Fibromyalgia 2021

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Congress Chairs

Jacob Ablin
Tel-Aviv Sourasky Medical Center, Israel

Piercarlo Sarzi-Puttini
L. Sacco University Hospital, Milan, Italy

Abstracts

IS-01

Fibromyalgia: year in review

Alessandra Alciati[1], Valeria Nucera[2], Valeria Giorgi[3]
[1]Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, Como, Italy; [1]Humanitas Clinical and Research Center, Milan, Italy; [2]Rheumatology Unit, Department of Clinical and Experimental Medicine. University of Messina, Messina, Italy; [3]Rheumatology Unit, ASST Fatebenefratelli "Luigi Sacco" University Hospital, Milan, Italy.

Fibromyalgia (FM) is a syndrome of unknown aetiology characterized by chronic widespread pain, fatigue, and disturbed sleep. The attention of the scientific community towards FM is constantly growing, and this year it has focused on the diagnostic, pathogenetic and therapeutic aspects of this syndrome. Regarding diagnosis, Salaffi *et al*. compared the concordance of ACR 2011, ACR 2016 and AAPT Criteria. Substantial agreement among the main sets of classification criteria exists, with the ACR 2011 Cr seeming to be the best performing, when compared with clinical judgment, while the AAPT Cr are the worst. They also explored the performance of an additional set of criteria: the modified Fibromyalgia Assessment Status (FAS 2019 modCr) (1). The same group developed and tested a new six-item self-administered tool for screening for FM, the SImple FIbromyalgia Screening (SIFIS) questionnaire (2).
Among the papers regarding the pathogenetic aspects, one investigated the role of mast cells in the skin of FM patients (3), and concluded that they have a key role in releasing neurosensitizing proinflammatory substances, such as cytokines and lipids, which can exacerbate low-grade inflammation, and could be inhibited in this process by interleukin (IL)-37. Another work investigated the prevalence of small fiber neuropathy in FM patients using laser-evoked brain potentials (LEP), which allows the functional assessment of the thermo-nociceptive system, and showed that there were no signs of a damaged thermonociceptive system in 92 patients with FM compared with 39 age- and gender-matched healthy controls (4).
In particular, the treatment options for FM, both pharmacological and non-pharmacological, have been extensively studied in 2020. Based on Bruun-Plesner *et al*. findings, the effective dose of naltrexone of 4.5mg seems to be a reasonable test dose in FM patients; and Wilderman and his group (6) published a study on the possible effective dose of intravenous lidocaine in the treatment of FM pain. To conclude, a big focus was put on electrotherapy. 60 sessions of home-based anodal transcranial direct current stimulation (tDCS) over left dorsolateral prefrontal cortex were done by Brietzke *et al*., and they found that there was a 45.65% improvement in the cumulative pain scores, increasing to 62.06% when extended to 60 sessions (12-week assessment), resulting in a cumulative effect without ceiling (7). Repetitive transcranial magnetic stimulation (rTMS) on the left M1 and the Left Dorsolateral prefrontal cortex was compared in another study (8), and pain relief effect was higher when the TMS was applied over the left primary motor cortex.

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IS-02

Chronic pain 2020: year in review

Valerie Aloush
Tel Aviv Sourasky Medical Center, Israel

Despite the intense focus of the medical community during 2020 on the COVID 19 pandemic and all its ramifications, significant contributions have nonetheless been published in the field of chronic pain and specifically fibromyalgia. In this review we aim to summarize the most relevant data on fibromyalgia that emerged during 2020. We will focus on new insights into the pathophysiology, related to sleep patterns disturbances, role of monocytes and IL5, role of hypothalamic-pituitary axis, neuro-imaging studies linking pain catastrophizing to widespread pain, and the role of psychological comorbidities. The search for the holy grail of an objective biomarkers, be it neuroimaging based or otherwise, continues to be a hot point of focus, with areas such as microbiome and serum proteom profiles attracting significant attention.
We will also browse new therapeutic directions (Metformin, Low dose Naltrexone, drugs targeting calcium channels in ganglion dorsal root, NMDA receptor antagonist) as well as novel non-pharmacological modalities (green light exposure, ozone autohemotherapy, neuromodulation strategies) and the role of nutrient supplementation in the management of chronic pain in fibromyalgia.
Last but not least, we will review recent studies focusing on aspects that influence patients' disease perception and quality of life (including COVID 19) and the need for a comprehensive treatment program targeting not only pain but also other somatic symptoms and improving function.

IS-03

Pain as a symptom vs. pain as a syndrome

Eva Kosek, Professor, MD
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm and Department of Surgical Sciences, Uppsala University, Sweden.

Is the pain in fibromyalgia best understood as a symptom, as a disease, or as part of a syndrome consisting of fatigue, disturbed sleep and mood disorders, in addition to pain? Given the heterogenous nature of fibromyalgia, arguments supporting all of these standpoints can be found.
Theoretically, at least in subgroups of fibromyalgia patients, the pain could be regarded as a symptom deriving from peripheral nerve pathology (1), autonomic nervous system dysregulation with muscle ischemia (2) and/or central nervous system pathology such as neuroinflammation (3). However, although all of these abnormalities have been reported in fibromyalgia, they are generally not strongly related to pain intensity and none of these findings are present in all fibromyalgia patients.
The view that pain in fibromyalgia is best understood as a disease is based on two fairly new concepts. The first being the introduction of nociplastic pain (4), a third mechanistic descriptor endorsed by IASP (in addition to nociceptive and neuropathic pain). Nociplastic pain is defined as "pain due to altered nociception" not explained by nociceptive or neuropathic mechanisms and clinical criteria and a grading system for nociplastic pain have been developed (5). In contrast with nociceptive and neuropathic pain states, where pain is a symptom, nociplastic pain is regarded as a disease caused by dysfunctional pain modulation (4). Fibromyalgia is considered as a prototype of a nociplastic pain condition based on the ample evidence of altered cerebral pain processing and altered nociceptive function in fibromyalgia patients (4). The view of nociplastic pain as a disease also harmonizes with the concept of primary and secondary pain introduced in the International Classification of Diseases 11th Revision (ICD-11) (6). In ICD-11 fibromyalgia, as well as other nociplastic pain conditions, are categorized as a primary pain conditions (pain as a disease), contrary to secondary pain conditions where pain is regarded as a symptom (6).
However, despite the arguments presented above regarding pain in fibromyalgia, the diagnosis of fibromyalgia is most frequently considered as a chronic pain syndrome characterized by widespread pain, fatigue, sleep problems and sometimes also cognitive dysfunction and mood disorders such as depression. The view of fibromyalgia as a syndrome harmonizes with the current diagnostic criteria, including the 2016 Modified ACR criteria (7) and the AAPT diagnostic criteria (8).

In conclusion, the pain in subgroups of FM patients could be regarded as a symptom. However, the concept of nociplastic pain as a disease, rather than a symptom is rapidly gaining support. Regardless of how we define the pain in fibromyalgia, the diagnostic concept of fibromyalgia is best understood as a chronic pain syndrome.

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IS-04

Time to stop the fibromyalgia criteria wars

Piercarlo Sarzi-Puttini[1], Jacob Ablin[2]
[1]*L. Sacco University Hospital, Italy;*
[2]*Tel-Aviv Sourasky Medical Center, Israel*.

The last decade saw 4 or 5 fibromyalgia syndrome diagnostic criteria coming in succession. This is happening since consistent biomarkers or neuroimaging findings characterizing fibromyalgia patients are lacking, still provoking debate in the scientific community and big challenges for the diagnosis in the clinic (1).

The abolition of tender point examination in 2010 (2) represented a substantial revolution in fibromyalgia diagnosis, facing the inevitability of a diagnosis based on subjectivity. However, the 2010 American College of Rheumatology (ACR) criteria initiated also the creation of other "questionnaire-based" diagnostic criteria, which were based on more and more refined self-reporting multicomposite indices, that comprehend all of the prevalent symptoms in ever-changing orders, not being substantially different from one another and retaining a modest specificity and sensitivity. Taking them individually, each criterion has its strong and weak points. One of the most debated issues is the one of the *painful areas count*. The nineteen areas included in the widespread pain index (WPI) (2, 3) may be too close from one another, thus forcing the patient to perform a mostly useless discrimination of painful nearby areas (*e.g*. upper arm and lower arm). On the other hand, the AAPT diagnostic criteria for fibromyalgia published in 2018 (4) included nine possible painful body sites, with six or more painful sites defining multisite pain (MSP) (4). This on the contrary does not allow a good discrimination of the painful sites and leaves space for a great generalization and probably over-diagnosis (5).

Therefore, self-administered questionnaires are undoubtably useful for fibromyalgia syndrome assessment, since there is no objective marker to measure disease activity, but they may have a low discriminative capacity when pertaining to definite diagnosis. It would be more convenient to administer the questionnaire to the patient (hetero administration) and use the same tools in their self-administered form in the subsequent follow-up, thus allowing the management of a higher number of patients.

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IS-05

Why do drugs work so poorly in fibromyalgia patients?

Daniel J. Clauw MD
Professor of Anesthesiology, Medicine and Psychiatry; Director Chronic Pain and Fatigue Research Center; The University of Michigan, USA.

Several classes of drugs can be helpful in individuals with FM, but each class of drug only works in about a third of patients, and many patients have significant side effects of all of these drugs. Why is this? There are several reasons. First, the small effect sizes seen with drugs used to treat FM are also seen with other classes of drugs used to treat pain. There is no analgesic for any chronic pain condition that has anything other than a small effect size, with significant off target effects. So although it is true that no drugs work well for FM, this is also true of other classes of drugs, and other chronic pain conditions.

Second, most or all of the drugs that have been shown to be effective in FM (*e.g*. TCAs, SNRIs, gabapentinoids) are thought to work primarily in the central nervous system (CNS). CNS acting analgesics typically work on a set of neurotransmitters that affect pain transmission. Mechanistic studies of the activity of these neurotransmitter systems in FM and related conditions suggests that several of these neurotransmitter systems are abnormal in subsets of FM patients (*e.g*. increased excitatory neurotransmission *e.g*. from glutamate, or decreased activity of GABA, serotonin, and norepinephrine). Many studies have shown that the subset of individuals with FM that has the underlying pathophysiological problem that drug can reverse are the ones that respond best to that particular drug. For example, the individuals with FM given pregabalin who had the highest levels of glutamate in the insula were those most likely to respond to the drug, whereas individuals with decreases in activity of descending analgesic regions were more likely to respond to a NSRI, milnacipran. Because individuals can get to a hyperexcitable CNS state via many different pathways, only the individuals who have the pathophysiological problem each drug addresses will respond to that drug. Because of this it is unlikely that any drug will ever work in all individuals with FM.

Fortunately, the good news is that we can do better. By phenotyping individuals at baseline, we will undoubtedly be able to improve the success of existing drug therapies simply by better knowing who is likely to respond to which drug. Many studies are underway in FM and other pain conditions to finally take a precision medicine approach to treating chronic pain. Many classes of drugs in development are also trying to circumvent the issues we have with our current therapies. Most new trials of analgesics are taking advantage of simple Patient Reported Outcomes (PROs) that can better phenotype patients to determine which subsets of patients respond best. Many of the compounds being newly developed are designed to potentially reduce or eliminate the significant off target effects of existing drugs, *e.g*. by using pro-drugs or allosteric modulators bather than classic agonists or antagonists.

IS-06

Fibromyalgia as a disease of misconnection

Serge Perrot
Cochin University Hospital, France.

Fibromyalgia represents a condition still controversial in its entity, pathophysiology, diagnosis and management. In a world where everybody is connected, and everybody is sharing their own image, fibromyalgia (FM) represents the emblematic pathology of misconnection and lack of specific biomarker. FM is an invisible experience with all normal tests and analyses, without any visible biomarker to exhibit to healthcare professionals, colleagues and relatives. In this context we propose to consider FM as a disease of misconnection at different levels: misconnection with society, misconnection with healthcare professionals, misconnection with pathophysiological concepts, misconnection between brain and body. The concept of misconnection defines FM in a different and holistic view, and proposes different views of assessment, management and representation:

- FM pathophysiology: the desynchronization of brain and body
- FM recognition: the broken link between patients and physicians
- FM assessment: merging the body and mind for an optimal diagnosis and management
- FM treatment: re-establishing the good connections at different levels

We hope to reconnect FM patients with all healthcare providers, help FM patients reconnect with their painful body, and integrate FM into regular medical practice.

IS-07

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Piercarlo Sarzi-Puttini[1], Daniela Marotto[2], Valeria Giorgi[1]
[1]Rheumatology Unit, ASST Fatebenefratelli "Luigi Sacco" University Hospital, Milan, Italy; [2]Rheumatology Unit, ATS Sardegna, P. Dettori Hospital, Tempio Pausania, Italy.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is known as a chronic debilitating disease having no specific diagnostic blood test or investigation tools (1, 2). There are a variety of consensus research and clinical definitions of ME/CFS in the literature including: Canadian Consensus Criteria (3), Fukuda (4), Holmes (5), International Criteria (6), Oxford (7), etc. The United States Institute of Medicine appointed a committee in 2015, which wrote new ME/CFS criteria and renamed it Systemic Exertion Intolerance Disease (SEID) (8).

In ME/CFS the fatigue is "pathological" or abnormal, more intense and different from normal tiredness. Post–exertional fatigue and malaise (PEM) is considered one of the distinguishing symptoms of ME/CFS. PEM refers to severe physical or mental/cognitive post-exertional fatigue. This means that there are worsening of symptoms after minimal physical or mental/cognitive exertion (7, 8).

ME/CFS also entails a varied kaleidoscope of other symptoms including migraine, flu-like symptoms, cognitive impairment ("brain fog"), and sensitivities to a variety of external stimuli that may include light, sound, or specific odors. This can be accompanied by comorbidities, such as fibromyalgia, postural orthostatic tachycardia (POTS), and Ehlers–Danlos syndrome (2).

Despite the lack of diagnostic biomarkers, there is a variety of hypothesis to explain the pathogenetic mechanism for the disorder across many body systems (9-12). This evidence is mostly comprised of disturbances to immunological and inflammatory pathways, autonomic and neurological dysfunction, abnormalities in muscle and mitochondrial function, shifts in metabolism, and gut physiology or gut microbiota disturbances.

Current treatments are symptomatic and limited to reduce the severity of the disease and to control psychological sequelae associated with long-term disability (13, 14).

With inconsistent ME/CFS criteria and an extreme heterogeneity among the cohort of patients, it's difficult to carry out definitive studies on patients with ME/CFS that would lead to new understanding of pathophysiology, new diagnostic tests, and treatment methods.

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IS-08

Functional gastrointestinal disorders

Maura Corsetti, MD, PhD
NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, University of Nottingham and Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK.

Functional bowel disorders account for most of the referrals to Gastroenterological departments and have a prevalence of 1 out 4 people in the general population as recently pointed out by the Rome Foundation Global Survey (1). Irritable bowel syndrome (IBS) is one of the most frequent functional disorders and it is characterized by the presence of recurrent abdominal pain or discomfort in association with abnormalities in stool frequency and form (1). The prevalence of IBS is about 10% in Western countries and due to its chronic relapsing course, up to 50% of the patients consult a physician for these symptoms (1). IBS frequently overlaps with fibromyalgia (1). Recent studies have revealed new understanding in the pathophysiology of IBS symptoms (2). The COVID pandemic has forced us to re-evaluate the current management of these patients, introducing remote consultations and treatment (including online CBT and hypnotherapy) and improving the use of the positive diagnosis. This lecture will present an update of the current management of IBS to offer a pragmatic guide to clinicians based on the recently accepted updated IBS Guidelines of the British Society of Gastroenterology (3).

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IS-09

Small-fibre neuropathy and neuropathic pain: differential diagnosis and therapeutic approach

Andrea Truini
Department of Human Neuroscience, Sapienza University, Rome, Italy.

Despite the large body of studies on the topic, the mechanisms underlying pain in patients with fibromyalgia are still a matter of debate. For years, the research highlighted central nervous system abnormalities (Truini et al., 2016). Recently, however, skin biopsy studies have demonstrated that approximatively 49% of patients with fibromyalgia (Grayston *et al*., 2019) have a reduced intraepidermal nerve fibre density. This finding, which closely resemble small-fibre neuropathy, is commonly defined as small-fibre pathology (Ucelyer *et al*., 2013). However, it is still unclear whether small-fibre pathology causes clinically significant abnormalities of somatosensory and autonomic nervous system function and how small-fibre pathology may influence symptoms like fatigue and cognitive disturbances. A recent study (Fasolino *et al*., 2020) showed that clinical measures, quantitative sensory testing, and nociceptive evoked potential variables do not differ between patients with and without small-fibre pathology; these findings therefore argue against the small-fibre damage as the leading mechanisms for the different symptoms patients with fibromyalgia experience. Still the differential diagnosis between fibromyalgia and pure small-fibre neuropathy is challenging. Patients with fibromyalgia and small-fibre pathology have seldom abnormalities of cold or warm detection threshold resembling those in patients with small-fibre pathology. In patients with fibromyalgia, therefore somatosensory system abnormalities need careful interpretation and patients with small-fibre pathology warrant periodic, follow-up evaluations to seek symptoms and signs compatible with small-fibre neuropathy. Recent studies also found rare variants of

voltage-gated sodium channels in patients with a diagnosis of fibromyalgia. This finding raises the possibility that some patients suffering from rare small-fibre neuropathies due to voltage-gated sodium channel mutation and exhibiting skin biopsy abnormalities might be misdiagnosed with fibromyalgia.

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IS-10

Fibromyalgia. How stress becomes neuropathic pain

Manuel Martínez-Lavín, MD
Chief, Rheumatology Department, National Institute of Cardiology, Mexico.

Fibromyalgia (FM) is a stress-related disorder. Psychological distress, physical trauma, infections and/or autoimmune stressors are frequent FM drivers. The autonomic nervous system is the main stress-response force. Autonomic dysfunction (dysautonomia) is prevalent in FM patients. Heart rate variability analyses in FM individuals show changes consistent with ongoing sympathetic hyperactivity associated to hypo-reactivity to stress. FM pain has clear neuropathic features, it is a stimulus-independent pain accompanied by allodynia and paresthesia. Skin biopsy demonstrates histologic small fiber neuropathy in most FM patients. Therefore, the key issue in FM research is to define how stress becomes neuropathic pain.
Humans have 31 pairs of dorsal root ganglia (DRG) lying along the spine. DRG possess unique pro-nociceptive physio-anatomy, these paravertebral ganglia have pain generating pseudo-unipolar structure. DRG lie outside the blood-brain barrier, so different infective agents and/or pro-nociceptive cytokines can gain direct DRG access. On the other hand, DRG are surrounded by meningeal layers and by cerebrospinal fluid, so they are in close contact with the central nervous system. DRG can sequester antigen-specific antibodies. These paravertebral ganglia house the pain-transmitting small nerve fiber nuclei, each nucleus is enveloped by immune-competent glial cells. Lymphocytes, macrophages, and different pro-nociceptive mediators populate DRG. Communicating nerves tightly link DRG with the paravertebral sympathetic chain. Specific DRG sodium channels (Nav1.7-9) modulate neuropathic pain transmission.
In the rodent model, different physical, chemical, and environmental ("psychological") stressors induce DRG inflammation and neuropathic pain. There is a clear female oriented sexual dimorphism in DRG nociceptive pathophysiology.
New clinical evidence supports DRG as the main FM pain factory. Most FM individuals have objective evidence of small nerve fiber pathology. Small nerve fiber neuropathy is a denervating disease. Intra-DRG nuclei degeneration may explain the characteristic distal small nerve axonal atrophy. We described the association of DRG Nav1.7 rs6754031 GG genotype with severe FM, we also found that FM women without severe anxiety/depression display strong correlation between corneal denervation with small nerve fiber neuropathy symptoms. Immunoglobulin G from FM patients induces hyperalgesia in mice. In such instances, immunohistochemical and Western blot analyses detected FM patients IgG in mice DRG, but not in brain or spinal cord tissue.
In conclusion, unfolding evidence proposes DRG as the key FM neural hub where different stressors, including psychological distress, are converted into neuropathic pain. This novel proposal can be tested using advanced DRG neuroimaging or *in-vitro* DRG culture assays. DRG nociceptive mediators are attractive target for the development of more specific FM analgesic medications. Stress response system malfunction (dysautonomia) explains FM multisymptomatic features.

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IS-11

Classical examples of the concept of the ASIA syndrome; CPI, SBI and vaccines

Yehuda Shoenfeld, MD, FRCP, MaACR
Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, 5265601 Tel-Hashomer, Israel; Sackler Faculty of Medicine, Tel-Aviv University, Israel; Ariel University, Israel.

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first introduced in 2011 by Shoenfeld *et al*. and encompasses a cluster of related immune mediated diseases, which develop among genetically prone individuals as a result of adjuvant agent exposure. Since the recognition of ASIA syndrome, more than 4400 documented cases have been reported so far, illustrated by heterogeneous clinical manifestations and severity. In this review, five enigmatic conditions, including sarcoidosis, Sjögren's syndrome, undifferentiated connective tissue disease, silicone implant incompatibility syndrome (SIIS), and immune-related adverse events (irAEs), are defined as classical examples of ASIA. Certainly, these disorders have been described after an adjuvant stimulus (silicone implantation, drugs, infections, metals, vaccines, etc.) among genetically predisposed individuals (mainly the HLA-DRB1 and PTPN22 gene), which induce an hyperstimulation of the immune system resulting in the production of autoantibodies, eventually leading to the development of autoimmune diseases. Circulating autonomic autoantibodies in the sera of patients with silicone breast implants, as well as anatomopathological aspects of small fiber neuropathy in their skin biopsies have been recently described. To our knowledge, these novel insights serve as a common explanation to the non-specific clinical manifestations reported in patients with ASIA, leading to the redefinition of the ASIA syndrome diagnostic criteria.
Key words: autoimmune diseases; ASIA syndrome; autoimmune/inflammatory syndrome induced by adjuvants; adjuvants; autoantibodies; silicone, vaccines.

IS-12

Central sensitization: neurophysiological mechanisms

Emanuel N. van den Broeke
Institute of Neuroscience, division Cognition and Systems, Université Catholique de Louvain, Belgium.

Since its discovery, the concept central sensitization has become increasingly popular. However, in the scientific literature central sensitization is defined and operationalized in many different ways (1), which seriously hampers scientific progression. The original description of central sensitization that derives from animal studies referred to a phenomenon of increased spinal excitability induced after peripheral noxious input and was thought to mediate increases in pain perception present after injury (*i.e.* the spread of hyperalgesia and allodynia restricted to a limited number of spinal segments) (2). The exact spinal mechanisms underlying these forms of hyperalgesia and allodynia are yet unknown, although our understanding is rapidly growing, for example (3-7). The results of recent studies clearly indicate that hyperalgesia and allodynia do not depend on one single mechanism, but can be triggered by a range of mechanisms. More recent interpretations of central sensitization, in particular those used in the clinical domain, are broader than the original concept; central sensitization refers to a general state of central nervous system hypersensitivity that explains a variety of symptoms, including pain and non-pain symptoms (*e.g.* increased sensitivity to bright light, sounds and odors) (9). We have recently argued that when central sensitization is interpreted too broadly, the chance of finding evidence of central sensitization increases (8, 9). Consequently, the presence of central sensitization is established in many patients but also the heterogeneity of underlying processes/mechanisms increases (8, 9). The biopsychosocial model considers that different interacting processes/mechanisms can contribute to a patient's clinical presentation. Grouping different processes/mechanisms under the same umbrella (central sensitization) does not seem to contribute to a mechanism-based approach and may not improve – and may even hamper – pain management (9).

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IS-13

Mechanism of pain in rheumatoid arthritis

Ernest H. Choy
CREATE Centre, Section of Rheumatology, Division of Infection and Immunity, Cardiff University, Cardiff, United Kingdom.

In rheumatoid arthritis (RA), cytokines are key mediators of joint inflammation and destruction. Pro-inflammatory cytokines drive synovitis, damage articular cartilage and mediate pain (1). Cytokines such as TNF-α, IL-1β and IL-6 activate cyclo-oxygenase 2 and convert arachidonic acid into prostaglandins which bind to nociceptors. During inflammation, sensory neurons in the periphery and secondary neurons in the central nervous systems go through functional, chemical, and structural alterations resulting in reduced pain threshold and increased responsiveness (2). These changes are mediated by pro-inflammatory mediators such as prostaglandins and bradykinin that are induced by cytokines that result in sensitization of peripheral nerves through specific cell-surface receptors, contributing to the generation and maintenance of pain (3). Therefore, inflammation is associated with peripheral sensitization with hyperalgesia and allodynia due to lowering of the activation threshold for nociceptive neurons (4). Cytokines can also create exaggerated pain state through effect on the central nervous system: central sensitization, through their actions in the spinal cord by their effects on excitatory and inhibitory neurotransmission, as well as synaptic transmission in the dorsal horn (5).

In animal models of RA, TNF-α could induce neuronal sensitization to benign stimuli by increasing the responsiveness of C- and Aδ- nerve fibers (6). In addition, TNF-α could sensitize nociceptors in the skin to heat. IL-1β, can induce pain and hyperalgesia in RA (7). Intra-plantar injections of IL-1β induced cutaneous hyperalgesia and transient spontaneous discharge in response to thermal stimuli in rats (8). gp130, the signal transduction molecule of the IL-6 pathway is expressed by afferent sensory neurons and has been shown to be a key regulator of mechanical hypersensitivity during inflammation (9). Injection of IL-6 or IL-6/sIL-6R into normal knees caused a sustained sensitization of C-fibres (10). gp130 deficient mice have reduced inflammation-induced pain (11). Spinal injection of soluble gp130, which block IL-6 signaling reduced neuronal hyperexcitability and release of IL-6 in the spinal cord induced by knee inflammation (12).

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IS-14

Pain chronification: what should a non-pain medicine specialist know?

Bart Morlion, MD, PhD, DEAA, EDPM
KU Leuven, Belgium.

Chronic pain affects 20 to 30% of the adult population. Modern paradigms recognize pain as a biopsychosocial phenomenon. Whereas acute pain is mostly a physiological protective event linked to structural changes and actual or potential harm, chronic pain can be considered as a non-adaptive neuroplastic pathological process.

Recently, WHO adopted ICD11 including a new classification of chronic pain. Accordingly, chronic pain is defined as persistent or recurrent pain lasting longer than 3 months.

The new term 'chronic primary pain' was introduced referring to chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) or functional disability (interference in daily life activities and reduced participation in social roles). Also WHO recognizes that chronic primary pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome. The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms. Fibromyalgia, the topic of this meeting, fits into the category chronic primary pain.

Pain chronification describes the process of transient pain progressing into persistent pain. Indeed, pain processing changes as a result of an imbalance between pain amplification and pain inhibition; genetic, environmental and biopsychosocial factors determine the risk, the degree, and time-course of chronification. This lecture gives an overview of underlying physiological, psychosocial processes and predictive factors for pain chronification. Better insight and education in this broad array of processes and factors should increase awareness and improve holistic management of pain by health care providers. Early intervention and timely referral to pain specialists is key in preventing and managing chronic pain.

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IS-15

Biologic and small molecules: do they work on pain?

Professor Peter C. Taylor
University of Oxford, United Kingdom.

Emerging evidence has demonstrated unusually high rates of depression and anxiety disorders in patients with various rheumatologic illnesses (1). These include rheumatoid arthritis (RA), and psoriatic arthritis (PsA), among others. This adds to the diease burden of our patients in terms of disease activity and functional impairment. In fact, a recent study revealed that of all the baseline prognostic indicators for disability at one year in a group of early inflammatory arthritis sufferers, depression ranked number 2 (odds ratio of 2.52) and anxiety ranked number three (odds ratio of 2.37) (2).
When people with inflammatory arthritis are asked about symptoms that matter most to them, pain and fatigue tend to predominate. Pain is a generic feature of inflammation, and in the context of an acute inflammatory setting, nociceptors send signals via afferent fibres to the dorsal horn and then via the fast transmitting neospinothalamic pathway to the brain where such pain can be well localised. Nociceptors are located throughout the joint so that pain may be arising from numerous structures including capsule, subchondral bone, muscle, tendon, ligament, enthesis and bursa. And signals that travel to the dorsal horn and then via the slower transmitting paleospinothalamic tract which synapses in the brainstem and mid brain as well as the cortex, lead to diffusely experienced, poorly localised pain. Pain is, in fact, a complex set of neural, humoral and emotional events.
We have long known that many of the symptoms associated with active arthritis, such as pain, represent generic features of inflammation. But it is also clear that such symptoms have multifactorial aetiologies and may be the result of both inflammatory and/or non-inflammatory processes. Furthermore, with respect to inflammatory causes, it is conceivable that different inflammatory pathways contribute differentially to distinct symptoms. Recent data from a Phase 3 clinical trial in people with RA, comparing addition of either a Jak inhibitor or biologic anti-TNF in rheumatoid arthritis patients with an inadequate response to methotrexate, showed that patients who were treated with a Janus kinase 1 (Jak1) and Jak2 inhibitor achieved significantly greater improvements in patient-reported pain than patients treated with anti-TNF, despite both treatments being associated with similar changes in standard markers of inflammation (3). This finding in patient-reported pain suggests that Jak inhibition may relieve pain in RA caused by both inflammatory and non-inflammatory mechanisms, and is consistent with the overarching involvement of Jak/STAT pathway in mediating the action, expression, and regulation of a multitude of pro- and anti-inflammatory cytokines. This observation may have important consequences for pain management in RA given that pain symptoms, being known only to the patient themselves, may be overlooked when treating to a disease activity target which does not directly assess pain experience (4).
Dramatic advances in contemporary neuroimaging have transformed our understanding of the biology and experience of pain. The pain circuit involves sensory, emotional and cognitive regions of the brain. The sensory (pain, stiffness), emotional (stress, depression, anxiety) and cognitive (catastrophizing) domains negatively impact patients. There are strong neurobiological underpinnings to such an overlap in patients seen in both psychiatric and rheumatology clinics (1).
If we are to adopt a holistic approach to care of patients with rheumatic diseases, specialists in rheumatology and psychiatry need to connect and collaborate with each other and to use techniques from each specialty. Biologic anti-cytokine therapies with efficacy for disease activity outcomes are also associated with amelioration of the subjective pain experience of people living with RA. Emerging data from trials of small molecule Jak inhibitors, which block multiple cytokines (directly and indirectly) involved in nociceptive signaling pathways (5), also rapidly and effectively ameliorate pain. It remains to be seen whether any of these benefits of small molecules can be attributed to centrally mediated effects.

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IS-16

Widespread pain, fatigue, depression and sicca symptoms are overlapping features in primary Sjögren's syndrome and fibromyalgia: differences and similarities of clinical and pathogenetic aspects

Claudio Vitali[1], Nicoletta Del Papa[2]
[1]Humanital 'Mater Domini' Hospital, Castellanza; [2]Department of Rheumatology, ASST G. Pini-CTO, Milan, Italy.

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disorder whose characteristic feature is the lymphocytic infiltration of the salivary and lachrymal glands, with a slow loss of function, and consequently oral and ocular dryness. Middle-aged women are predominantly affected by pSS, (F/M ratio 9:1). The spectrum of pSS is extremely variable. In around 50% of the patients the clinical symptoms related to glandular involvement (GI) are accompanied by extraglandular manifestations that mainly involve joints, kidney, lung, peripheral nervous system, and small vessels. In the rest of the patients the GI-related sicca symptoms are often accompanied by fatigue, widespread pain (WP), and depression (1).
Fibromyalgia (FM) is another cause of chronic WP that predominantly affects women (F/M ratio 6:1). WP is very frequently associated with fatigue, depression, and dry eye and mouth. It is commonly believed that in FM patients a stress-related imbalance of the hypothalamic-pituitary-adrenal axis and noradrenergic and serotonergic systems may induce these complaints (2).
The diagnostic approach to pSS is based on ocular tests for the assessment of lachrymal production, such as Schirmer's test and break up time, while dye tests are used to quantify damages in the ocular surface. Salivary dysfunction is usually measured by collecting the whole saliva volume produced in a given time. Salivary gland ultrasound examination is now the most common method used to evaluate the anatomical changes related to pSS in this target organ. The presence of hypoecogenic areas in the glands is considered the most specific finding in pSS patients. Finally, lip biopsy (LB) is considered the gold standard to demonstrate the presence of focal lymphocytic infiltrates in the minor salivary glands (3).
According to current classification criteria, the diagnosis of pSS can be established by the presence of specific anti-SSA(Ro) antibodies in the serum and/or of focal sialoadenitis in LB, in concert with at least one measure of ocular or oral dryness (3).
All of these diagnostic tests are usually normal in patients with FM-related sicca syndrome.
Although the pathogenetic mechanisms of pSS and FM appear strongly different, a number of data suggest that common pathways may underlie the features shared by the two disorders, *i.e*., WP, fatigue and depression.
Gene expression analysis in pSS suggests the possibility that specific inflammatory mediators may play a role in triggering the pathways involved in the development of WP, and namely the activation of glia and neuronal cells that are responsible of pain sensitization (4). Similar studies have shown that there was also an upregulation of several inflammatory mediators in FM (5).
It is well known that the activation of tryptophan catabolic pathway induced by indoleamine-2,3 dioxygenase-1(IDO-1) interferes with serotonergic and glutamatergic neurotransmission. It has been suggested that the activation of this pathway observed in pSS may be responsible for some manifestations such as hyperalgesia, WP, and depression in the disease. Similarly, IDO-1 activation has been observed in other conditions characterized by chronic pain and depressive state, including fibromyalgia (6).

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IS-17

Salivary biomarkers in fibromyalgia

Laura Bazzichi
U.O. Rheumatology Unit Pisa, Italy.

Fibromyalgia is a chronic non inflammatory musculoskeletal disorder characterized by widespread pain and by the presence of at least 11 out of 18 specific tender points on physical examination. Other associated unspecific symptoms may be present (sleep disturbances, memory problems, headache, depression). This condition is associated with significant disability. The diagnosis of fibromyalgia relies on the clinicians' experience, due to the lack of laboratory test. Currently, no validated laboratory biomarkers are available. Recent review (1) examines published data on the utilization of salivary biomarkers to facilitate and complement the diagnosis of fibromyalgia. Salivary biomarkers suggested in fibromyalgia diagnosis include cortisol; calgranulin; and the enzymes α-amylase, transaldolase, and phosphoglycerate mutase. However, none of the candidate biomarkers showed a statistical correlation with the patients' clinical features. In a our study (2) was investigated the presence in saliva of potential diagnostic and/or prognostic biomarkers which could be useful for the management of fibromyalgia patients. In the present study, we used two-dimensional electrophoresis (2DE), proteins were identified by NanoLC-ESI-MS/MS analysis or also SELDI-TOF-MS. The identified proteins were validated by Western Blot or ELISA kit. To evaluate the global changes in salivary profile of fibromyalgia patients. The salivary profile of fibromyalgia patients was compared with those of healthy subjects, subjects suffering migraine (model of non-inflammatory chronic pain), and patients affected by rheumatoid arthritis (model of inflammatory chronic pain). A total of 180 patients were consecutively recruited from the Rheumatology Unit at University- Hospital of Pisa. Sixty patients with a diagnosis of fibromyalgia [mean age 49.85±12.5 years, 51 females and 9 males], 60 patients affected by RA mean age 45.38±13.23 years; (52 females and 8 males), and 60 patients with migraine. Sixty healthy subjects, with similar mean age (42.57±6.22; 40 females and 20 males), Ninety patients and 30 healthy subjects were included in the discovery phase, the remaining were included in the validation phase.
Salivary samples were collected from patients and controls with a saliva collector sponge. WS samples were collected early in the morning according to a standard protocol and were pooled according to their diagnosis. The analysis of the protein profiles allowed us to find 26 spots with a different expression in FM respect to RA (p-value<0.05), 28 spots from the comparison of FM with migraine, and 32 in FM respect to healthy subjects. Fibromyalgia patients versus control subjects (healthy plus migraine) were investigated to obtain the discriminative power of biomarkers. Moreover, ROC curve was calculated by comparing fibromyalgia patients versus control subjects (healthy plus migraine) to investigate the discriminative power of biomarkers. The best performance was obtained by combining alpha-enolase, phosphoglyceratemutase-I and serotransferrin. Therefore, our results seem to support the inflammatory and autoimmunity hypothesis for fibromyalgia in fact, also the network built with our proteins highlights the involvement of inflammatory response in fibromyalgia and the immune cell trafficking. In addition, proteomic profile of fibromyalgia patients is more similar to that of RA patients, rather than migraine and healthy subjects. We defined a panel of 3 salivary proteins which could be one of the criteria to be taken into account. In conclusion we propose new biomarkers which can collectively allow to distinguish fibromyalgia patients. Consequently, the proteomic approach could be useful both to define a panel of potential diagnostic biomarkers and to shed new light on the comprehension of the pathogenetic pathways of fibromyalgia.

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IS-18

Neuroimaging of fibromyalgia: where do we stand?

Diana M. Torta, PhD
Health Psychology Research Group, Faculty of Psychology and Educational Science, KU Leuven, Belgium.

Recent consensus papers have underlined that imaging techniques cannot represent a substitute for self-report in patients suffering from chronic pain (1, 2). As pain is defined as a subjective experience, what the patients report remains the gold standard. However, neuroimaging techniques can be used to complement and integrate the diagnosis, to attempt predictions about the clinical direction, and to potentially aid the therapeutic choice (2). Also, neuroimaging may offer a window to the study of structural and functional changes purportedly associated with a pathological condition, for instance fibromyalgia (FM). Across the years, several studies have compared the resting state functional connectivity (rsFC) and sensory evoked activity in patients suffering from FM, with that of healthy controls (HC), or patients suffering from other pain conditions (3-11). Neuroimaging techniques have also been used to quantify neuronal changes after both pharmacological and non-pharmacological interventions (12-14).
Several functional resonance imaging studies (fMRI) in FM have focused on the functional connectivity between the Default Mode Network (DMN), the insula, and other cortical regions such as the primary somatosensory cortex (3, 10, 15). Overall, these studies have shown increased functional connectivity between the DMN, S1, and insula in patients with FM at rest or after evoked activity (3, 10, 16, 17), a correlation between such parameters and clinical pain (10), and a reduction of "aberrant" activity after therapeutic intervention (12). Along with the observation of increased functional connectivity is that of potentially reduced descending controls operating via prefrontal regions and the Periacqueductal gray (PAG) (11, 18, 19).
However, the choice of the control population, and the clinical ongoing pain at the time of testing appear to be crucial elements to take into consideration when interpreting the findings. Kutch and colleagues (20) have observed that the increased connectivity between the insula and sensorimotor cortices is not a prerogative of FM, but can be also found in patients suffering from urological chronic pain syndrome and reporting a widespread distribution of their pain. These findings are in line with others pointing to increased DMN-insular connectivity in patients suffering from chronic back pain (CBP) (21, 22). Very interestingly, Čeko and colleagues have recently observed that the increased functional connectivity between the DMN and the insula could be related to ongoing pain at the moment of the scan (15), as it was not present when FM patients without ongoing pain were compared to HC. Also, it is unclear whether increased responsiveness to painful stimuli in FM patients may in fact represent hyperresponsiveness to salient stimuli, rather than to the painfulness of the stimuli themselves (23).
Overall, the neuroimaging literature of FM points to several potential (reversable) changes in patients suffering from FM. However, the exact functional meaning of such changes, their predictive value and their origin remains to be fully disclosed.

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IS-19

Why opioids should not be used to treat fibromyalgia

Mary-Ann Fitzcharles, MB ChB
Division of Rheumatology and Alan Edwards Pain Management Unit, McGill University Health Centre, Canada; Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada, H3G 1A4.

With pain as the foundation symptom of fibromyalgia (FM), it is intuitive to look towards a treatment with analgesic properties for symptom management. From the late 1980's, in parallel with the recognition that FM was a valid condition, opioids were promoted as an effective treatment for chronic pain conditions and doubters were identified as having opiophobia. The uptake of opioids as a treatment strategy for FM was rapid, with up to 30% of North American FM patients receiving opioid prescriptions, even into the last decade. Apart from the well-known risks related to the opioid epidemic, opioids are not the panacea for FM care for a number of reasons: 1) dysfunction of the endogenous opioid system in FM with increased opioid concentration in the CSF, and decreased availability of mu-receptors in the CNS; 2) opioid side effects mimic FM symptoms such as increased fatigue, sleep disturbance and more pain as in hyperalgesia, 3) tolerance to opioids develops in time with need for higher doses; 4) almost no study of opioids in FM with only study of tramadol, a low-potency opioid in combination with acetaminophen, with dual mechanism of mu-receptor antagonism and serotonin norepinephrine uptake inhibition, but with concern about increased mortality in elderly patients with osteoarthritis 5) as FM is mostly lifelong, continued opioid treatments into later years of life is associated with considerable risks. Taken in sum, there is sufficient concern to recommend against the use of opioids in FM, with strong encouragement to focus on non-pharmacological measures and only selected use of medications.

IS-20

Why and to what extent do cannabinoids work in fibromyalgia patients?

Silviu Brill, MD EDPM
Director of Institute of Pain Medicine, at Tel Aviv Medical Center, Israel.

In recent years, cannabis had been approved for medical use in many countries: from United States to Europe and Israel. Worldwide, cannabis is the third most commonly used substance after alcohol and tobacco.
The use Medicinal cannabis is highly controversial amongst doctors.
There are only a few studies in the literature on the use of cannabis by fibromyalgia patients. In these studies, the patients used unlicensed/illegal cannabis from different suppliers, and the studies contained no information on either the type or amount of cannabis used.
The medical community needs to adhere to the principle that substances intended for therapeutic purposes be fully characterized chemically, pharmacologically and toxicologically. The use of medications, including medicinal cannabis, should not be the core component of therapy.
Although herbal cannabinoids may offer some therapeutic effect, caution regarding any recommendation should be exercised pending clarification of general health and psychosocial problems and a clear follow-up program should be used. Standardization of compounds and treatment regimens should be a priority
At the present time, the scientific evidence for the efficacy of cannabinoids in the management of people with fibromyalgia patients is insufficient to justify endorsement of clinical guidelines.
Specific concerns should address also risk of doctor shopping, risk of harms, media and public pressure and the emergence of a new industry, rather than on the foundation of robust evidence.

IS-21

Effect of different drugs: does it make sense in fibromyalgia?

Winfried Häuser
Klinikum Saarbrücken, Germany.

Current pharmacotherapies for fibromyalgia (FM) are often ineffective and poorly tolerated. Combining different medications with different modes of action is seductive. Physicians and patients expect superior pain relief and possibly also fewer side effects. Some surveys with FM patients have shown that combination pharmacotherapy is rather the rule than the exception in FM.
As for most therapies used in FM, the quantity and quality of evidence for a combination of medications in FM is low. A Cochrane review identified 16 studies with 1474 participants. Three studies combined a non-steroidal anti-inflammatory drug (NSAID) with a benzodiazepine (306 participants); two combined amitriptyline with fluoxetine (89 participants); two combined amitriptyline with a different agent (92 participants); two combined melatonin with an antidepressant (164 participants); one combined carisoprodol, paracetamol (acetaminophen), and caffeine (58 participants); one combined tramadol and paracetamol (acetaminophen) (315 participants); one combined malic acid and magnesium (24 participants); one combined a monoamine oxidase inhibitor with 5-hydroxytryptophan (200 participants); and one combined pregabalin with duloxetine (41 participants). Three studies found low quality evidence that combination pharmacotherapy reduced pain compared to monotherapy; these trials tested three different combinations: melatonin and amitriptyline, fluoxetine and amitriptyline, and pregabalin and duloxetine. Adverse events experienced by participants were not serious, and where they were reported (in 12 out of 16 studies), all participants experienced them, regardless of treatment. Common adverse events were nausea, dizziness, somnolence, and headache.
I will present my clinical experience with combination of medications: When and for what symptoms.

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IS-22

Multicomponent treatment strategies in fibromyalgia

Jacob N. Ablin
Tel-Aviv Sourasky Medical Center, Israel.

Complex problems rarely have a simple solution… Fibromyalgia is no exception. While the pathogenesis and etiology of fibromyalgia remain only very partially understood, and multiple novel aspects continue to gain recognition, it is not really surprising to acknowledge that there is no "one-size-fits-all" approach to the management of fibromyalgia. Notably, fibromyalgia patients differ from one another in many clinical aspects, not the least for instance – the presence or absence of significant psychiatric comorbidity. In view of this complex reality, treating fibromyalgia is somewhat of an art. The physician taking on this task must start with a carful and comprehensive evaluation of the clinical manifestations cardinal for the specific patient. Formulating a differential diagnosis is imperative, not only as far as identifying altogether other diagnoses, which may explain major parts of the clinical presentation (*e.g.* inflammatory spondyloarthropathies), but also as far as identifying specific peripheral nociceptive and / or neuropathic pain - generators which often coexist together with centralized pain, and which deserve targeted treatment. In addition, specific clinical characteristics must be factored into the therapeutic design. For example, patients with significant obesity are better not treated with medications which may cause weight gain (*e.g.* Pregabalin); Patients with cardiac disorders are not good candidates for tricyclic medications etc.
The early introduction of non-pharmacological modalities of therapy is now universally recommended. But this also must be tailored to the particular patient's needs, capacities and circumstances. If reaching a hydrotherapy facility requires riding an hour and a half by bus back and forth, any symptomatic advantages may well be overcome by the hassle and so on. Furthermore, pharmacological management of fibromyalgia patients is a process of carful and meticulous titration, requiring repeated encounters (and often in-between phone calls or texts) in order to finetune treatment, minimize side effects and enhance compliance.
Lastly, while relatively "dramatic" cases of success are encountered while treating fibromyalgia, performing a "copy-paste" approach from one case to the next remains perplexingly fruitless and each journey must start on its own.

IS-23

Therapeutic validity of exercise interventions in the management of fibromyalgia

Giorgio Ferriero[1,2], Roberto Casale[3]
[1]Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy; [2]Physical and Rehabilitation Medicine Unit, Scientific Institute of Tradate, Istituti Clinici Scientifici Maugeri IRCCS, Tradate (VA), Italy; [3]Opusmedica, Persons Care & Research network, NPO, Piacenza, Italy.

Initial management of fibromyalgia should focus on non-pharmacological therapies. Among the non-pharmacological therapies, exercise interventions are recommended as the most important ones, with the strongest level of evidence of efficacy.
Exercise interventions are generally shown to effectively and safely reduce pain intensity or frequency (or both), in chronic pain, reducing its impact on function, quality of life, and healthcare use. One of the possible reasons for these effects is the increased production of endogenous opioids caused by exercise, leading to transient anti-nociception. This anti-nociception effect may become long-lasting when exercise is frequently repeated, as in an organized program. Exercise seems able to stimulate brain regions involved in descending pain inhibition, decreasing sensitivity to pain. Regular aerobic fitness training increases the level of serotonin - an important neuromodulator with both nociceptive and antinociceptive effects - suggesting stimulation of the descending pain modulation. Exercise is also effective in reducing anxiety and depression symptoms.
Taking into account the major findings from literature two kind of exercise intervention are potentially beneficial in fibromyalgia: aerobic and strengthening exercises. However, it is worth of mentioning that there is evidence that muscle fatigue in fibromyalgia is more due to a central motor control failure than a muscle deconditioned status. Aerobic exercise is any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature. Training based on aerobic exercise is mainly aimed to increase the endurance. Examples of aerobic exercise include walking, cycling (not only using the lower limbs), jogging, long distance running, and swimming. In fibromyalgia, low-impact aerobic exercise, such as walking, swimming, biking, or water aerobics, is associated with improvements in pain and physical function.
Strengthening exercise is a voluntary activity designed to increase the strength of specific or groups of muscles, including the use of weight machines, exercise bands, hand-held weights, or own body weight. It is important to increase intensity slowly and use, at least initially, light weights. Strength training is associated with large improvements in global well-being and physical function.
In fibromyalgia the incidence of side effects related to exercise programs is low. Exercise may determine as possible adverse effects an increase in symptoms (*e.g.* fatigue, pain, and stiffness). Therefore, it is recommended customizing exercises according to both fitness characteristics and psychological risk factors of the patient, by means of an individually tailored program. Thus, it is important not to start a vigorous exercise program, but it is preferable a start and go slow, for a few minutes of activity per day. Once the subject becomes confident that the exercise frequency is under control, the duration of the exercise bout can gradually be increased. The final exercise characteristic that should be addressed is the exercise intensity.

IS-24

Mind and body therapies for fibromyalgia syndrome

Piercarlo Sarzi-Puttini
L. Sacco University Hospital, Italy.

It is now more than confirmed the importance of mind-body therapies in the management of fibromyalgia syndrome. They belong to the big group of *nonpharmacological therapies* which are fundamental for a multimodal approach to these patients (1), and that appear even to be effective in more domains with respect to pharmacological approaches (2). Mind-Body therapies use movement and concentration to augment the relationship between the mind (mental activity) and body (motor control). This allows to intervene on centrally-mediated pain mechanisms, which have a pivotal role in nociplastic fibromyalgia pain (3). We can divide mind-body therapies in two groups: meditation-mindfulness therapies and meditative movement approaches (yoga, Tai-Chi, Feldenkrais method, etc.), based on physical movement integrated with mental relaxation and breathing techniques.
Mindfulness is based on the principle of the non-judgemental acceptance of one's condition, thoughts and suffering, recognizing that nothing is intrinsically positive or negative. The effect of mindfulness approaches is fibromyalgia syndrome has been more and more studied, giving encouraging results (4, 5), following the principle that those patients who have a preponderant catastrophizing or negative affect may particularly benefit from this approach. A recent study (6) highlighted that higher mindfulness levels are associated with better sleep quality, less pain interference, lower depressive and anxiety symptoms scores.
Meditative movement therapies may be efficacious and safe in the integration of fibromyalgia treatment (7). As an example, Tai-Chi is also a martial art style which is based on coordinated movements, meditation and breath control. Tai-Chi is one of the most studied meditative movement therapies for fibromyalgia, with a high-quality randomized controlled trial published in the *BMJ* in 2018 (8), concluding that it has a notable positive effect on many aspects of the condition and could become a promising alternative to conventional exercise by possibly attracting less compliant patients.
However, mind-body therapies still lack well-conducted studies and robust randomized controlled trials to sustain the preliminary results of observational studies, which anyway are important to support the hypothesis of them being promising and even fundamental approaches for integrating fibromyalgia treatment.

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IS-25

European network of fibromyalgia associations and scientific advisory committee

KØ Forseth, PhD[1], G. Göran, Stefano Coaccioli[3]
[1]Rheumatologist (retired) Department of Rheumatology, University of Oslo, member of ENFA board; [2]President of ENFA board; [3]President, European League against Pain, Professor (retired) of Int. Medicine and Rheumatology, Perugia University, Italy and member of ENFA).

Almost 14 million people in Europe are affected by fibromyalgia (FM). There prevails a huge scepticism around FM, and consequently an arbitrary and insufficient managing of FM. Thus, it is a serious need to fight against this and call on medical communities and National and European policy makers to change it.
National guidelines for holistic managing of FM with individual and interdisciplinary treatment programmes and patient education might be useful tools to do so. In-depth training of medical expert professionals by courses is mandatory to secure the necessary level of quality and to assist awareness programmes for general practitioners which will facilitate the early diagnosis and early treatment of FM, as well as access to care at any time.
Moreover, including FM as a disease with patient rights to have a specialist consultation, to allocate the adequate aid for scientific research, and finally to put in place a European programme on the exchange of best practices on FM are important.
In 2008 the European Parliament accepted these set of problems and issues by a written declaration on FM. This spurred the EU Commission to develop a community strategy to recognise FM as a disease and to help raising awareness of FM by supporting European and national awareness campaigns, to encourage Member States to improve access to diagnosis and treatment and to stimulate research on FM.
The European Network of Fibromyalgia Associations (ENFA) was founded in 2009 with the purpose to gather and disseminate information about FM, with a view to establish contacts and make suggestions on how to heighten awareness of the illness among the public, the business community, health professionals and politicians. Further, ENFA aims to forge links between the medical profession and research institutes.
However, there have been no significant ameliorations whatsoever. To come closer to the purposes of improving knowledge and awareness about FM, as well as to gather the medical disciplines potentially interested in FM, ENFA has involved scientists and health professionals from a broad field of FM and recently established a Scientific Advisory Committee (SAC) with members from several European countries. SAC contains almost all professionals involved in FM. Committee members will be invited to participate in sharing ideas and scientific initiatives, medical information's, information of socio-economic consequences and to establish programmes of research to realise position papers, diagnostic and therapeutic pathways.
Finally, we will underline that the mission of ENFA is to conquer the myths and misunderstandings around FM. To do so, ENFA will help to push forward boundaries which currently exist in understanding, experiencing, and treating FM. As such, ENFA aims to provide FM with the recognition it deserves across Europe as an illness. The purpose is to support and represent the interest of FM patients and to represent the interests of the pain disease community as partner of European policy makers, to improve prevention, treatment, and rehabilitation, and to reduce the burden of pain disease on the individual and the society, to bring together scientific societies, scientists, clinicians, patients associations, politicians, health professionals of various disciplines and stakeholders with an interest in FM research and management, to stimulate the societal discussion and to exchange information and to share best practices across all member states of the EU.
SAC will be a useful tool in obtaining this.

IS-26

The role of patient associations: Italy

Giuseppina Fabio
AISF-ODV, ASST Fatebenefratelli "Luigi Sacco" University Hospital, Milan, Italy.

Patient Associations are non-profit social utility organizations. They are engaged both in activities of collective interest and in the protection of individual patients, working to ensure them a better quality of life in terms of medical, pharmacological and social assistance.
Fibromyalgia Patients' Associations create and develop dedicated programs for the improvement of fibromyalgia patients' lives. One of these Patient Associations is Aisf-Odv (Italian Association of Fibromyalgia Syndrome), which was born in 2005 in Milan, but operates throughout the national territory. Our Patient Association created a nation-wide Network able to directly support patients, listening to them and educating them to actively self-manage their condition: these interventions were shown to be particularly effective in many chronic conditions, especially in fibromyalgia, and self-management programmes have been at the core of many interventions (1, 2). This is done through educational interventions about the disease (which are organized not only for patients, but also for healthcare professionals and Institutions), various workshops and activities. Examples of such activities are the Art therapy workshop, which helps patients transform their suffering with a greater and more correct awareness, movement activity projects and psychoeducational support groups. A recent nation-wide, ambitious project is to build up Reference Centres for the multidisciplinary management of fibromyalgia syndrome.
In this moment of sanitary emergency, our activity has not stopped, but keeps going. Every activity is carried out online in order to be able to assist patients so as not to leave them alone.
In Italy, fibromyalgia syndrome is not recognized as a chronic and disabling disease at an institutional level. Patient Associations' main objective is to ensure this recognition, in order to give dignity to those who suffer from this condition, who very often are not even believed to be ill.

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IS-27

The role of patients association: Israel

Sharon Gur
Chairperson, ASAF The Israeli CFS & Fibromyalgia NPO.

Since its foundation 20 years ago, when FM was known only to a handful of people, ASAF has been promoting the rights of patients, creating awareness and assisting wherever needed in order to help FM patients. As a result of our activities, awareness of the public and the medical community has been vastly increased. We take pride in the fact that all of us are volunteers and all of our modest budget is dedicated to the benefit of the patients.
Our yearly program includes initiating and participating in conferences and Grand Rounds, reaching out to rheumatologists, neurologists, general physicians, psychiatrists and pain management physicians, to social workers, nurses, psychologists and other specialists in integrative medicine. We aim to educate and promote the importance of finding a faster and more accurate diagnosis, encourage medical research, and introduce the patients' point of view and their struggle in order to cultivate empathy and a wider understanding of the illness.
Another effective tool we use to help connect and empower FM patients are a variety of support groups that we have formed throughout Israel, including groups for special populations such as the Jewish orthodox community or for teenagers, adjusting the content and information to suit their specific needs. All groups share knowledge and offer support and comfort.
Since 2000, in honor of the international awareness day on May 12th, we organize a yearly conference, cooperating with leading hospitals and the best specialists in Israel, where patients and their families are introduced to

the newest innovations and various ways to cope with FM. In preparation for this awareness day, we collaborate with active Facebook groups and volunteers, together organizing the awareness campaign. Our activities encouraged HMOs, hospitals and private practice providers to open complementary medical centers throughout Israel, providing a variety of treatments.
ASAF has been actively promoting patients' rights for 15 years, and have been instrumental in the fight to have the Social Security Institute recognize FM as a disability, enabling patients to receive fair entitlements and proper pension payments. We appealed to the Supreme Court three times, and they eventually ruled in our favor.
This past year the Covid -19 pandemic created a unique challenge and we adjusted our activities accordingly. Among chronic patients, especially FM patients, the unknown is problematic and very difficult, as even in normal times they feel that their body has betrayed them and they can't keep a normal routine. Staying at home for a long and unknown period of time added more stress. It exposed their condition, which they had often concealed, to family members. Our support line became crucial for the patients and family members, contacting us as they longed for a sympathetic ear. We were there for them.
Cancellations of events, support groups and conferences occurred and we adapted by moving the lectures from the halls to zoom sessions, lectures on Facebook and webinars. We offered patients knowledge in diverse areas of interest.
When the vaccines finally arrived to Israel, a new concern arose. Is the vaccine safe for Fibromyalgia and CFS patients? What are the side effects? We have published clarifications and guidelines to ease the concerns of the patients, and indeed many of the patients in the appropriate age group have been vaccinated, with no significant side effects thus far.
In addition, we are receiving inquiries from Covid 19 recoverees describing symptoms very similar to FM, and some actually been positively diagnosed. We are studying the findings, and are looking for answers.
We are always pleased to be a source of comfort when needed, and a reliable source for information - especially in times of crisis like this.

IS-28

The role of registries in the analysis of FM data

Marco Di Carlo
Rheumatology Clinic, Università Politecnica delle Marche, "Carlo Urbani" Hospital, Jesi (Ancona), Italy.

In the field of chronic diseases, alongside data from clinical trials, there is an increasing need to obtain data from real life. With the information technology available today, it is possible to computerize the process of data collection, applicable on a large scale, and organize them in a registry. A patient registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specific outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose."
For fibromyalgia syndrome, there were no European registries until the creation of the Italian Fibromyalgia Registry (IFR), whose implementation was supported by both the Italian Society of Rheumatology ("Società Italiana di Reumatologia" - SIR) and the Italian Ministry of Health.
The IFR, to date, has essentially allowed the achievement of multiple objectives, the main ones summarized as 1) to assess and monitor patients condition over time by means of demographic data, clinical descriptors, and uniform outcome measures estimated using standardized and validated tools at each participating site; 2) to establish cut-off points of disease severity to support health care decision-making 3) provide researchers with reliable real-world data to answer important research questions, test hypotheses regarding various aspects of chronic widespread pain and its management, assess study feasibility, and facilitate patient recruitment into clinical research; and 4) support collaborative research projects by promoting cooperation among centers and assisting in the implementation of research projects.

IS-29

What is relevant to assess clinical improvement?

José António Pereira da Silva
University of Coimbra, Portugal.

A variety of instruments have been developed for use in clinical trials and shown to be valid and sensitive to change by interventions. Among these, the Fibromyalgia impact Questionnaire (FIQ) and its revised form are paramount. A large number of instruments are also available for each of the specific domains of impact, such as pain, sleep, fatigue and depression. Selecting the most appropriate one is faced with conflicting evidence and lack of established gold standards. General instruments of Health Related Quality of Life can also be considered, depending on the objectives of the measurement.
These instruments can also be applied sequentially in clinical practice to gauge the progression of patients and adapt medication. However, caution is advised in this setting. Progression should, at least, take into account the different domains of the disease that can be informative for the personalized selection of interventions, such as Anxiety and depression, sleep disturbance, and pain. Comorbidities that can influence the impact of the disease, such as restless leg syndrome, sleep apnea and depressions should also be regularly assessed, and interventions adapted accordingly.
The risk of metrology instruments should be taken into account. The regular use of research scales or even of clinical assessment sheets can induce the practitioner into a mechanistic and impersonal approach that can be especially harmful in fibromyalgia, for a number of reasons. Despite its nosological coherence, fibromyalgia is a highly heterogeneous condition regarding the variety of manifestations and their relative weight for the individual person, the trigger and maintenance mechanisms in play. Recognizing these nuances is impossible with standardized measures of disease impact but represents a crucial ingredient for successful management of these patients. Fibromyalgia patients are exquisitely sensitive to interpersonal relationships and demand a carefully nurtured therapeutic rapport with physicians and other health professionals - this can be easily lost if the consultation becomes impersonal, namely through excessive metrology.
Individually tailored goals and metrics ought to be considered and agreed upon in every case, to ensure the personal relevance of the measurement and to foster adherence to the proposed interventions. Common understanding and mutual acceptance of the objectives and methods of the intervention strategy is key to achieve significant improvements and, must, therefore be assured at the start and regularly confirmed. Adherence and commitment to the agreed strategy are, in and by themselves, such critical factors of success that they deserve regular evaluation and support.
In clinical practice, managing and adapting the strategy, while evaluating progress and keeping the patient involved and motivated represents a very complex task. Its success probably depends more on the attitude of the physician and patient and the quality of their therapeutic relationship than on technicalities of what and how to measure.

IS-30

Can patients achieve a persistent remission?

Eduardo S. Paiva, MD, PhD, FACR
Professor, Rheumatology; Chief of Fibromyalgia Clinic, Universidade Federal do Parana – Curitiba, Brazil.

What does it mean, remission in fibromyalgia (FM)? One must consider that remission is usually the goal in the chronic conditions seen by the rheumatologist, like rheumatoid arthritis and lupus. It is different from cure, and it is important that providers and patients find a common ground in their definition of it. In remission, the objective is the absence the symptoms, but the disease state is present, and follow-up and constant management are usually necessary. In FM patients, the evidence that there is always something "lurking below the surface" are the frequent relapses, specially in stressful situations, and the fact that even well controlled, satisfied patients will show signs of hyperalgesia in muscle palpation (the famous "tender points").
In fibromyalgia, as in other chronic pain states, it is now clear that the goal must be gain of function and better quality of life. To keep the focus only in pain levels is to mislead the patient in thinking that he or she could only feel "in remission" if the pain level approaches zero. This is an unattainable goal, and usually leads to frustration for both patients and health professionals.
Rheumatoid arthritis brought a great lesson: quantification of the disease state in every visit and "treat to target" led to better disease control and the possibility of remission; so, quantify FM is very important. One should reach for multidimensional tools, that go beyond the VAS (visual analogue scale) for pain. The FIQR (Fibromyalgia Revised Questionnaire, revised version) is arguably the best of these tools and is widely validated and translated. It focuses on quality of life and function. The Polysymptomatic Distress Scale (PDS or "fibromyalgianess" scale) is the simple sum of the Widespread Pain Index and the Symptom Severity Scale of the fibromyalgia 2010 criteria. It measures something different from the FIQR, and maybe it is the real disease activity score in FM, as it was well correlated to central sensitization, the main motor of this condition.
After quantifying, how does one know when the FM patient will be in remission? Should we use cutoffs for the FIQR, as suggested by Salaffi et al. (1)? Is the PDS useful? Should we subgroup the patients and verify which domains are to be accessed first, as recommended by Vincent at al. (2)? Or should we be content with the plain statement "I am no longer a patient and no longer suffer due to my pain (which may still be present)"? (3). Most likely, contrasting with diseases like rheumatoid arthritis, these approaches will be different for each FM patient, and the provider will have to choose which remission criteria will fit for each individual case.

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O-01 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Fibromyalgia severity according to age categories: results of a cross-sectional study from a large national database

Marco Di Carlo[1], Sonia Farah[1], Laura Bazzichi[2], Fabiola Atzeni[3], Marcello Govoni[4], Giovanni Biasi[5], Manuela Di Franco[6], Flavio Mozzani[7], Elisa Gremese[8], Lorenzo Dagna[9], Alberto Batticciotto[10], Fabio Fischetti[11], Roberto Giacomelli[12], Serena Guiducci[13], Giuliana Guggino[14], Mario Bentivegna[15], Roberto Gerli[16], Carlo Salvarani[17], Gianluigi Bajocchi[18], Marco Ghini[19], Florenzo Iannone[20], Valeria Giorgi[21], Mariateresa Cirillo[3], Sara Bonazza[4], Stefano Barbagli[5], Chiara Gioia[6], Noemi Giuliana Marino[7], Annunziata Capacci[8], Giulio Cavalli[9], Antonella Cappelli[10], Francesca Carubbi[22], Francesca Nacci[13], Ilenia Riccucci[16], Maurizio Cutolo[23], Luigi Sinigaglia[24], Piercarlo Sarzi-Puttini[21], Fausto Salaffi[1].
[1]*Rheumatology Clinic, Department of Clinical and Molecular Science, Università Politecnica delle Marche, Italy;*
[2]*Rheumatology Unit, AOU Pisana, Pisa, Italy, Italy;*
[3]*Rheumatology Unit, Department of Internal Medicine, University of Messina, Italy;*
[4]*Rheumatology, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliera-Universitaria S. Anna di Ferrara, Italy;*
[5]*Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy;*
[6]*Department of Internal Medicine, Anesthesiological and Cardiovascular Sciences Rheumatology Unit, Policlinico Umberto I, Sapienza University of Rome, Italy;*
[7]*Internal Medicine and Rheumatology Unit, Azienda Ospedaliero-Universitaria di Parma, Italy;*
[8]*Rheumatology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy;*
[9]*Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Italy;*
[10]*Rheumatology Unit, Internal Medicine Department, ASST Settelaghi, Ospedale Di Circolo - Fondazione Macchi, Italy;*
[11]*Unit of Rheumatology, ASUGI and Clinical University Department of Medical, Surgery and Health Sciences, University of Trieste, Italy;*
[12]*School of Medicine, Division of Rheumatology and Clinical Immunology, University of Rome "Campus Biomedico", Italy;*
[13]*Department of Experimental and Clinical Medicine, Divisions of Rheumatology AOUC, University of Florence, Italy;*
[14]*Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties, University of Palermo, Italy;*
[15]*Integrated Reference Center of Rheumatology, ASP 7, Scicli Hospital, Italy;*
[16]*Rheumatology Unit, Department of Medicine & Surgery, University of Perugia, Italy;*
[17]*University of Modena and Reggio Emilia, Azienda USL-IRCCS di Reggio Emilia, Italy;*
[18]*Rheumatology Unit, S. Maria Hospital - USL, IRCCS Institute, Italy;*
[19]*Rheumatology Unit, Azienda USL di Modena, Italy;*
[20]*Rheumatology Unit, Department of Emergency and Organ Transplantations, University of Bari, Italy;*
[21]*Rheumatology Unit, Internal Medicine Department, ASST Fatebenefratelli-Sacco, Milan University School of Medicine, Italy;*
[22]*Clinical Unit of Rheumatology, School of Medicine, University of L'Aquila, Italy;*
[23]*Research Laboratory and Division of Clinical Rheumatology, Department of Internal Medicine, University of Genoa, IRCCS San Martino, Italy;*
[24]*Division of Rheumatology, ASST Gaetano Pini-CTO, Italy.*

Background. The role of age in influencing the severity of fibromyalgia (FM) is still controversial. The aim of this study is to define the contribution of age in the severity of FM from data from a large national database.
Methods. This cross-sectional study included adult patients with FM diagnosed according to the 2010/2011 American College of Rheumatology criteria. Disease severity was assessed with the revised Fibromyalgia Impact Questionnaire (FIQR) and the modified Fibromyalgia Assessment Status (FAS 2019mod). Patients were grouped into five age categories (between 18-40 years, between 41-50 years, between 51-60 years, between 61-70 years, and ≥71 years). Differences in disease severity between groups were assessed by one-way analysis of variance (ANOVA).
Results. The study included 2889 patients (199 males and 2690 females), mean age of 52.58 (±11.82) years, with a mean FIQR score of 59.22 (±22.98) and a mean FAS 2019mod of 25.50 (±8.66). Comparing the mean values of the various indices between age categories, there were no statistically significant differences between the groups for FIQR total score and FAS 2019mod (Fig. 1). However, the 60-70 years category showed the lowest scores for both scales. The main difference emerged for the FIQR physical function subscale, where the ≥71 years category showed significantly higher scores (p 0.05) compared the 18-40 years category (Fig. 2).
Conclusion. The severity of FM has a significant level of stationarity according to age categories. Patients between 60-70 years have a lower disease burden. Physical function is the health domain with the most significant difference between the groups.
Key words: fibromyalgia; disease severity; age; FIQR; FAS 2019mod

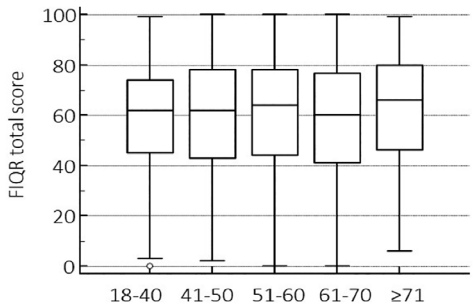

Fig. 1. Box-and-whisker plot for the revised Fibromyalgia Impact Questionnaire total score according to age categories differences (one-way analysis of variance).
Boxes represent the interquartile range. The middle line within the plot represents the mean. X-axis age categories expressed in years.

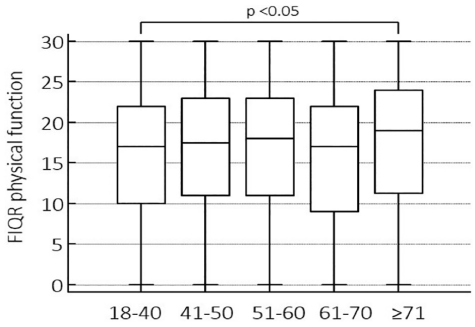

Fig. 2. Box-and-whisker plot for the revised Fibromyalgia Impact Questionnaire subscale physical function according to age categories differences (one-way analysis of variance).
Boxes represent the interquartile range. The middle line within the plot represents the mean. X-axis age categories expressed in years. Significative difference between the first (18-40 years) and the last (≥71 years) category.

O-02 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Implication of the nociplastic features for clinical diagnosis of fibromyalgia

Banafsheh Ghavidel-Parsa[1], Ali Bidari[2]
[1]*Rheumatology, Rheumatology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran;*
[2]*Rheumatology, Department of Rheumatology, Iran University of Medical Sciences, Tehran, Iran.*

Objectives. This study aimed to propose core clinical features of nociplastic pain (NP) into a new diagnostic tool named as Nociplastic-based Fibromyalgia Features (NFF) for fibromyalgia (FM) diagnosis. We also sought to explore the performance of the NFF with comparison to the expert diagnosis (ED) and the 2011 and 2016 ACR criteria.
Methods. Items requiring ''yes/no'' responses and relating to the most relevant clinical NP features of FM were compiled by a group of expert rheumatologists. The provisional list was tested in a prospective study on the consecutive 185 patients with chronic pain (126 FM and 59 non-FM non-inflammatory chronic pain patients) which were diagnosed based on the expert decision. Identification of the most discriminant combinations of items for FM and the calculation of their sensitivity and specificity were based on both univariate and multivariate (stepwise logistic regression) analyses. All participants were investigated through the final NFF, the 2011 and 2016 ACR criteria. The NFF performance was assessed with receiver operating characteristic curve analysis.
Results. Based on multivariate analyses, we retained only seven items in the final version of NFF. A cut-off score of 4 (corresponding to the number of positive items) gave the highest rate of correct identification of patients (85%), with a sensitivity of 82% and a specificity of 91%. The NFF showed the highest concordance rate with ED (85%) and lowest value (77%) with the ACR 2016 criteria.
Conclusion. The NFF with respect to the various aspects of NP showed the good performance for detection of the FM in the clinical setting. It could provide more pragmatic approach to the timely diagnosis of FM.

O-03 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Misdiagnosis in fibromyalgia and related influencing factors

Dongfeng Liang[1], Ying Zhang[1], Xiaojian Ji[1], Ronghuan Jiang[2], Jian Zhu[1], Feng Huang[1]
[1]*Department of Rheumatology,* [2]*Department of Psychology, The First Medical Center, Chinese PLA General Hospital, China.*

Background. The knowledge of FM in the doctors is still insufficient in China.
Objective. To investigate the misdiagnosis of FM, and explore the factors leading to the misdiagnosis.
Methods. The patients diagnosed as FM in the department of rheumatology of Chinese PLA General Hospital from June 2016 to December 2017, with a visiting history to other hospitals were included. Clinical features and previous diagnosis were collected. The differences of clinical features between the patients correctly diagnosed and those misdiagnosed were compared.
Results. The study included 70 FM patients who had 110 clinic visits in other tertiary and secondary hospitals. The mean age of the patients was 38 years, and 88.6% of the patients were female. Only 9 visits (8.2%) were correctly diagnosed as FM. The most common misdiagnosis was spondyloarthritis (27 visits, 24.5%), followed by rheumatoid arthritis (6 visits, 5.5%), Bi syndrome (11 visits, 10.0%), anxiety and/or depression (7 visits, 6.4%), other diseases (24 visits, 21.8%) and no definite diagnosis (26 visits, 23.6%). The patients who were misdiagnosed had less tenderness points (8.0 vs 14.5, p=0.039) than the correctly diagnosed patients.
Conclusion. FM is underdiagnosed in the secondary and tertiary hospitals in China, and the knowledge of FM in the doctors including rheumatologists is still severely insufficient. The doctors tend to diagnose FM heavily depending on the number of tenderness points, while they ignore the value of other signs and symptoms, which is the major reason for misdiagnosis of FM.

O-04 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

The fibromyalgia solution

Virgil Stenberg, Ann Baldwin
Chemistry, University of North Dakota, USA.

The cause of fibromyalgia is a defective HPA axis during stress. The solution is patient self-administration of hydrocortisone with stress management. By examination in a clinic trial, 601 fibromyalgia participants averaged 77% symptom improvement in 3 weeks with no significant adverse reactions using patient self-administration of hydrocortisone. By comparison, duloxeline averages 17-30% symptom improvement; pregabalin, 26-31% symptom improvement; and milnacipran, 35-42% symptom improvement. The results are in Irwin JB, Baldwin AL, Stenberg VI [2019] General Theory of Inflammation: patient self-administration of hydrocortisone safely achieves superior control of hydrocortisone-responding disorders by matching dosage with symptom intensity. *J Inflam Res* 12: 161-166.

O-05 *Neuro-biological Underpinnings of Fibromyalgia and Centralized Pain*

New model of fibromyalgia pathogenesis based on a thalamocortical loop network

Ilaria Demori[1], Giulia Giordano[2], Viviana Mucci[3], Serena Losacco[4], Lucio Marinelli[5], Paolo Massobrio[6], Franco Blanchini[7], Bruno Burlando[8]
[1]*DISTAV, University of Genova, Italy;*
[2]*Department of Industrial Engineering, University of Trento, Italy;*
[3]*School of Science, Western Sydney University, Australia;*
[4]*DIFAR, University of Genova, Italy;*
[5]*DINOGMI, University of Genova, Italy;*
[6]*DIBRIS, University of Genova, Italy;*
[7]*Department of Mathematics, Computer Science and Physics, University of Udine, Italy;*
[8]*DIFAR, University of Genova, Italy.*

Background. Fibromyalgia (FM) is a central pain processing disturbance which remains unsolved and unclear up to now.
Objectives. We aim at providing a unifying model for FM pathogenesis, by combining ideas from Systems and Control Theory and Psycho-Neuro-Endocrine-Immunology (PNEI). A loop system can be identified involving thalamocortical regions, (i.e. ventroposterior lateral thalamus (VPL), somatosensory cortex (SC), and thalamic reticular nucleus (TRN)).
Methods. The dynamics of the loop system have been described by three differential equations having neuron mean firing rates as variables and containing Hill functions to model the mutual interactions among thalamocortical regions.
Results. A computational analysis conducted with MATLAB has shown a transition from monostability to bistability for a weakening of the GABAergic inhibitory pathway connecting TRN and VPL. This involves the appearance of a high-firing-rate steady state in SC that is assumed to represent a pathogenic pain processing activity giving rise to chronic pain. The analysis of our model is consistent with known correlations between FM and different immunoendocrine conditions, such as altered stress response, perimenopause, chronic inflammation, obesity, and chronic dizziness. Glucocorticoids and neurosteroids related to stress, as well as different cytokines, are known to affect the GABA/glutamate ratio, while FM neuroimaging and pharmacological data argue for GABA/glutamate imbalance in thalamocortical networks.
Conclusion. Our model describes the onset of FM as the dynamics of a bistable switch in a thalamocortical network. The model is consistent with neurophysiological data and comorbidities of FM patients, and points to GABA/glutamate imbalance as a critical pharmacological target.

O-06 *Treatment of Fibromyalgia*

Baseline pain sensitivity predicts responder rates of wearable TENS use in fibromyalgia: analysis of a double-blinded randomized sham-controlled trial

Robert N. Jamison[1], Samantha Curran[1], Limeng Wan[1], Robert R. Edwards[2], Edgar L. Ross[1], Christopher Gilligan[2], Shai Gozani[3]
[1]*Pain Management Center, Brigham and Women's Hospital, Harvard Medical School, USA;*
[2]*Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, USA;*
[3]*Pain Medicine, NeuroMetrix, Inc., USA.*

Background. Fibromyalgia is characterized by widespread pain, reduced function and additional morbidity.
Objectives. To investigate the efficacy of a wearable TENS device for symptom relief and improved function in fibromyalgia.
Methods. 119 subjects were randomized to an active (n=62) or sham (n=57) device for 3-months. The active device provided continuous stimulation during each 1-hour therapy session while the sham device provided 6-minutes (2-minutes x^3/ hour). Subjects were administered quantitative sensory testing (QST) at baseline. The following outcome measures were assessed at baseline, 6-weeks and 3-months: PGIC (except baseline), FIQR, BPI, painDETECT, PDI, HADS and PCS. Responder analyses for PGIC (≥moderate improvement), FIQR (≥15% improvement) and pain intensity (≥30% improvement, FIQR pain-item) were conducted by logistic regression for all subjects (n=119) and the subgroup with higher baseline pain sensitivity (n=60).
Results. Subjects averaged 50.4±13.5 years and 93.3% were female. The PGIC responder rate was (active vs. sham) 42.5% vs. 34.5% (difference 8.0%, p=0.37). The FIQR responder rate was 46.6% vs. 28.7% (difference 17.9%, p=0.04). The pain intensity responder rate was 39.9% vs. 23.6% (difference 16.3%, p=0.05). In the subgroup with higher pain sensitivity, the PGIC responder rate was 58.0% vs. 30.2% (27.8%, p=0.02). The responder rate differences for FIQR (29.3%, p=0.01) and pain intensity (38.5%, p0.01) were also significant.
Conclusion. Among all subjects, 40-47% using the active device were responders for PGIC, FIQR or pain intensity compared to 24-35% for sham. The absolute responder rates and differences between active and sham treatment were greater in subjects with higher pain sensitivity.

O-07 *Treatment of Fibromyalgia*

Randomized controlled trial of an anti-inflammatory nutritional intervention in patients with fibromyalgia

Ana Silva[1,2], Alexandra Bernardo[2], Maria Fernanda Mesquita[2], José Vaz Patto[3], Pedro Moreira[1,4,5], Maria Leonor Silva[2], Patrícia Padrão[1,4]
[1]*Faculdade de Ciências da Nutrição e Alimentação, Universidade do Porto, Portugal*;
[2]*Centro de Investigação Interdisciplinar Egas Moniz, Instituto Universitário Egas Moniz, Portugal*;
[3]*Instituto Português de Reumatologia, IPR, Portugal*;
[4]*EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Portugal*;
[5]*Centro de Investigação em Atividade Física, Saúde e Lazer, Universidade do Porto, Portugal.*

Background. Fibromyalgia (FM) is associated with dysbiosis (1) and intestinal inflammation (2).
Objectives. To evaluate the effect of an anti-inflammatory and low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet on patient-reported outcomes and inflammatory biomarkers of FM patients.
Methods: This RCT (3) included 46 FM adult female patients allocated in two groups. Intervention group (n=22) adopted an anti-inflammatory low-FODMAP diet for 3 months. Control group (n=24) followed healthy eating recommendations. Before and after intervention, participants were assessed regarding pain, fatigue, gastrointestinal symptoms, quality-of-sleep and quality-of-life, through: Revised Fibromyalgia Impact Questionnaire (FIQR), Visual Analogue Pain Scale (VAS), Brief Pain Inventory (BPI), Fatigue Severity Survey (FSS), Visual Analogue Scale from gastrointestinal symptoms (VAS_GI), Pittsburg Sleep Quality Index (PSQI) and Short Form 36 (SF36), Ultra-sensitive C-Reactive Protein (usCRP) and Erythrocyte Sedimentation Rate (ESR) were quantified. Wilcoxon test was used to assess the intervention impact.
Results. After intervention, there was an improvement in FM symptoms (FIQR median 59.6 vs. 53.7; z=-3.59, p0.001), pain (VAS median 8.0 vs. 7.0; z=-2.64, p=0.008; and BPI median 13.8 vs. 12.000; z=-3.33, p=0.001), fatigue (FSS median 6.0 vs. 5.0; z=-3.33, p=0.001), gastrointestinal symptoms (median VAS_GI 3.2 vs. 1.8; z=-4.08, p0.001), quality-of-sleep (median PSQI 15.0 vs. 12.0; z=-2.99, p=0.003), and quality-of-life (SF36 median 41.0 vs. 46.2; z=3.62, p0.001) in intervention group. Inflammatory biomarkers (usCRP, ESR) did not change.
Conclusion. An anti-inflammatory and low-FODMAP diet improved patient reported outcomes in this sample of FM patients.

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O-08 *"Transparent Pain": How Society Deals with Fibromyalgia*

Working related problems faced by women with fibromyalgia in Spain. A discourse analysis

Erica Briones-Vozmediano[1,2], Daniel Sanjuán-Sánchez[1,2], Carolina Climent-Sanz[1,2], Mar Patiño-Vera[3], Montserrat Gea-Sánchez[1,2], Francesc Rubí-Carnacea[1,2]
[1]*Department of Nursing and Physiotherapy, University of Lleida, Spain;*
[2]*Research Group on Healthcare (GRECS), Biomedical Research Institute of Lleida, Spain. De Psicologia, Univsersidad de Almeria, Spain;*
[3]*Disability Assessment Service, Generalitat Valenciana, Spain.*

Background. People with fibromyalgia experience limitations in their daily activities, mainly due to the pain and fatigue they suffer.
Objectives. The objective of this study was to analyze women with fibromyalgia' discourses on workability.
Methods. A qualitative study based on personal interviews and a focus group, with a total of 29 women with fibromyalgia in Spain. Data was collected between 2016 and 2020 in two Spanish regions.
Results. Nine main discourses related to the workability of women with fibromyalgia were identified: 1. "I have always been a hard worker"; 2. "I realized at work that something was wrong"; 3. "I lost my job"; 5. "There came a time when I couldn`t physically do it, and I got depressed"; 6. "You want to work, but you say.. but where am I going to go if I run three chairs in my house and I can`t move", 7. "When employers hear fibromyalgia, they get scared"; 8. "You need support and flexibility at work", and 9. "When you obtain the diagnosis, they explain that you are not going to be able to work, but that they are not going to give you a disability compensation".
Conclusions. Not being able to work has emotional and economical consequences for women with fibromyalgia. Those who feel unable to work because of the limitations suffered need to receive disability compensations. Those who feel still able to work need adaptations at work, such as a reduction in working hours or working from home as facilitators to remain at work.

P-01 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Psychosocial variables and healthcare resources in patients with fibromyalgia, migraine and comorbid fibromyalgia and migraine

Elena Calandre[1], Juan Garcia-Leiva[1], Jorge Ordoñez-Carrasco[2], Lina Guapacha-Borrero[1]
[1]*Instituto De Neurociencias, Universidad de Granada, Spain;*
[2]*Departamento De Psicologia, Univsersidad de Almeria, Spain.*

Background. Both fibromyalgia and migraine are central sensitization syndromes that frequently coexist.
Objective. To compare the burden caused by fibromyalgia (FM), migraine (M) and comorbid fibromyalgia and migraine (FM+M) by assessing different psychosocial variables and the use of healthcare resources.
Methods. An online survey was uploaded in the websites of different patients' associations. It included sociodemographic data, the Patients Health Questionnaire-9, the Insomnia Severity Index, the EuroQOL-5D-5L, and a questionnaire evaluating the use of healthcare resources (family doctor visits, specialist's visits, emergency room visits, medical analyses, hospitalization, and surgical interventions) during the past six months.
Results. One hundred thirty-eight FM patients (20-73 years, 92.8% female), 169 M patients (18-72 years, 93.5% female) and 149 FM+M patients (29-73 years, 96.6% female) participated in the survey. Mean scores for depression and insomnia were clinically relevant in every group and significantly higher in FM+M than in FM or M. Suicidal ideation was frequent in every group but significantly more frequent in FM+M patients. EQ-5D-5L and EQ-5D-5L VAS scores were lower than the reported mean population values and lowest in FM+M. FM and FM+M patients used more healthcare resources than M patients, mostly family doctor visits and clinical analyses.
Conclusion. Psychosocial burden was high in the three samples. FM and FM+M had more relevant impact in patients wellbeing and required more medical attention than M. The burden caused FM+M was higher that both individual diseases.

P-02 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Is it really always fibromyalgia? Alas no! Consistency between ACR 2016 criteria and clinical judgement in a referral specialized clinic

Gianniantonio Cassisi[1], Valeria Giorgi[2], Daniela Marotto[3], Piercarlo Sarzi-Puttini[2]
[1]*Rheumatology Unit, Rheumatic Disease Care Center, Italy;*
[2]*Rheumatology Unit, ASST Fatebenefratelli "Luigi Sacco" University Hospital, Italy;*
[3]*Rheumatology Unit, ATS Sardegna, P. Dettori Hospital, Italy.*

Background. Fibromyalgia (FM) is a complex syndrome, whose hallmarks are chronic widespread pain, sleep disturbances, fatigue and cognitive dysfunctions. Despite the recent development of new diagnostic criteria, physicians still struggle to find consensus on a precise FM diagnosis. Albeit 2010/2016 American College of Rheumatology (ACR) diagnostic criteria gave more value to the non-pain symptoms compared to the old 1990 criteria, physicians still complain of the difficulties in diagnosing the syndrome. In fact, a significant proportion of patients do not fulfill the criteria even if already diagnosed with FM, a subgroup of patients considered as having incomplete FM (IFM) by some authors. Moreover, in many cases diagnosis is incorrect and many comorbidities are not taken into due consideration.
Objective. To examine the accuracy of a previous diagnosis or hypothesis of FM according to ACR 2016 diagnostic criteria.
Methods. All patients newly referred to a private rheumatologic clinic, with the specific request of a consultation for FM, were evaluated, over an 18-month period, in order to determine whether they fulfilled the 2016 ACR diagnostic criteria for FM. Patients were divided in three groups: 1) previous diagnosis, 2) medical hypothesis, and 3) personal hypothesis, and then they were classified as FM, IFM (borderline [VG1] scores) or non-FM. Some clinical characteristics, ACR 2016 diagnostic criteria parameters (generalised pain [GP], widespread pain index [WPI], symptom severity scale [SSS])

and tender point count (TPC) were assessed in all patients. When possible, an alternative diagnosis was given, furthermore, possible comorbidities and the physician who made the diagnosis was put in evidence.
Results. 216 pts (25 males, 191 females) participated in the study, 112 belonging to group 1, 49 to group 2, 55 to group 3. Overall, only 89 pts (41.2%) fulfilled the ACR criteria; 42 pts (19.44%) met the protocol-defined numerical range for an IFM; 85 pts (39.35%) were diagnosed as non-FM. Among group 1 patients, fifty percent of them fulfilled ACR criteria, less than 25% of them were not FM. Almost 50% of medical hypothesis were not FM; 20% of the personal hypothesis fulfilled ACR criteria. GP scores and TPC significantly differed among groups: FM IFM, FM non-FM, and IFM non-FM. WPI, SSS, PSD were significantly different in FM IFM.
Rheumatologists made the previous diagnosis in 92.85% of cases: 53.84% of these met the ACR criteria, whilst about 20% were not FM. Regarding the non-rheumatologist physicians, as many as 37.5% of the previous diagnosis were not FM. In non-FM group 84 alternative diagnoses were given, of which 78.5% were rheumatic diseases. Eighty-six comorbidities (of which 94.1% were rheumatic diseases), closely pain related, were highlighted in 131 patients.
Conclusions. This study shows the considerable frequency of inaccurate FM diagnoses in daily clinical practice, highlights that FM diagnosis is not always based on consensus criteria and that the risk of misdiagnosis is high. This study underlines and emphasizes the importance of a correct diagnosis and an accurate differential diagnosis based on ACR criteria.

P-03 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Fibromyalgia, the queen of rheumatology that must not be forgotten!

Claudia Silvia Ciofu, Bogdan Ion Gavrila, Paula Grosu, Ioan Ancuta, Mihai Bojinca
Internal Medicine and Rheumatology Department, "Dr.I.Cantacuzino" Clinical Hospital, University of Medicine and Pharmacy "Carol Davila", Romania.

We present the case of a 35-year-old man, who is hospitalized accusing pain in the spine accentuated following a recent trauma by falling from his own height.
We note that 6 months ago, he presented generalized musculoskeletal pain, with biological and imaging samples within normal limits, with a WPI of 10, with SS score 8, being diagnosed with fibromyalgia.
Gabapentinum 600 mg treatment is recommended, after which the evolution was favorable, until the moment of the trauma.
The case is re-evaluated, and the presence HLA B27 antigen is identified.
The investigations are continued with:
- MRI examination of the sacroiliac joints without elements of acute inflammation (edema, synovitis, enthesitis, capsulitis).
- MRI examination of the lumbar spine - within normal limits.

Tips or tricks, fibromyalgia or spondylarthritis?

P-04 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Comparative analysis between lumbar and thoracic spondylodiscitis

Fatma Hammami, Makram Koubaa, Amal Chakroun, Khaoula Rekik, Chakib Marrakchi, Fatma Smaoui, Mounir Ben Jemaa
Infectious Diseases Department, Hedi Chaker University Hospital, University of Sfax, Tunisia, Tunisia.

Background. Spondylodiscitis is characterized with a wide spectrum of clinical presentation. The level of spinal disease is known to vary according to the underlying etiology.
Objectives. We aimed to compare demographic and clinical features between lumbar spondylodiscitis (LSD) and thoracic spondylodiscitis (TSD).
Methods. We conducted a retrospective study including patients hospitalized for LSD and TSD in the infectious disease department between 1996 and 2019.
Results. We encountered 92 cases of LSD (60.9%) and 59 cases of TSD (39.1%). Male gender was significantly affected with LSD (68.5% vs 45.8%; p=0.006). The mean age was 54±17 years for LSD patients and 52±19 years for TSD patients (p=0.55). Diabetes mellitus was significantly noted among patients with TSD (20.3% vs 7.6%; p=0.021). The revealing symptoms were back pain (96.7% vs 91.5%; p=0.26), fever (64.1% vs 57.6%; p=0.42), asthenia (50% vs 54.2%; p=0.61) and weight loss (41.3% vs 44.1%; p=0.73) among patients with LSD and TSD respectively. Spinal tenderness was significantly more frequent among LSD patients (87.9% vs 70.7%; p=0.009), while sensory deficit (20.3% vs 6.6%; p=0.011) and symptoms of cord compression (15.3% vs 4.4%; p=0.021) were significantly more frequent among TSD patients. Tuberculosis was significantly associated with TSD (59.3% vs 32.6%; p=0.001), while brucellosis was significantly associated with LSD (35.9% vs 20.3%; p=0.042). Pyogenic etiology was more frequently reported among LSD patients (31.5% vs 11.9%; p=0.006). The number of involved vertebrae was significantly higher among TSD cases (3.1±2.1 vs 2.2±0.8; p=0.005).
Conclusion. Particularities in physical examination and causative agents were reported between LSD and TSD, while the revealing symptoms were similar.

P-05 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Difference in functional impairment and symptomatic burden in male and female patients with fibromyalgia

Stephany Harris, Anna Andreou, Adnan Al-Kaisy, Min Liu
Pain Management and Neuromodulation Center, Guy's and St. Thomas' Hospital, United Kingdom.

Fibromyalgia could contain heterogeneous conditions with distinct underlying mechanisms. Our hypothesis is that male patients might have a distinct mechanism, therefore, a different clinical picture from the female counterpart. We analysed 186 fibromyalgia patients with 158 female and 28 male, who has no identifiable pain conditions such as diabetes. There is no difference in age (47.6±0.9 in females vs 48.5±2.1 in males, mean ±SE), widespread pain index (WPI: 14.3±0.4 vs 15.1±0.8), symptom severity score (SSS: 9.1±0.4 vs 9.1±0.2) or duration of pain (years: 13.8±0.8 vs 14.3±0.4). There is no difference in weekly pain score (NRS: 8.4±0.1 vs 8.0±0.4) and weekly disturbance in sleep score (NRS: 8.2±0.2 vs 8.2±0.3). All patients had quantitative sensory test (QST), which was performed on the dorsum of right foot. We found that 32% of male patients had reduced sensitivity to thermal stimuli, which was not significant different from that of 28% of female patients. However, female patients had significant high scores in all three domains of revised fibromyalgia questionnaire (rFIQ). The total score of rFIQ was 79.5±1.2 in female patients and 67±3.9 in male patients (p0.001, Student t test). In conclusion, we found that functional impairment and symptomatic burden in male patients were significantly less severe than that of female. It will be of importance of study mechanisms in male fibromyalgia patients.

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P-07 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

End-tidal CO2 levels in rest, during and after respiratory challenges: a comparison between patients with medically unexplained physical symptoms, panic disorder patients and healthy controls

Indra Ramakers[1], Maaike Van Den Houte[1,2], Omer Van den Bergh[3], Lukas Van Oudenhove[2], Katleen Bogaerts[1,3,4]
[1]*REVAL - Rehabilitation Research Center, Faculty of Rehabilitation Sciences, UHasselt - Hasselt University, Belgium;*
[2]*Laboratory for Brain-Gut Axis Studies (LABGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine, University of Leuven, Belgium;*
[3]*Health Psychology, Faculty of Psychology and Educational Sciences, University of Leuven, Belgium;*
[4]*Tumi Therapeutics, Tumi Therapeutics, Belgium.*

Background. Although a dysregulated autonomic stress physiology is hypothesized to play a crucial role in the etiology and perpetuation of Medically Unexplained Physical Symptoms (MUPS), the respiratory system tends to be overlooked in current available literature.
Objectives. The aim of our study was 1) to examine end-tidal CO2 concentration (PetCO2) in patients experiencing MUPS in daily life, diagnosed with overstrain, burnout, and functional somatic syndromes (FSS), compared to patients with panic disorder (PD) and healthy controls (HC) and 2) to explore the triangular relationship between psychological variables (maladaptive perfectionism, experiential avoidance, and exposure to traumatic experiences), the stress response system, and MUPS.
Methods. Three groups of MUPS patients (overstrain [n=35], burnout [n=44] and fibromyalgia/chronic fatigue syndrome (CFS) [n=36]), PD patients (n=36) and HC (n=30) filled out trait questionnaires and went through a baseline measurement of PetCO2 and two respiratory challenges with recovery whilst PetCO2 was continuously monitored by a capnograph.
Results. Our data showed respiratory abnormalities in MUPS and PD patients compared to HC, suggesting a transdiagnostic mechanism for both stress and anxiety related disorders. This dysfunction was found to be partially mediated by maladaptive perfectionism, experiential avoidance, and exposure to traumatic experiences. Furthermore, we found preliminary evidence for a chronicity and severity-based MUPS-continuum underlying 1) overstrain, 2) burnout, and 3) fibromyalgia/CFS in ascending order, characterized by an increasing depletion of the stress-response system.
Conclusion. Our results are indicative for dysfunctional activity of the autonomic nervous system, including the respiratory system, to be an underlying working mechanism of MUPS.

P-08 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Dominance of the sympathetic nervous system in patients with fibromyalgia/chronic fatigue syndrome compared to healthy controls

Indra Ramakers[1], Maaike Van Den Houte[1,2], Omer Van den Bergh[3], Lukas Van Oudenhove[2], Katleen Bogaerts[1,3,4]
[1]*REVAL - Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Belgium;*
[2]*Laboratory for Brain-Gut Axis Studies (LABGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine, University of Leuven, Belgium;*
[3]*Health Psychology, Faculty of Psychology and Educational Sciences, University of Leuven, Belgium;*
[4]*Tumi Therapeutics, Tumi Therapeutics, Belgium.*

Background. A dominance of the sympathetic nervous system (SNS) is hypothesized to play a crucial role in the etiology and perpetuation of functional somatic syndromes. However, literature on this topic is still inconsistent.
Objectives. The aim of our study was to examine physiology of the autonomic nervous system (ANS) by measuring heart rate (HR), skin conductance (SC), and peripheral skin temperature (ST) in response to psychosocial stressors in patients with fibromyalgia/chronic fatigue syndrome (CFS) and healthy controls (HC).
Methods. Patients with fibromyalgia/CFS (n=26) and HC (n=30) went through a stress test consisting of a baseline phase (120s), a Stroop Color and Word Test (120s), a mental arithmetic task (120s) and a stress talk (120s). Each stressor was followed by a 120s recovery period. HR, SC, and ST were monitored continuously. Random intercept random slope linear mixed model analyses were performed on the different phases. Results. Our main findings were that fibromyalgia/CFS patients had a significantly higher HR during all phases compared to HC. Fibromyalgia/CFS patients also had significantly higher SC compared to HC during all phases. No significant difference was found between fibromyalgia/CFS patients compared to HC regarding ST.
Conclusion. Our results showed a dominance of the SNS regarding HR and SC in fibromyalgia/CFS patients compared to HC, suggesting the presence of ANS dysfunctionalities as an underlying working mechanism of fibromyalgia/CFS.

P-09 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Body illusions and misperception in fibromyalgia: how chronic pain impacts on body representation and imagery of actions

Michele Scandola[1], Cristina Lonardi[1], Giorgia Pietroni[1], Vittorio Schweiger[2], Valentina Moro[1]
[1]*Department of Human Sciences,* [2]*Departmen of Surgical Science, University of Verona, Italy.*

Background. That chronic pain changes individuals' perception of the body is a well-known notion. However, to date, data on which kinds of misperceptions are experienced by patients suffering from Fibromyalgia (FPs) and how these may impact action representations are meagre.
Objective. The study assesses the body misperceptions in FPs and their potential correlations with clinical symptoms and motor imagery.
Methods. A comprehensive questionnaire battery investigated Corporeal Illusions (Body Feelings and Illusions questionnaire), Motor Imagery (Vividness of Motor Imagery 2) and mood disorders (Hospital Anxiety and Depression Score) in 30 FPs and 30 age- and gender-matched control participants. A comparison between the two groups was executed and correlations with clinical symptoms were carried out. Furthermore, Explorative Factor Analysis assessed the potential integration among pain, body misperception and motor imagery.
Results. FPs report feelings of disownership of body parts and somatoparaphrenic-like sensations (e.g., detachment or changes in form and size of body parts). They also show reduced abilities in motor imagery and the presence of illusory movements of body parts. Although the feeling of misoplegia towards the sore body parts are reported, these bodily misperceptions are not associated with mood disorders (which are not different between the two groups). The disorders in motor imagery (but not bodily illusions) correlate with the pain.
Conclusion. Specific disorders in body representations and motor imagery are present in FPs. This should be specifically investigated and taken into consideration when interventions are planned to help patients in maintaining autonomy and ameliorate their body perception.

P-10 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Ear nose and throat symptoms analysis in a cohort of Chilean fibromyalgia patients

Lilian Soto[1,2], Francisca Tala[1], Cristian Olavarria[1,2], Jaxaira Maggi[1]
[1]*Facultad De Medicina, Universidad De Chile, Chile;*
[2]*Hospital Clinico, Universidad De Chile, Chile.*

Background. Fibromyalgia (FM) is a common health problem,that affects mainly women, where it exists diffuse muscle-joint pain and a broad and variable number of sensitive symptoms caused by Central Sensitization (CSs). FM has association with other chronic visceral Pain syndromes as Irritable Bowel Syndrome (IBS) or Interstitial Cystitis, but more data from are needed.
Objective. Exploring prevalence of ENT symptoms in a cohort of Chilean FM patients.
Methods. This is an analytic descriptive study in a cohort of 32 patients from CoFibroChile. All patients filled the 2010-2016 ACR criteria for FM classification, FIQ, Sensitive Symptoms Scale (SSS), Widespread Pain Index (WPI) and ENT surveys about Hearing Impairment (HI), Dysphonia (D), Swallowing Alteration (SA), Tinnitus (T), Dizziness Evaluation (DE). We used T-tests, Chi-Square tests or Fisher`s exact tests.
Results. The media for age was 54.34 years old (30 to 76), 100% females. Time between symptoms onset to diagnosis was 88,94 months (~7 years). FM assessments: WPI media 12.32 (1-19); SSS media 9.61 (4-12), VAS of pain media 6.91 (0–10), FIQ media 67.60 (10,01–90,9), 56.3% showed signs of HI, 75% showed D; 78% SA, 62.5% showed T, 65.6% physical DE and 59.4% functional DE. Data shows significant relation between higher WPI and Dysphonia (p=0.030) as well as higher VAS and D (p=0.030). A statical significance between HI and TMD (p=0.016) in FM patients.
Conclusion. More than 50% in this cohort, had at least one of the ENTs. Dysphonia has the higher significance with WPI, EVA and SSS.

P-11 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Psychosomatic syndromes and traumatic events discriminate between patients with fibromyalgia and patients with rheumatoid arthritis

Ada Ghiggia[1,2], Annunziata Romeo[1], Marialaura Di Tella[1], Lorys Castelli[1], Valentina Tesio[1]
[1]*Department of Psychology, University of Turin, Italy;*
[2]*Clinical Psychology Unit, A.O.U. Città della Salute e della Scienza Hospital, Italy.*

Background. Many studies have highlighted the importance of the psychological component in fibromyalgia (FM), although the underlying implications are not yet clear.
Objectives. The current study aims to assess the prevalence of psychosomatic syndromes and traumatic events in patients with FM and patients with Rheumatoid Arthritis (RA), and to evaluate their group membership (FM vs. RA) predictive abilities.
Methods. The Visual Analogue Scale (VAS) for pain, the State-Trait Anxiety Inventory (STAI-Y), the Beck Depression Inventory - II (BDI-II), the Toronto Alexithymia Scale (TAS-20), the Traumatic Experiences Checklist (TEC) and the Diagnostic Criteria for Psychosomatic Research (DCPR) were administered to 107 women with FM and 104 with RA.
Results. Group comparison showed that patients with FM had significantly higher levels of anxiety and depressive symptoms and difficulties in identifying feelings (TAS-DIF subscale), and a higher prevalence of psychosomatic syndromes and traumatic events, compared to patients with RA. The binary logistic regression showed that pain (OR=0.584; 95% CI=4.74 -0 .719), psychosomatic syndromes (OR=0.596; 95% CI=0 .459-0.773) and trauma score (OR=0.859; 95% CI=0.759-0.971) were statistically significant predictors of group membership (FM vs. RA). The final model explained 62% of the variance, with 83.3% of patients correctly classified.
Conclusion. The present study confirmed the higher prevalence of psychosomatic syndromes and trauma events in patients with FM compared to patients with RA, further supporting their role in FM symptoms exacerbation and maintenance and thus their importance in the treatment planning.

P-12 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Gender differences in depression comorbidity of fibromyalgia

Hsin Ting Tsai
Medical Science Industries, Chang Jung Christian University, Taiwan.

Background. The mechanism of fibromyalgia, characterized by chronic widespread pain (CWP), is complex, hindering the development of effective treatments to release patients from poor life quality.
Female with fibromyalgia syndrome usually show higher pain intensity than male, yet more research studies have been done in male.
Furthermore, the prominent comorbidity of fibromyalgia is found to be depression, where they share similar pathophysiology and the same dual serotoninergic and noradrenergic agonists in pharmacological treatments, supporting the concept that they are “differential symptom presentations of a single underlying conditions”, yet it is unclear about the intensity of depression symptoms between genders.
Objectives. To investigate the differences in depression symptoms and respective intensity between male and female rats of Chronic Widespread Pain (CWP) model.
Methods. Bilateral mechanical hyperalgesia in rats of both genders will be developed through repetitive unilateral intramuscular injections of acid saline. The intensity of pain and depressive comorbidity of acid-induced pain model of rats are evaluated by Von Frey filament testing on pain behaviors, and by forced swimming, sucrose consumption, and sucrose preference tests on depression-like behaviors.
Results. The study is in progress. We are interested to understand if the types of depression symptoms and respective intensity are in proportion to the intensity of muscle pain between male and female rats.
Conclusion. The differences in depression symptoms and respective intensity between male and female rats would suggest a different phenotype for each gender, thus future drug development with gender specific considerations may be of benefits to the patients.

P-13 *Complex CNS*

Walking on treadmill or on the ground? a fibromyalgia case study based on multiscale dispersion entropy

Nancy Brígida[1,4], Marco Branco[1,2,4], Cristiana Mercê[1,2,4], David Catela[1,3,4]
[1]*Escola Superior de Desporto de Rio Maior, Instituto Politécnico de Santarém, Portugal;*
[2]*CIPER, Faculdade de Motricidade Humana, Universidade de Lisboa, Portugal;*
[3]*Centro de Investigação da Qualidade de Vida (CIEQV), Instituto Politécnico De Santarém, Portugal;*
[4]*Centro de Investigação do Instituto Politécnico de Santarém (UIIPS), Instituto Politécnico de Santarém, Portugal.*

Background. Use of ergometers alters the perceptual layout, so a person needs to adapt to new constraints, meaning a change in motor complexity; that non-linear methods can measure, based on the action process analysis.
Objective. To analyse if different context constraints result in different levels of motor complexity in a person with fibromyalgia.
Methods. Case study of a 59-year-old sedentary woman with fibromyalgia. An inertial sensor placed above the external malleolus was used for data collection, while walking on a treadmill and on the ground, each performed for 2 minutes, with a 24h interval. Refined Composite Multiscale Dispersion Entropy was estimate based on gyroscope data.
Results. Higher complexity was found when the body adjustments occur at shorter perception-action cycles, and lower complexity was found at longer perception-action cycles, reaching its lowest entropy value at cycles around 500ms. Walking on the treadmill resulted more complex than on the ground, which can be explained by unusual perceptual stimulations, as optic array and surface elasticity.
Conclusions. Probably, perceptual novelty resulted in greater complexity in motor behavior, which may have required more adjusts from the neuromotor system; therefore, preparing the fibromyalgia patient to more attuned daily live tasks, and to faster response to unexpected unbalances.

P-14 *Complex CNS*

Event-related potentials during implicit processing of facially expressed emotions in patients with fibromyalgia

Laura Rachel Fischer-Jbali[1], Casandra Isabel Montoro[2], Pedro Montoya[3], Wolfgang Halder[4], Stefan Duschek[1]
[1]*Institute of applied Psychology, Umit Tirol - University for Health Sciences, Medical Informatics and and Technology, Austria;*
[2]*Department of Psychology, University of Jaén, Spain;*
[3]*Department of Psychology, University of the Balearic Islands, Spain;*
[4]*Rheumatology, County Hospital Hochzirl, Austria.*

Background. Fibromyalgia syndrome (FMS) is a chronic pain condition characterized by widespread pain, emotional problems, fatigue and cognitive impairments. Emotional dysregulation and central nervous sensitization seem to be involved in FMS pathogenesis.
Objectives. Knowledge about neural correlates underlying these affective peculiarities in FMS is scarce. This study explored the central nervous processing of implicitly presented facial expressions in FMS using a picture frame task.
Methods. Twenty-five FMS patients and 37 pain-free controls, aged 18 to 70 years, participated in this study; where they were asked to name the frame color of pictures displaying different emotional faces (happy, neutral, painful, angry). Stimuli were presented implicitly and were task irrelevant. EEG was recorded and symptoms of depression, anxiety and pain were also evaluated.
Results. FMS patients exhibited reduced P2 and LPP as well as increased N250 amplitude. N250 amplitude varied according to the emotional content in FMS, but not in controls. No group differences were seen for P1 or N170 amplitude. Behavioral parameters revealed longer RTs and more errors in FMS; where performance was mainly related to pain severity.
Conclusion. Results point towards a deficient short-term mobilization of attentional resources and sustained attention in FMS. Moreover, increased N250 in FMS seems related to greater engagement in decoding complex facial features reflecting a consequence or a mechanism to compensate attentional impairments. Additionally, in FMS the neural mechanisms underlying these complex visual processes seem particularly susceptible to emotional influences. Attentional deficits and the influence of pain are confirmed by the behavioral findings in FMS.

P-15 *Genetics, Pharmacogenentics, and Epigenetics*

Evidencing microRNA-mRNA networks of manual therapy for the treatment of fibromyalgia

Javier Bonastre Férez[1], Ignacio Bonastre-Férez[1], María García-Escudero[2,4], Francisco Javier Falaguera-Vera[1], Teresa Sánchez-Fito[1], Elisa Oltra-García[3,4]
[1]*Escuela De Doctorado, Universidad Católica De Valencia, Spain;*
[2]*School of Health Sciences, Universidad Católica De Valencia, Spain;*
[3]*School of Medicine, Universidad Católica De Valencia, Spain;*
[4]*Centro De Investigación Traslación Al San Alberto Magno, Universidad Católica De Valencia, Spain.*

Fibromyalgia (FM), classified with the international code ICD-10 M79.7, is a chronic disease of undetermined etiology characterized by multiple symptoms and comorbidities including hyperalgesia and allodynia. Affecting around 5% of the population globally, with a clear incidence in females (6:1), it is commonly treated in the Clinic with palliative chemical drugs. The extended use of these drugs turns into ineffective responses and, sometimes, the appearance of secondary effects, further deteriorating patient´s health. Although the evidence of benefits for the treatment of FM pain by physiotherapy approaches is growing, the identification of the cellular pathways and the molecules driving the claimed benefits are missing. Our group has recently shown that a pressure-controlled protocol of Manual Therapy (MT) based on animal experimentation leads to patient´s pain threshold improvement and that the results rely on patient´s initial health status. It has also identified microRNAs whose levels change upon MT and thus represent candidate epigenetic effectors of MT. In this work, we are taking a step forward into revealing the mRNAs whose expression are affected by MT in an effort to identify miRNA-mRNA networks of MT for the treatment of FM. Revealing the molecular factors implicated in the response of FM to MT treatment should set the basis for protocol optimization and perhaps allow for a deeper understanding of the pathways underlying FM.

P-16 *Genetics, Pharmacogenentics, and Epigenetics*

Fibromyalgia and alpha-1 antitrypsin variants: common, rarely diagnosed

Donald Schmechel
Sponsored Research, Across Alpha, USA.

Background. Alpha-1 antitrypsin (A1AT) variants may be found in 15-20% of patients presenting to neurology clinics (expected prevalence 5-7%). 2% of all patients had history of juvenile idiopathic arthritis (JIA) and 16% had diagnosis of fibromyalgia (femalesmales). A1AT variants were present in 60% of all patients with JIA and 40% of all patients with fibromyalgia. (DE Schmechel and CL Edwards, Neurotoxicology 2012;33(6):1454. These findings raise issue of antecedent or subsequent inflammatory illness in these A1AT carriers.
Objectives. To examine antecedents and sequelae of A1AT patients presenting to neurology clinic with a diagnosis of fibromyalgia or history of JIA.
Methods. Patients received full physical, neurological exam and fibromyalgia assessment per guidelines. A1AT phenotyping was done regardless of level. Particular attention was paid to childhood history of asthma or chronic otitis media, PTSD and psychiatric history. We reviewed 3472 previous patient records and 149 randomly chosen A1AT carriers from separate series.
Results. Patients with childhood chronic otitis media or asthma presented on average 15-20 years prior to patients without that history. Patients with fibromyalgia and A1AT variants had age of presentation 11 years earlier than non-fibromyalgia patients (n=149, p=0.001). Patients with history of JIA presented 20 years earlier than without JIA (n=1479, p=7.5 E-7). Attributes of art, mood disorder, and increased PTSD were again noted.
Conclusion. A1AT variants may be silent or associated with inflammation in early childhood, adulthood, or eventually with significant neurological or psychiatric disorders. This process may involve A1AT functional deficiency and impaired modulation or priming of inflammatory response.

P-17 *Neuro-biological Underpinnings of Fibromyalgia and Centralized Pain*

Understanding and restoring dopaminergic function in the brain of fibromyalgia patients using the mindfulness-oriented recovery enhancement (MORE) intervention: a multi-center, randomized 18F-DOPA PET-study

Maya Burckhardt[1], Katharina Ledermann[1,2], Chantal Berna[5], Petra Schweinhardt[8], Valerie Treyer[4], Joelle Nsimire Chabwine[6,7], Haiko Sprott[3], Josef Jenewein[2], Roland Von Känel[2], Chantal Martin-Soelch[1]
[1]*Department of Psychology, University Fribourg, Switzerland;*
[2]*Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine, University Hospital Zurich, Switzerland;*
[3]*Arztpraxis Zurich, University of Zurich, Switzerland;*
[4]*Department of Nuclear Medicine, University Hospital Zurich, Switzerland;*
[5]*Department of Anaesthesiology, Lausanne University Hospital, Switzerland;*
[6]*Neurology Unit, University Fribourg, Switzerland;*
[7]*Neurorehabilitation Division, Hospital of Fribourg, Switzerland;*
[8]*Department of Chiropractic Medicine, Balgrist University Hospital and University of Zurich, Switzerland.*

Background and objectives. Fibromyalgia Syndrome (FMS) is a complex chronic pain condition. Its unknown etiology makes the development of specific treatments with long-lasting results difficult. An altered dopamine (DA) response to reward in FMS in comparison to healthy participants has been shown previously. The aim of this study is to investigate whether the Mindfulness-Oriented Recovery Enhancement (MORE) intervention will improve pain and mood symptoms in participants with FMS. Indeed, MORE has shown beneficial effects in chronic pain patients with opioid abuse and might have the potential to restore neurophysiological and behavioural responses to reward.
Methods. We will include 64 women with FMS randomly assigned to the MORE intervention or to a wait-list control group (WL). They will be compared at baseline with a group of healthy women (HC). Before and after the intervention, participants will undergo 18F-DOPA PET (measuring DA influx) and fMRI (measuring neural activation) while performing a reward task. We expect FMS patients to show reduced 18F-DOPA binding in stri-

atal regions and decreased striatal fMRI responses to reward compared to HC at baseline; and FMS patients undergoing the MORE intervention to show an increased 18F-DOPA influx and increased neural responses to reward after the intervention.
Conclusion. The investigation of potential changes of the DA reactivity after the intervention will provide new insights on the functionality of the DA system in FMS and the neural effect of MORE. If clinical effects are shown, MORE might be considered in for treating FMS.

P-18 *Neuro-biological Underpinnings of Fibromyalgia and Centralized Pain*

The baroreflex in fibromyalgia: beyond the cardiac branch

Ana M. Contreras-Merino, Pablo de la Coba, Gustavo A. Reyes Del Paso
Psychology, University of Jaén, Spain.

Background. Autonomic cardiovascular control is diminished in fibromyalgia. The baroreflex is a main source of cardiovascular autonomic regulation. Studies analyzing non-invasively the baroreflex in fibromyalgia have been performed for its cardiac-vagal branch, but not for its sympathetic branches.
Objective. To assess non-invasively the myocardial and vasomotor branches of the baroreflex in fibromyalgia using the spontaneous sequence method.
Method. Forty fibromyalgia patients and 30 aged-matched healthy individuals undertook the cold pressor test after a 10-min rest baseline. Interbeat interval, systolic blood pressure, total peripheral resistance and pre-ejection period were obtained using electrocardiogram, impedance cardiography and beat-to-beat blood pressure recordings. Baroreflex sensitivity was calculated through the analysis of spontaneous sequences of covariation between systolic blood pressure and pre-ejection period (for the myocardial branch, ms/mmHg) and total peripheral resistance (for the vascular branch, dyne_s/cm^5/mmHg).
Results. Fibromyalgia patients showed smaller baroreflex sensitivity at baseline, in both the myocardial and vasomotor branches compared to healthy controls. This reduction was also observed during the stress task. Baroreflex sensitivity in the vasomotor branch decreased during the cold pressor test in fibromyalgia patients, while no change was observed in healthy participants. Baroreflex sensitivity in the myocardial branch did not change during this task.
Conclusion. Results suggest alteration of baroreflex-mediated cardiovascular regulation in fibromyalgia. The baroreflex allow adaptation to and proper cardiovascular functioning in daily living activities and seem to be altered in fibromyalgia. The study of vasomotor and myocardial branches of the baroreflex may open new paths for the research on autonomic regulatory processes in fibromyalgia.

P-19 *Neuro-biological Underpinnings of Fibromyalgia and Centralized Pain*

Weight, continuous positive airway pressure therapy and rapid eye movement sleep in fibromyalgia: retrospective study

Edwin Meresh, Yooha Park, Sthitadhi Chakraborty, Murali Rao
Department of Psychiatry, Loyola University Medical Center, USA.

Background. Obesity is common in FM and OSA and is associated with pain (1). Pain perception is related to decreased rapid eye movement (REM) sleep (2). In healthy individuals, REM sleep is 21.4% of total sleep time (TST). Research has demonstrated a 57% relative increase in REM duration following treatment with continuous positive air pressure (CPAP). In order to improve the care of these patients, we need a better understanding of overlapping presentation of FM, OSA and obesity.
Methods. After Institutional Review Board (IRB) approval for this retrospective chart review, patients diagnosed with FM who received polysomnography testing (PSG) were identified using ICD 10 codes and sleep study results were reviewed. Weight, Body Mass Index (BMI), REM duration in minutes and REM TST percentages were reviewed at baseline PSG and following CPAP treatment.
Results. FM n=47, female n=39, male =8, mean weight 225.73 lb, BMI 38.37, mean REM sleep duration 41.33 minutes, mean REM TST 12.97%. FM+OSA CPAP recommended n=37, baseline weight 229.17 lb, BMI 38.27, REM 35.71, TST 11.90%, weight and sleep study analysis after CPAP: weight 226.30, BMI 38.47, REM 48.93, TST 15.04. Pre- and post-CPAP titration REM duration percentage increased from 11.90% to 15.04%, indicating a mean difference of 3.14% which corresponded to a 31% relative increase in REM duration.
Conclusion. These findings in retrospective analysis suggest delivery of CPAP to patients with FM and OSA improve REM sleep duration. CPAP may be a non-pharmacological alternative to pain management. Prospective study should explore changes in pain perception following treatment of OSA in patients with FM (3).

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P-20 *Treatment of Fibromyalgia*

Efficacy and tolerability of a nutraceutical product (tensiva) in patients with fibromyalgia

Emilio Battisti[1], Antonietta Albanese[1], Federico Filippi[2]
[1]*DSFTA, University of Siena, Italy;*
[2]*Fisiomed, Sanimed, Italy.*

Background. Fibromyalgia is a common condition characterized by musculoskeletal pain, fatigue, and defined by the presence of tender points. It is a syndrome of unknown etiology, which mainly affects women with a 9: 1. The aim of this study is to evaluate a nutraceutical product with L-Tryptophane, Magnesium bisglycinate, Calcium, Potassium, Vit.B2, B6, B12 and D3 (TENSIVA) in the treatment of Fibromyalgia.
Tools and methodologies. The sample included 60 women suffering from Fibromyalgia who have been divided into 2 groups by ACR criteria. All of them were asked to complete a test with the Visual Analog Scale (VAS) and Revised Fibromyalgia Impact Questionnaire (R-FIQ). Tests were conducted on days 1, 30 and 60. The first group was taking Paroxetine 20 mg once daily for 60 days, the second was taking TENSIVA 2 sachets per day for 60 days.
Results. After 30 days, no patient from the first group was showing any improvement. Therefore, painkillers were administered to all of them. After 60 days, 20 of them were showing improvement in terms of pain. In the second group, after 30 days, 15 patients were getting better in terms of pain. After 60 days, a total of 25 subjects experienced progress in terms of pain and R-FIQ indexes.
Conclusions. Fibromyalgia predominantly affects women with myalgia, sleep disorders, asthenia, anxiety and depression. There are not any specific diagnostic tests or therapies, although antidepressants, antiepileptics and analgesics are used associated with physical and cognitive-behavioral therapies. In this study we aimed at evaluating a supplement containing L-Tryptophane, Magnesium bisglycinate, Calcium, Potassium, Vit.B2, B6, B12 and D3 in the treatment of Fibromyalgia. Results show that TENSIVA appeared to be safe, efficacious and well-tollerated treatment for patients is effective in reducing pain and in improving motor functions, without side effects. Additional studies will confirm its validity and tolerability for those patients not responding to current therapies.

P-21 *Treatment of Fibromyalgia*

Overactive bladder syndrome and sexual dysfunction in women with fibromyalgia and their effect on disease severity

Marco Di Carlo[1], Fausto Salaffi[1], Sonia Farah[1], Valeria Giorgi[2], Piercarlo Sarzi-Puttini[2]
[1]*Rheumatological Clinic, Ospedale "Carlo Urbani", Università Politecnica delle Marche, Italy;*
[2]*Rheumatology Unit, Internal Medicine Department, ASST Fatebenefratelli-Sacco, Milan; University School of Medicine, Italy*

Objective. The aim of this study was to evaluate the prevalence and severity of overactive bladder syndrome (OAB) and sexual dysfunction in fibromyalgia (FM) patients, as well as how they affect disease severity.
Methods. Consecutive adult female patients with FM were consecutively enrolled. Patients filled in a comprehensive questionnaire package including demographic variables, disease severity assessment (Revised Fibromyalgia Impact Questionnaire [FIQR]), neuropathic pain features (Pain Detect Questionnaire [PDQ]), severity of OAB symptoms (Overactive Bladder Symptom Score [OABSS]), and determining sexual functioning (Female Sexual Function Index [FSFI]).
Results. The study included 481 patients, 116 (24.11%) had mild OAB, 82 patients (17.04%) had moderate OAB, and 34 patients had serious OAB (7.06%). In 14.17% of patients the bladder condition was causing them major issues in terms of discomfort. In 7.87% of patients the bladder condition was causing them significant problems. Sexual dysfunctions were found in 91 patients (18.91%). Using the FSFI as dependent variable, multivariate analysis revealed a positive relationship between sexual dysfunction and variables of disease burden (FIQR, p 0.0001; PDQ, *p* 0.0001, widespread pain index [WPI], *p*=0.0037). Using OABSS as the dependent variable, multivariate regression revealed a substantial contribution from FIQR (*p* 0.0001), PDQ (*p*=0.0037), and WPI (*p*=0.0030) (Table I).
Conclusion. FM has the potential to affect both psychological and physiological processes in women with OAB and sexual dysfunction. These results emphasize the importance of a multidisciplinary approach to treat patients with overactive bladder syndrome and sexual dysfunction in FM.

Table 1. Regression analyses using OABSS and FSFI as dependent variables.

OABSS - Dependent variable	Coefficient	Standard error	t	p	r partial
(Constant)	-2.1785				
Age	0.0005753	0.01149	0.0501	0.9601	0.002300
Disease duration	0.003425	0.02313	0.148	0.8823	0.006801
BMI	0.02100	0.03982	0.527	0.5981	0.02422
FIQR total score	0.1088	0.009419	11.554	<0.0001	0.4688
PDQ	0.06731	0.02305	2.920	0.0037	0.1329
WPI	0.1028	0.03446	2.984	0.0030	0.1358
FSFI - Dependent variable					
(Constant)	0.2974				
Age	-0.02658	0.02967	-0.896	0.3708	-0.04111
Disease duration	0.07392	0.05971	1.238	0.2163	0.05677
BMI	0.03540	0.1028	0.344	0.7307	0.01581
FIQR total score	0.1695	0.02432	6.971	<0.0001	0.3050
PDQ	0.4100	0.05952	6.888	<0.0001	0.3016
WPI	0.2594	0.08898	2.915	0.0037	0.1327

OABSS: Overactive Bladder Symptom Score; FSFI: Female Sexual Function Index; BMI: Body Mass Index; FIQR: Revised Fibromyalgia Impact Questionnaire; PDQ: Pain Detect Questionnaire; WPI: Widespread Pain Index.

Key words: fibromyalgia, overactive bladder symptoms, sexual dysfunction, neuropathic pain, health-related quality of life

P-22 *Treatment of Fibromyalgia*

No effect of approved fibromyalgia drugs on the social pain (invalidation) contrary to physical pain; an open-label short-term randomized clinical trial

Banafsheh Ghavidel-Parsa[1], Ali Bidari[2]
[1]*Rheumatology, Rheumatology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Science, Rasht, Guilan, Iran, Iran;*
[2]*Rheumatology, Department of Rheumatology, Iran University of Medical Sciences, Tehran, Iran., Iran.*

Objectives. The social pain or invalidation denoting painful feeling following social conflicts or misunderstanding about illness legitimacy has recently been proposed as a salient disabling symptom besides physical pain or non-pain symptoms in fibromyalgia (FM). We sought to evaluate the effect of one-month administration of duloxetine or pregabalin on the invalidation dimensions in FM patients with respect to the comparison of these two drugs on this issue.
Method. This open-label randomized clinical trial study was performed on FM patients whose diagnosis were confirmed by a rheumatologist based on the 2016 American College of Rheumatology (ACR). Primary outcome measure (Illness Invalidation Inventory (3*I)) and secondary outcome measures (Beck Depression Inventory-II (BDI-II), widespread pain index (WPI) and polysymptomatic distress scale (PSD)) were compared before and after treatment, using paired t-test or Wilcoxon signed test.
Results. Of 81 eligible FM patients, 44 patients in duloxetine arm and 27 patients in pregabalin arm completed the study protocol. Overall, no significant improvement was seen in 3*I scores after treatment with either duloxetine or pregabalin, except in the lack of understanding of medical professionals, which improved after treatment with pregabalin (2.43±1.38 to 1.79±0.94, *p* value: 0.01). There were no intragroup and intergroup differences in the effects of duloxetine and pregabalin on 3*I scores when adjusted with the cofounders. Both duloxetine and pregabalin improved WPI, BDI-II and PSD scores significantly.
Conclusions. Short-term FM pharmacological treatment had no effect on the social pain. This finding was regardless of drug type, improvement of physical pain and depression.

P-23 *Treatment of Fibromyalgia*

Efficacy of non-invasive neuromodulation in combination psychological therapies for physical and emotional pain in fibromyalgia

Mª Auxiliadora Páez Pérez[1,2,3,4], Ana Sánchez Kuhn[1,3], Fernando Sánchez Santed[1,3,4], José María Calés de Juan[2]
[1]*Psychology, Universidad De Almería, Spain;*
[2]*Psychobiology, Universidad Nacional de Educación a Distancia, Spain;*
[3]*CEINSA, Centro de Investigación en Salud, Spain;*
[4]*Neuropsychology, Centro de Neurorrehabilitación y Autonomía Imparables, Spain.*

The present study aims to evaluate the effectiveness of reducing some of the most disabling symptoms in fibromyalgia such as pain, fatigue, sleep, depression, anxiety, pain catastrophizing, fear of movement and physical exercise, poor quality of life and interference of fibromyalgia in daily life, using transcranial direct current stimulation (tDCS), in combination with psychological third-generation therapies.
We present a series of cases with a clinical sample with a diagnosis of fibromyalgia. The treatment protocol consisted of 10 sessions of 20 minutes of stimulation every 24 hours for 10 days, with a 2-day interruption corresponding to the weekend. Every session was accompanied with psychotherapy based on third generation techniques: mindfulness and acceptance and commitment.
The results indicate a general improvement shown by a statistically significant decrease in the scores in depression, anxiety, fibromyalgia interference, pain catastrophism, sleep and an increase in the quality of life score Kinesiophobia did not show any statistical change. Thus tDCS, as previously published, is effective for improving physical and psychological health of fibromyalgia patients.
Key words: transcranial direct current stimulation, third generation therapy, fibromyalgia, quality of life.

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P-24 *Treatment of Fibromyalgia*

Benefit of therapeutic exercise in women with fibromyalgia

Ângela Maria Pereira
Physiotherapy, Escola Superior De Saúde Egas Moniz; Hospital Garcia De Orta, Portugal

Background. Women with Fibromyalgia Syndrome ability to complete occupational tasks and/or daily living activities is significantly reduced, resulting in poor quality of life
Objective. The purpose of this study was to analyse the benefit of a therapeutic exercise program (TEP) at the level of functional capacity and quality of life in women with Fibromyalgia Syndrome.
Methods. Fifteen women (59.3±6.18) with fibromyalgia participate in a therapeutic exercise program 3 times a week, for 8 weeks. Each session had an average duration of 45 minutes and ventilation control exercises, dynamic muscle strength exercises, and walking were performed. The Functional capacity was assessed by 6-minute walk distance (6MWD). The health status was evaluated through the Fibromyalgia Impact Questionnaire (FIQ) and Medical Outcomes 36-item Short Form Health Survey (SF-36) questionnaire. This study follows all the principles of the Declaration of Helsinki
Results. It was possible to observe an increase (p=0.01) in the distance covered in the 6MWD (382.7±61.2; 466.0±44.5), as well as a significant improvement in the general and subscale scores of the FIQ (p=0.03) expressed as time-integrated values associated with an increase (p 0.05) in the perception of the state in all domains of the SF-36, except for body pain.
Conclusion. This study concludes that the therapeutic exercise program was effective in improving the overall well-being of in women with Fibromyalgia Syndrome with improvements on functional capacity and health-related quality of life.

P-25 *Treatment of Fibromyalgia*

Multimodal integrative treatment of FM patients: first results of a longitudinal study using patient-reported-outcome (PRO)

Tobias Romeyke[1,2], Elisabeth Noehammer[1], Harald Stummer[1]
[1]*Institute for Management and Economics in Health Care, University of Health Sciences, Medical Informatics and Technology, Austria;*
[2]*Waldhausklinik, Waldhausklinik Acute Hospital for Internal Medicine, Pain Therapy, Complementary and Individualized Patient Centered Medicine, Germany.*

Background. The search for adequate concepts to treat fibromyalgia poses a challenge for health professionals worldwide. Due to the high burden of disease and the economic impact of the illness, existing treatments need to be evaluated.
Objectives. The aim of the current study is the appraisal of an officially approved multimodal, holistic treatment concept for fibromyalgia (coded OPS 8-975 in Germany) by the patients themselves.
Methods. 221 patients with a fibromyalgia diagnose checked by a medical specialist were treated in an intramural setting based on the regulations of the German operations and procedures code (OPS) 8-975 (naturopathic complex treatment). Patient reported outcomes were assessed with standardized tools regarding pain intensity (visual analogue scale), physical functionality (FFbH), emotional complaints (PHQ-D), plus subjective physical and general impairment (von Zerssen).
Results. All patients had a high degree of chronicity (stage 2-3 according to Gerbershagen). After an average 11.45 days of therapy, pain intensity could be reduced from 6.43 to 4.29 (average, data based on visual analogue scale). Emotional complaints could be significantly improved from 14.61 at admission to 8.66 at discharge while physical functionality remained almost stable. General complaints were reduced from 38.43 to 31.91.
Conclusions. Multimodal treatment concepts lead to good results for patients with fibromyalgia, even with a high degree of chronicity. For a better database, more patient reported outcomes together with information on therapy density and comorbidities are required.

P-26 *Treatment of Fibromyalgia*

Cannabidiol: a retrospective review of patient outcomes for pain, sleep, anxiety, depression and function

Daniel Roth[1,2], Rene Alonzo[1], Hari Ailinani[2], Thomas Straub[2], Brian Henriksen[1]
[1]*Research, Fort Wayne Medical Education Program, USA;*
[2]*Medical, Summit Pain Management, USA.*

Purpose. The objective of this study was to examine the self-reported benefits, that chronic pain patients perceived using a hemp-derived (less than 0.3% THC) sublingual CBD product, in the five most common clinical symptoms routinely encountered in fibromyalgia.
Methods. The inclusion criteria included patients currently using an orally administered CBD oil product. We assessed the self-reported benefits using a standard 11-point Likert scale. An ANOVA statistical analysis of data was performed to assess for statistically significant changes in outcomes based upon dosing frequency within each individual metric tested.
Results. Of 4,578 patients receiving a questionnaire, 648 patients reported current usage of some form CBD Oil for an average duration range of 122±8 days. The total mean improvement range for each condition is as follows; pain 4.81-6.48, insomnia 5.56-6.15, anxiety 5.36-5.94, depression 5.08-5.93 and overall function 5.06-5.50. These retrospective data indicate that patients perceive significant relief with CBD oil usage in each metric examined. Moreover, at QID dosing, pain has a statistically significant improvement compared to QD, BID or TID dosing.
Conclusion. Cumulatively, these data support the potential safety and efficacy for the routine use of CBD in the chronic pain population, including but not limited to fibromyalgia. Large scale controlled and blinded studies should be created to further test CBD for the clinical conditions assessed in this study.

P-27 *Treatment of Fibromyalgia*

A nervous system dysregulation in fibromyalgia and the application of an integrative approach to healing

Juliana Sanchez
Applied Clinical Psychology, The Chicago School of Professional Psychology, USA.

Background. Fibromyalgia (FM) is a complex syndrome characterized by chronic widespread pain associated with complexities of physiological and psychosomatic symptoms, including psychological distress. Individuals with FM desire and often seek less adverse treatments through complementary alternative therapies. The purpose of this study is to develop a complementary program for medical and mental health professionals (MMHPs) for client support and symptoms management.
Objectives. Utilize a program development framework to convey an understanding of FM and underlying components that contribute to somatic and emotional stressors from a transpersonal psychological perspective based on evidence-based and effective integrative treatments.
Methods. A mixed-methods study was used to test the validity, efficacy, and potential applicability of the proposed program amongst MMHPs. An expert panel evaluated the proposed program for observational evidence of quantitative/qualitative viewpoints.
Results. An expert panel (N=8) strongly supported the use of mind-body-spirit therapies and found the proposed program to be effective (efficacy M=4.53, SD= 0.75; would recommend to clients M= 4.37, SD=0.91; symptoms management M= 4.75, SD= 0.46) along with categories with themes in (strengths, limitations, recommendations).
Conclusion. This applied research study was the first known of its kind to examine a proposed program with a transpersonal psychological perspective for the treatment of FM. The research examined in this study helped to corroborate the interrelationship between the individual, social, psychological, neurological, and transpersonal aspects of FM. The resulting efficacy and application of this program may enhance MMHP's knowledge of fibromyalgia, assist in client-centered communication and enhance treatments.

P-28 *Treatment of Fibromyalgia*

Oxygen ozone therapy (OOT) in 130 patients with fibromyalgia (FM)

Umberto Tirelli
CFS and Fibromyalgia Unit, Tirelli Medical Group, Italy.

Background. FM is a chronic disorder with a very complex symptomatology with generalized severe pain and fatigue being the cardinal symptoms of the disease.
Objectives. OOT acting by exerting a mild, transient, and controlled oxidative stress that promotes an up-regulation of the antioxidant system and a modulation of the immune system.
Methods. 130 patients with FM were treated at our Clinic (Pordenone, Italy) from February 2016 to December 2020. Treatment was made by autohemotransfusion and by ozone rectal insufflations, according to SIOOT (Scientific Society of Oxygen Ozone Therapy) protocols.
Results. We found a significative improvement (50%) of symptoms in 90 patients (70%). No patient reported important side effects.
Conclusion. At knowledge, this is the largest study of patients with FM treated with OOT reported in the literature and it demonstrates that the OOT is an effective treatment for FM patients without significant side effects.

P-29 *Treatment of Fibromyalgia*

Amigos de FIBRO (FIBRO Friends): development of a multidisciplinary health promotions program for individuals with fibromyalgia in Brazil

Sarina Torres[1], Mateus Antunes[1], Susan Yuan[2], Ana Carolina Schmitt[1], Amélia Marques[1]
[1]*Program of Rehabilitation Sciences. Medical School, University of Sao Paulo, Brazil;*
[2]*Rehabilitation Service, Embu das Artes Health Department, Brazil*

Background. Fibromyalgia (FM) has a great impact on physical and psychological health being frequently associated with multimorbidity. Thus, there is the need of a non-pharmacological approach.
Objective. To develop a multidisciplinary educational program for health promotion to improve the quality of life of individuals with FM.
Methods. A qualitative study was carried out using the focus group technique in a Primary Health Care Unit, in São Paulo, Brazil. The sample included ten primary health care professionals and twelve individuals with FM. Guiding questions that addressed their demands and needs were used to conduct the group discussions. Data were analyzed using the content analysis technique proposed by Bardin, specifically the thematic content analysis.
Results. The "Amigos de FIBRO" program has a total of 15 sessions of 1h20min. The structure of the sessions were: 1) introduction of the program and activities for social interaction; 2) overview of fibromyalgia (physician); 3) practices and environmental factors that contribute to self-care (nurse); 4) social support (social worker); 5) physical activities (physical therapist); 6) balanced and healthy diet (nutritionist); 7) mental health practices (psychologist); 8) information about medication (pharmacist); 9, 11 e 13) home activities (participants); 10) integrative and complementary practices (naturopath); 12) energy conservation techniques (occupational therapist); 14) quality of sleep (speech therapist); 15) closure activity .
Conclusion. This program is proposed to give multidisciplinary educational information to individuals with fibromyalgia in a primary health care system.
Key words: fibromyalgia, quality of life, health promotion, health education, primary health care

P-30 *Treatment of Fibromyalgia*

Beneficial effect of nutritional supplementation with Myolax® in patients with fibromyalgia

Antonio Tristano Romano
Rheumatology, Centro Medico Carpetana, Spain.

Background. Non-pharmacological treatments with food supplements have been proposed as safe alternative to reduce the morbidity as well as the cost of treating fibromyalgia.
Objectives. The aim of the study was to evaluate the effectiveness of the Myolax® (coenzyme Q10, melatonin, vitamins D,C,E,B1, magnesium, selenium, D-ribose, creatine, carnitine, ginkgo biloba, tryptophan) in fatigue, pain, quality of life and the impact of the disease in patients with fibromyalgia.
Methods. Fibromyalgia patients are routinely assessed through questionnaires measuring pain (VAS), fatigue (FACIT-F, FAS), quality of life (HAQ) and impact of fibromyalgia (FIQ) to control its evolution. Patients with fibromyalgia that received Myolax®, and who were assessed through these questionnaires before (baseline) and 2 to 4 months after receiving the Myolax® (final) were retrospective included.
Results. Data from 7 patients who completed treatment were analyzed. An improvement of 28% in the FIQ, 25% in pain measured by VAS, and 127% in the FACIT-F was observed (p 0.05). Although there was an improvement in quality of life of 13.3%, this did not reach a significant difference (p 0.05). Likewise, it was observed that there was an improvement in the FAS questionnaire. At baseline, 100% of the patients reported severe fatigue, at the end of the study 57.4% presented mild fatigue, 28.6% presented moderate fatigue and only 28.6% maintained severe fatigue, with a reduction in severe fatigue to mild / moderate of 71.2%.
Conclusion. Myolax® could be an effective and well-tolerated option to improve pain, fatigue, the impact of fibromyalgia on the daily lives and possibly improving quality of life.

P-31 *Treatment of Fibromyalgia*

Which exercise can affect the pain characteristics of fibromyalgia patients?

Sotiria Vrouva[1,2], Vasileios Papatsimpas[1], Varvara Sopidou[3]
[1]*Neuromuscular & Cardiovascular Study of Motion Lab Lanecasm - Faculty of Health Sciences, University of West Attica, Greece;*
[2]*Department of Physical Therapy, 401 Army General Hospital of Athens, Greece;*
[3]*Department of Biomedical Sciences, Faculty of Health and Caring Professions, University of West Attica, Greece.*

Background. Patients with fibromyalgia experience chronic pain Objectives: Investigation of the possible influence and change of the pain characteristics of these patients, if we add to the exercise program that they follow, breathing exercises.
Method. 106 patients with age range from 35 to 57 formed two groups. Each group followed the same exercise program for 3 weeks with the difference that in the second, the exercise applied was combined with diaphragmatic breathing, at the point where the trajectory began to become painful. At the beginning as well as at the end of the study users completed the questionnaires: FiRST (performance of fibromyalgia rapid screening tool, BRIEF PAIN INVECTORY, and PAIN QUALITY ASSESSMENT SCALE.
Results. In the first group, the characteristics associated with neuropathic pain appear persisting while in the second, they appear to be in remission.
Conclusions. For best results, exercise should focus on controlling movement pain.

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