systemic lupus erythematosus and Sjögren's syndrome: symptoms of the inflammatory disease or associated fibromyalgia? *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S117-21.
11. WOLFE F, RASKER JJ, HÄUSER W: Hearing loss in fibromyalgia? Somatic sensory and non-sensory symptoms in patients with fibromyalgia and other rheumatic disorders. *Exp Rheumatol* 2012; 30 (Suppl. 74): S88-93.
12. GARCÍA JJ, CIDONCHA A, BOTE ME, HINCHADO MD, ORTEGA E: Altered profile of chemokines in fibromyalgia patients. *Clin Biochem* 2013 Oct 8.
13. OKTAYOGLU P, TAHTASIZ M, BOZKURT M *et al*.: Serum levels of high mobility group box 1 protein and its association with quality of life and psychological and functional status in patients with fibromyalgia. *Int J Rheum Dis* 2013; 16: 403-7.
14. CORDERO MD, ALCOCER-GÓMEZ E, CULIC O *et al*.: NLRP3 Inflammasome Is Activated in Fibromyalgia: The Effect of Coenzyme Q10. *Antioxid Redox Signal* 2013 Sep 19.
15. SALAFFI F, SARZI-PUTTINI P: Old and new-criteria for the classification and diagnosis of fibromyalgia: comparison and evaluation. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S3-9.
16. LAUCHE R, HÄUSER W, JUNG E *et al*.: Patient-related predictors of treatment satisfaction of patients with fibromyalgia syndrome: results of a cross-sectional survey. *Clin Exp Rheumatol* 2013; 31 (Suppl. 79): S34-40.
17. VELTRI A, SCARPELLINI P, PICCINNI A *et al*.: Methodological approach to depressive symptoms in fibromyalgia patients. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S136-42.
18. ALCIATI A, SARZI-PUTTINI P, BATTICCIOTTO A *et al*.: Overactive lifestyle in patients with fibromyalgia as a core feature of bipolar spectrum disorder. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S122-8.
19. BAPTISTA AS, VILLELA AL, JONES A, NATOUR J: Effectiveness of dance in patients with fibromyalgia: a randomized, single-blind, controlled study. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S18-23.
20. MADDALI BONGI S, DEL ROSSO A, DI FELICE C, CALÀ M, GIAMBALVO DAL BEN G: Rességuier method and Qi Gong sequentially integrated in patients with fibromyalgia syndrome. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S51-8.
21. BELTRÁN-CARRILLO VJ, TORTOSA-MARTÍNEZ J, JENNINGS G, SÁNCHEZ ES: Contri-

butions of a group-based exercise program for coping with fibromyalgia: a qualitative study giving voice to female patients. *Women Health* 2013; 53: 612-29.
22. CRAMER H, LAUCHE R, LANGHORST J, DOBOS G: Yoga for rheumatic diseases: a systematic review. *Rheumatology* (Oxford) 2013; 52: 2025-30.
23. LIPTAN G, MIST S, WRIGHT C, ARZT A, JONES KD: A pilot study of myofascial release therapy compared to Swedish massage in fibromyalgia. *J Bodyw Mov Ther* 2013; 17: 365-70.
24. IANNUCCELLI C, MANNOCCI F, GUZZO MP *et al*.: Complementary treatment in fibromyalgia: combination of somatic and abdominal acupuncture. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S112-6.
25. BATEMAN L, PALMER RH, TRUGMAN JM, LIN Y: Results of switching to milnacipran in fibromyalgia patients with an inadequate response to duloxetine: a phase IV pilot study. *J Pain Res* 2013; 6: 311-8.
26. BERNSTEIN CD, ALBRECHT KL, MARCUS DA: Milnacipran for fibromyalgia: a useful addition to the treatment armamentarium. *Expert Opin Pharmacother* 2013; 14: 905-16.
27. ANG DC, JENSEN MP, STEINER JL, HILLIGOSS J, GRACELY RH, SAHA C: Combining cognitive-behavioral therapy and milnacipran for fibromyalgia: a feasibility randomized-controlled trial. *Clin J Pain* 2013; 29: 747-54.
28. OGINO S, NAGAKURA Y, TSUKAMOTO M *et al*.: Systemic administration of 5-HT(2C) receptor agonists attenuates muscular hyperalgesia in reserpine-induced myalgia model. *Pharmacol Biochem Behav* 2013; 108: 8-15.
29. YOUNGER J, NOOR N, MCCUE R, MACKEY S: Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum* 2013; 65: 529-38.
30. NÜESCH E, HÄUSER W, BERNARDY K, BARTH J, JÜNI P: Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. *Ann Rheum Dis* 2013; 72: 955-62.
31. MARTÍN J, TORRE F, PADIERNA A *et al*.: Six-and 12-month follow-up of an interdisciplinary fibromyalgia treatment programme: results of a randomised trial. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S103-11.
32. BERNARDY K, KLOSE P, BUSCH AJ, CHOY EH, HÄUSER W: Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev* 2013 Sep 10; 9: ì.
33. CARBONARIO F, MATSUTANI LA, YUAN SL, MARQUES AP: Effectiveness of high-frequency transcutaneous electrical nerve stimulation at tender points as adjuvant therapy for patients with fibromyalgia. *Eur J Phys Rehabil Med* 2013; 49: 197-204.
34. VILLAMAR MF, WIVATVONGVANA P, PATUMANOND J, BIKSON M, TRUONG DQ, DATTA A, FREGNI F: Focal modulation of the primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. *J Pain* 2013; 14: 371-83.
35. TAYLOR AG, ANDERSON JG, RIEDEL SL, LEWIS JE, BOURGUIGNON C: A randomized, controlled, double-blind pilot study of the effects of cranial electrical stimulation on activity in brain pain processing regions in individuals with fibromyalgia. *Explore* (NY) 2013; 9: 32-40.
36. LEE SJ, KIM DY, CHUN MH, KIM YG: The effect of repetitive transcranial magnetic stimulation on fibromyalgia: a randomized sham-controlled trial with 1-mo follow-up. *Am J Phys Med Rehabil* 2012; 91: 1077-85.
37. BAUDIC S, ATTAL N, MHALLA A, CIAMPI DE ANDRADE D, PERROT S, BOUHASSIRA D: Unilateral repetitive transcranial magnetic stimulation of the motor cortex does not affect cognition in patients with fibromyalgia. *J Psychiatr Res* 2013; 47: 72-7.
38. CORDERO MD, ALCOCER-GÓMEZ E, DE MIGUEL M *et al*.: Can coenzyme q10 improve clinical and molecular parameters in fibromyalgia?. *Antioxid Redox Signal* 2013; 19: 1356-61.
39. HOLTON KF, TAREN DL, THOMSON CA, BENNETT RM, JONES KD: The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S10-17.
40. BAGIS S, KARABIBER M, AS I, TAMER L, ERDOGAN C, ATALAY A: Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? *Rheumatol Int* 2013; 33: 167-72.
41. HIDALGO-TALLÓN J, MENÉNDEZ-CEPERO S, VILCHEZ JS, RODRÍGUEZ-LÓPEZ CM, CALANDRE EP: Ozone therapy as add-on treatment in fibromyalgia management by rectal insufflation: an open-label pilot study. *J Altern Complement Med* 2013; 19: 238-42.
42. HÄUSER W, SARZI-PUTTINI P, TÖLLE TR, WOLFE F: Placebo and nocebo responses in randomised controlled trials of drugs applying for approval for fibromyalgia syndrome treatment: systematic review and meta-analysis. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S78-87.