



The International Congress on **Controversies in Fibromyalgia**

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Congress Chairs

Jacob Ablin

Tel-Aviv Sourasky Medical Center, Israel

Piercarlo Sarzi-Puttini

L. Sacco University Hospital, Milan, Italy

Abstracts

Invited Speaker Presentations	S-117
Oral Presentations	S-129
Poster Presentations	S-132
Author index	S-142

IS-1

Fibromyalgia: state-of-the-art overview

Ernest H. Choy

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

Fibromyalgia (FM) as a clinical diagnosis was brought about by the 1990 American College of Rheumatology (ACR) classification criteria (1). Although these were developed initially to facilitate research, it gained widespread acceptance as a diagnostic tool. However, pain is a subjective symptom. The lack of specific pathology or diagnostic test, as well as the association with depression or anxiety, led many to question the legitimacy of FM as a medical illness. Over the last decade, there is a significant shift in the increasing acceptance of FM among Rheumatology community, driven by the recognition that improving the diagnosis and management of chronic pain in musculoskeletal diseases is a major unmet medical need.

First, FM is common. Prevalence of fibromyalgia in the general population is 2% (2). A UK study found that the incidence of FM increased from 33.3 in 2001 to 38.2 per 100,000 people in 2013 (3). The healthcare and societal burden associated with FM is high (4). Delay in diagnosis led to inappropriate investigations and referrals to multiple specialties (5). With functional neuroimaging, objective evidence of abnormal pain processing has been consistently demonstrated (6) removing the stigma of pain in FM being psychogenic. Furthermore, whilst FM cannot be cured, systematic reviews based on national and international guidelines such as European League Against Rheumatism (2016), Canadian Pain Society and Canadian Rheumatology Association (2012), as well as the Association of the Scientific Medical Societies in Germany (2012), agreed on the overall approach to FM should be multi-modal approach using non-pharmacological and with necessary pharmacological treatments to reduce pain and improve function (7-9). Exercise and psychological/mind-body therapies are recommended by guidelines. If the response to non-pharmacological treatments is inadequate, low dose amitriptyline, serotonin-noradrenaline reuptake inhibitors (duloxetine, milnacipran) and the anti-convulsant, pregabalin may be added. The approval of duloxetine, milnacipran, and pregabalin by the Food and Drug Administration for the treatment of FM further emphasized FM being a treatable condition. The ACR 2010 provisional criteria for FM (10), which has been updated in 2011 and 2016, allowed FM to be diagnosed by using questionnaire. One of the major advantages of these provisional criteria is that the diagnosis of FM can be made by primary care physician and the first-line treatment be initiated without referral to secondary care. Such an approach was recommended by the Canadian guidelines (8). This may avoid delay in diagnosis and reduce unnecessary investigations and referral to secondary care. More recently, comorbid FM is increasingly recognized in many chronic musculoskeletal diseases. Patients with comorbid FM have higher disease activity score and more severe pain. Disease activity scores used in "treat-to-target" guidelines are higher in these patients. The management of these patients with comorbid FM poses an important challenge for Rheumatologists.

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IS-2

A longitudinal perspective of fibromyalgia: past - present - future

Jacob Ablin

Tel Aviv Sourasky Medical Center, Israel

The story of fibromyalgia (FM) brings to mind Paul McCartney's epic lyrics – "the long and winding road". While some may still consider FM to be a new entity, somehow contrived by various forces and incentives, when looking back into history it becomes obvious that patients suffering from the constellation of symptoms which we currently designate to title "fibromyalgia syndrome" have been around all the time, whether recognized or not. Indeed, when examining the description of patients suffering from "neurasthenia" in the Nineteenth century, or from "colitis" in Axel Menche's "The Story of San Michele" it is obvious that no matter what misconceptions were abundant at the time regarding both the nature of the problem, it's pathogenesis and its treatment, many patients suffering from such diagnoses would currently be identified as suffering from FM.

Notably, eminent Nineteenth century scholars such as George Beard associated neurasthenia with malfunction of the central nervous system (1), a concept not so far from the way we look at "central sensitization" a century and a half later. Subsequently however, medical thinking about the problem shifted and gyred with the introduction of the "fibrositis" title by William Gower in 1904 (2). While this term inherently implied the assumption of an underlying inflammatory etiology affecting connective tissue, a concept which subsequently fell out of favor, Gower did however direct attention at the possibility of fibrositis appearing as the results of physical trauma, such as the overturning of a tramcar, an etiological issue which continues to be discussed and debated to this very day.

Subsequently, over many decades, the fibrositis concept languished in a state of lack of interest. Despite the large numbers of individuals suffering from the clinical hallmarks of fibrositis/fibromyalgia, major medical textbooks paid little attention to the topic and students were usually instructed, either directly and/or by insinuation and innuendo, to regard the whole topic as somehow dubious, and definitely not very important.

The modern era of FM was ushered in at the last decade of the 20th Century, with the well – known ACR classification criteria published by Wolfe *et al.* (3). These criteria, formulating the concept of FM as a chronic widespread pain syndrome characterized by diffuse musculoskeletal tenderness, had tremendous impact. Once criteria were established and officially endorsed by the prestigious rheumatology body, FM suddenly started to gain in legitimacy. Studies were initiated, patients recruited based on criteria, and an onslaught of publications appeared. In parallel, public awareness regarding the syndrome rapidly increased. All this happened despite the fact that the 1990 criteria have subsequently been recognized as in fact missing out on important clinical aspects of the FM syndrome, *e.g.* chronic fatigue, disturbed sleep etc. Intriguingly, while all this was happening, a gradual paradigm shift was evolving regarding the nature of FM. Initially, FM was regarded as a discrete illness, which one either had, based on criteria, or had not. Thus, a patient with 10 tender points did not have FM, despite suffering from chronic widespread pain, while one more tender point would establish the diagnosis. Moreover, based on this dichotomy, multiple studies examined the concept of comorbidity between FM and other "functional" disorders, reporting findings such as the frequent overlap between FM and Irritable Bowel Syndrome (IBS). However, over a relatively short period, FM came to be considered more as a spectrum than as a yes-or-no condition and the concept of "central sensitization", denoting an increase in the gain of pain processing in the central nervous system (4) was first formulated and subsequently attributed to the pathogenesis of FM, as well as to other functional syndromes.

Current thinking regarding the FM concept has definitely come a long way. Over the last two decades, major progress has been made in the field of functional neuroimaging, allowing us for the first time to add objective

meaning to the subjective heightened pain sensitivity classically described by patients. Starting with groundbreaking studies which showed that pain processing centers in the CNS of FM patients have a lower threshold for pain than in normal individuals (5), subsequent research has delved into abnormal patterns of connectivity (6) and eventually led to an effort to develop a specific FM pain fingerprint with high specificity (7). Simultaneously, multiple studies have shed light on the genetic (as well as epigenetic) underpinnings of FM (8).

So, where is FM going to be in 10-20 or 30 years from today? Although it's hard to tell, it seems safe to assume that a lot will change. Similar to other complex CNS conditions, the understanding of FM is likely to become ever more complicated and multi-leveled. In the future, a strive towards precision medicine is likely to include the creation of a matrix of novel parameters for each patient, profiling individuals on the basis of multiple parameters such as genetic mapping, functional connectivity, psychosocial factors etc. This is also likely to lead to novel sub classifications of the large group of patients currently collectively labeled as suffering from FM. Furthermore, the development of better and more objective diagnostic tools holds the promise to reduce the "transparent" nature of FM and to reduce the numbers of "fibro-skeptics". While it is hard to anticipate whether FM will remain strictly within the realm of rheumatology, what really matters is that FM continues to be treated and studied by those most interested in the subject, which may evolve into a more heterogeneous and multidisciplinary group. On the therapeutic side, huge interest regarding the role of cannabinoids in the management of chronic pain is likely to lead to a radically more extensive understanding of the cannabinoid system and its therapeutic potential. Other, non-pharmacological treatment modalities such as neurofeedback, hyperbaric oxygen, and magnetic stimulation are likely to gain a place in the therapeutic armamentarium. Thus, the story of FM will continue to evolve.

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IS-3

A sociological perspective: why are doctors so afraid of fibromyalgia?

Winfried Häuser

Professor of Psychosomatic Medicine, Technische Universität München, Germany. Specialist in Internal Medicine and Pain Medicine. He is working with FMS patients since 25 years. He is head of the steering committee of the German guideline for FMS and member of the steering committee of the EULAR recommendations for the management of FMS. He is member of the medical board of the German Fibromyalgia Association.

Norwegian physicians ranked FMS on two separate occasions in 2002 and 2014 as the disease with the lowest prestige of 38 "low ranking" conditions. In my lecture, I will give some very personal explanations for the bad reputation of FMS among doctors.

- a) GPs: Physicians may be poorly knowledgeable in the recognition and diagnosis of FMS. Physicians are attuned to using objective abnormalities on examination or biomarkers on laboratory testing to confirm clinical

cal diagnoses, a scenario completely lacking in the diagnosis of FMS. Outside of psychosocial and pain medicine, there are uncertainties and reluctance to use symptom-based diagnosis.

- b) Rheumatologists: They prefer patients with inflammatory rheumatic diseases for which a broad spectrum of effective drug therapies is available – in contrast to FMS. Rheumatologists are (better) paid for technical investigations than for educating and reassuring FMS-patients.
- c) Mental health care specialists: There are still some health care professionals with a narrow psychiatric view on these patients which claim that FMS is an unhelpful diagnosis for the patient and that (masked) depression is the appropriate diagnosis.
- d) The FMS community: The rapid change of FMS diagnostic criteria (ACR 2010, 2011, 2016, ACTTION) criteria leave specialists and GPs helpless which criteria to use for the diagnosis of FMS. Scientific controversies in a field can be very stimulating. However, some controversies between the protagonists of a neurobiological and sociological perspective in the FMS community were not helpful at all.
- e) Patients: a) A substantial part of FMS patients have experienced childhood adversities and traumatic life events. FMS patients show a higher frequency of insecure attachment styles and lower frequencies of secure attachment styles in comparison with healthy women. Insecure attachment styles increase the risk of interpersonal problems including the doctor-patient relationship. Analyses of facial expressions of interviews with FMS patients demonstrated that elements which stabilize relationships were lacking and that dissociative elements were implanted in the interaction. Doctors (without psychiatric knowledge) experience (some patients) with FMS to be time-consuming and stressful. Some FMS patients provoke a negative counter-transference of the doctors. b) The powerful actions of some FMS self-help organisations (partially supported by pharmaceutical companies) claiming that FMS is a somatic disease deserving disability pensions has raised resentments by insurances, pension providers and physicians providing medical expertise.

IS-4

The good, the bad and the ugly sides of "psychosomatic"

Riccardo Torta, Rossana Botto

Clinical Psychology and Psycho-Oncology Unit, Department of Neuroscience, University of Turin, Turin, Italy

The presentation proposes to summarize the evolution of the concept of "Psychosomatic" and the approach to it. The Mind-body problem is a philosophical matter of concern to science since its inception. In ancient Greece, Hippocrates, proposing the humoral theory, tried to provide a unitary conception of human being, in which the body, the mind and the environment were strictly interconnected. According to his theory, four humors, blood, yellow bile, black bile, and phlegm combine in the human body, and manifest in the form of temperaments. A few centuries later, in the modern age, Descartes replaced this perspective with his reflections on *res extensa* versus *res cogitans*. It distinguished between psychic and physis reality, contemplating the existence of two distinct domains, i.e. that of thinking (*cogito*) and that of the material world (*sum*). The introduction of such dichotomy, known as Cartesian dualism, had a protracted harmful impact on science. The term "Psychosomatic" has been introduced at the beginning of the 19th century, and the first phase of development of the modern psychosomatic medicine started in the early 1900s. Originally, due to the strong influence of psychoanalysis, the nucleus of psychosomatic diseases were the individual intrapsychic conflicts. It was thought that such unconscious instincts and drives generated emotional states that could determine pathological modifications in tissues and organs, and had a direct causal relationship with somatic diseases. For example, in the hysterical conversion, neurological deficits, such as paralysis or somatosensory alterations, were considered as caused by psychogenic stressors. In this way, the physical symptoms that could not be explained by organic reasons, were the resulting effects of psychic issues. Subsequently, thanks to the scientific advances especially in genetics and neurobiology, these first theories were questioned, and the mind and the body started to be considered as interconnected and exerting reciprocal influences. Multi-factorial circular models replaced the causal-linear ones, and the study of other individual aspects, such as attachment, subjective development and cognitive domain became salient. Furthermore, Psychosomatic received a fundamental support from the bio-psycho-social model and the concept of heterogeneity of diseases, according to which psychosomatic diseases do not exist, but psychosomatic factors could be

central in some diseases. Therefore, the actual hypothesis is that multiple aspects, such as bio-chemical, psycho-social and environmental contribute to the manifestation of a certain clinical condition. This is sustained also by neuroscientific evidences, that are demonstrating how neurobiological processes can impact on both soma and psyche. For example, it has been shown the double role of oxytocin that, on the one hand, stimulates uterine contractions during delivery and milk secretion and, on the other, promotes maternal care and attachment. Also the function of proinflammatory cytokines both on mood and physical disease well represents this new actual psychosomatic perspective.

Paradigmatic in this context is the problem of fibromyalgia syndrome (FMS) in which both biological and psychosocial factors play significant roles in its pathogenesis. In FMS there is a greater presence of psychological distress and psychosomatic syndromes than in rheumatoid arthritis (RA) patients (Ghiggia *et al.*, 2017). A better understanding of the psychosomatic manifestations of FM syndrome could allow clinicians to structure tailored interventions that take more account of the emotional distress associated with the physical complaints. Also the current evidence strengthens the relevance about the management of FMS from a psychosomatic perspective (Sancassiani *et al.*, 2017). In agreement with these considerations an integrated model of Psychosomatic Medicine could help the approach to FMS in clinical practice (Deter, 2018).

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IS-5

Transparent pain. But you don't look sick at all...

Manuela Di Franco, Cristina Iannuccelli

Rheumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza – University of Rome, Italy

The IASP (International Association for the Study of Pain) defines *pain* as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Fibromyalgia (FM) is one of the most severe and disabling chronic pain syndromes characterized by the absence of structural pathology (so-called “organic cause”) and accompanied by fatigue, sleep, memory and mood issues. FM patients complain of strange and variable pain described from time to time as burning, aching, sharpening, stabbing, exhausting, cramping, gnawing, tingling, etc.

This description of the pain changes during the hours, the days, the months, the years often with different and capricious characteristics.

Because of that the patients are not taken into consideration by relatives and sometimes also by physicians. Their inexplicable pain is transparent and consequently the patients result “transparent”: they are not considered sick at all.

The problem is that FM etiopathogenesis is still a matter of debate and consequently validated biological biomarkers have not yet been identified. Currently, according to 2016 ACR criteria, FM diagnosis is based exclusively on a comprehensive clinical assessment.

A recent study showed as a patient-centered care and an empathetic behavior towards the patient are significantly higher for patients who have visible signs of pain (rheumatoid arthritis and complex regional pain syndrome) than for those who have no visible signs (Ehler-Danlos syndrome and fibromyalgia).

How this disease can be made non-transparent? How those patients can be made “non-transparent”?

During the years there have been numerous attempts to find some markers for the disease but no one was conclusive. Recent attempts to make the pain objective included studies with functional magnetic resonance imaging that showed an abnormal resting state functional connectivity of the periaqueductal gray suggesting that patients with FM have an endogenous pain modulatory system dysfunction, possibly causing an impaired descending pain inhibition. Moreover some authors described a high prevalence of small fiber pathology in FM.

Unfortunately those data are not so strong to be used in the clinical practice. Likely it is necessary to look not only for biological or instrumental markers, but also for other possible markers such as psychological and anthropological findings.

From a psychological point of view, various subgroups based on distinct characteristics have been identified (essential pain, concurrent distress, particularly depression and anxiety) suggesting the existence of heterogeneous and interacting etiopathogenetic processes. Clusters of patients have been also described using psychological measures but findings are not univocal. FM patients have been found to show a dysfunctional representation of their illness and to adopt coping strategies that are ineffective and focused on a catastrophic view. Conversely, one of the few protective factors that has been investigated in the context of chronic pain is pain acceptance, which seems to reduce negative emotions in response to pain and to favor effective pain coping strategies.

From an anthropological point of view, chronic pain is a phenomenon determined by the interaction of several factors, which include cultural and social determinants. Specifically, experiences such as isolation and marginalization, sense of abandonment, lack of support, or complications in family, social, and work relationships can aggravate the level of psychological distress, which in turn adversely affects pain perception. At the same time, personal and social factors, such as lived trauma, subordination status, social suffering, or forced identity redefinition, can be considered as illness' determinants in themselves.

The development of clinimetric assessment tools and/or patient-centered questionnaires tested on large population could be useful to evaluate FM pain and consequently to bring out the transparent pain.

To conclude pain invisibility can be a barrier to quality of care. It is necessary to educate caregivers to look to the transparent FM pain and to “transparent” FM patients in order not to underestimate this frequent condition.

IS-6

The complexity and difficulties of handling disability of patients with fibromyalgia

Howard Amital

Head of Department of Medicine 'B' & Head of The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.

Associate Professor and former Chair of Internal Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Chronic pain conditions are the most common cause for disability leave from work. In addition, these conditions account for the highest indirect costs for society and also accounts for an individual economic, social, educational and vocational burden.

The leading symptoms limiting vocational tasks in patients with fibromyalgia were found to be pain (87%), tiredness (80%), muscle weakness (73%) and memory and concentration problems (51%).

Many of these disabled subjects are dependent on the government health care systems. Given the complexity of the medical community toward patients with fibromyalgia they are often regarded as malingerers and in many cases their appeals are denied.

The following presentation will shed light on the current situation that patients with fibromyalgia face and suggest ways to solve this issue.

IS-7

Evolving concepts in the classification, diagnosis and epidemiology of fibromyalgia

Marco Di Carlo

Rheumatological Clinic, Università Politecnica delle Marche, Ospedale “Carlo Urbani”, Jesi (Ancona), Italy

Different studies, coming from different countries and settings estimated the prevalence of fibromyalgia (FM). The worldwide prevalence of FM is around the 2.7%, ranging from values of 0.4% (Greece) to 12% (Tunisia). Across the various continents, the prevalence of FM is of the 3.1% in the Americas, 2.5% in Europe, and 1.7% in Asia. Globally, FM mean prevalence is 4.2% in females and 1.4% in men, with a female-to-male ratio of 3:1. The prevalence of the disease is also influenced by the diagnostic criteria

adopted: applying the 2010 criteria of the American College of Rheumatology (ACR) seems to be higher than the 1990 criteria that required the objective examination of the tender points. Some studies have also evaluated the incidence of the disease. A Norwegian study shows an incidence of 5.83 cases/1000 people in women between 20 and 49 years of age, while Weir and coworkers detected an age-adjusted incidence rate of 6.88 cases/1000 person-years for males and 11.28 cases/1000 person-years for females. Over the last decades, numerous efforts have been made to establish valid diagnostic/classification criteria for FM, and this area of research is still extremely dynamic. FM is still a complex disease to diagnose, and the diagnostic delay is about two years. As a result, FM is still an under-diagnosed and under-treated disease. The 1990 ACR criteria were extremely focused on chronic widespread pain (CWP) (defined as pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist, and axial skeletal pain) and tenderness (defined as pain on palpation of 11 or more of 18 specific tender point sites on the body), with little relevance to symptoms for diagnostic purposes. Therefore, for over 20 years, a history of CWP and the presence of tender points have been the cornerstones for the diagnosis of FM. However, over the years a number of critical issues have emerged with regard to this diagnostic/classification approach. First of all, it has been revealed that in primary care many physicians do not know how to evaluate tender points and, refusing to do so, in practice the diagnosis is based on symptoms. Secondly, the literature has increasingly valued the presence of symptoms, such as fatigue, unrefreshing sleep, and cognitive symptoms, as key elements for the diagnosis of FM. A third important objection was that a complex pathology such as FM is that characterized by manifestations that are a continuum, whose diagnosis is difficult to interpret in a simple cut-off point. Consequently, the 2010/2011 criteria have been developed with the intention of enhancing the non-tender point symptoms by translating them into a symptom severity (SS) scale. In addition, the formal count of tender points was replaced by the widespread pain index (WPI), avoiding the objective examination. Recently, one of the criticisms levelled against the 2010/2011 ACR criteria, is that they have allegedly moved away from chronic pain. The latest development of diagnostic criteria for FM has been provided by the FM Working Group of the AAPT (Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks [ACTION] - American Pain Society [APS] - Pain Taxonomy). In these criteria, FM has again been classified as a disease characterised predominantly by chronic pain (a self-reported of the multi-site pain [MSP], defined by the presence of at least six of nine pain sites throughout the body), along with fatigue and sleep problems as two key associated symptoms.

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IS-8

Is fibromyalgia really all that different from other rheumatological disorders?

Giuliana Guggino

Department of Internal Medicine, Rheumatology Section, University of Palermo, Italy.

There is still a great debate on the definition of fibromyalgia (FM) and how to deal with patients affected by this condition. Although FM has been considered a musculoskeletal disorder rather than a central sensitization syndrome, its classification is not easy since it is a systemic disease. The complexity of the symptoms reflects an intriguing pathogenesis in which the neuroimmune axis seems to be widely involved. It is for such complexity that, in reality, we should ask whether FM is really so different from other rheumatic diseases. The crucial points is to understand which pathogenetic factors are at the base of FM, where patients report severe pain. The experience of pain is the cardinal element of the disease, making it the first element of treatment. Nowadays, the treatment of chronic pain is widely debated and new therapeutic approaches have been borrowed and made available also for FM. One of these approaches is based on the hyperbaric oxygen therapy (HBOT), which has been found able to modulate immune system response. Recent findings, in this stream of research, have demonstrated that FM patients show a significant increase in inflammatory mediators such as TNF-alpha, an activation of T helper 1 lymphocytes and a reduction of

central nervous mediators such as serotonin. These alterations are correlated with widespread pain, fatigue, sleeping disorders and the quality of life. After HBOT the modulation of immune system is rapidly obtained restoring the balance of CD4⁺ T cell subsets and relative cytokines. CD4⁺ T cell subsets have significant cross-talk, with the ability to "differentiate" given appropriate environmental signals, suggesting that environmental factor could participate to the activation of immune system. These findings suggest a great involvement of immune systems in the pathogenesis of FM. The proinflammatory status detected in FM patients makes FM not so different from other rheumatic diseases in pathogenetic terms. On the contrary, the conventional treatments used for rheumatic disease appear ineffective for FM making it different in regards to therapy. The end of the pattern towards the definition of FM is still open and many other studies will be necessary to put together the pieces of a still incomplete puzzle.

IS-9

Chronic fatigue syndrome and fibromyalgia following immunization: another angle of the 'Autoimmune (Auto-Inflammatory) Syndrome Induced by Adjuvants' (ASIA)

Yehuda Shoenfeld

The Zabłudowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer, Israel. The Mosaic of Autoimmunity Project of Saint Petersburg University.

The objectives of this study were to gather information regarding demographic and clinical characteristics of patients diagnosed with either fibromyalgia (FM) or chronic fatigue (CFS) following hepatitis B vaccination (HBVv) and furthermore to apply the recently suggested criteria of autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA), in the aim of identifying common characteristics that may suggest an association between fibromyalgia, chronic fatigue and HBV vaccination. Medical records of 19 patients with CFS and/or fibromyalgia following HBVv immunization were analyzed. All of which were immunized during 1990–2008 in different centers in the USA. All medical records were evaluated for demographics, medical history, the number of vaccine doses, as well as immediate and long term post-immunization adverse events and clinical manifestations. In addition, available blood tests, imaging results, treatments and outcomes were analyzed. ASIA criteria were applied to all patients.

This study suggests that in some cases CFS and FM can be temporally related to immunization, as part of ASIA syndrome. The appearance of adverse event during immunization, the presence of autoimmune susceptibility and higher titers of autoantibodies all can be suggested as risk factors. ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and CFS/FM. **Keywords.** Autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA), vaccines, autoimmunity, fibromyalgia, chronic fatigue syndrome.

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IS-10

Mechanisms underlying the transition from acute to chronic pain

Daniel Clauw
University of Michigan, USA

We are beginning to better understand the mechanisms that underlie the transition from acute to chronic pain. As with many other complex chronic diseases, although chronic pain runs strongly in families, there are no single genes that confer strong effects, so at present this risk is thought to be polygenic with likely epigenetic factors playing a significant role. Other risk factors for developing chronic pain include female sex, previous chronic pain elsewhere, a history of trauma or stress, a history of mood or sleep problems, and cognitions such as catastrophizing. Biological mechanisms that may contribute include altered pain and sensory processing on quantitative sensory testing, changes in brain connectivity patterns, structure, or neurochemistry on functional neuroimaging, and a primed immune system.

IS-11

Mechanistic similarities between fibromyalgia and other chronic pain conditions

Lars Arendt-Nielsen
Sensory-Motor Interaction (SMI) Center, School of Medicine, Aalborg University, Aalborg, Denmark

It is generally accepted that pain diagnosis and therapy should be mechanism based and hence pain assessment tools (pain biomarkers) should be sufficiently sensitive and advanced to provide such mechanistic information. Translating clinical observations to mechanisms and vice versa is not trivial, and tools to assess quantitatively the different phenomena are mandatory. This approach has provided new insight into how reorganization of the pain system is manifested in fibromyalgia and other chronic pain conditions. Common features across different pain patient populations have been identified utilizing this approach. Peripheral and central sensitization are important mechanisms for fibromyalgia (FM) and musculoskeletal pain conditions in general. Many similarities exist between different chronic musculoskeletal pain conditions. Musculoskeletal pain may transit from a localized pain problem through a regional representation to a widespread pain condition such as FM. As the pain condition transits from one to the other, more and more sensory abnormalities occur with many sensory abnormalities in FM. There is evidence that as well the intensity of ongoing pain as the duration of pain determine the degree of generalized hyperalgesia. This is important to realize as it underpins the importance of the ongoing nociception for the chronification process in conditions (e.g. osteoarthritis) where the peripheral nociceptive drivers are known, whereas it is more complicated in, e.g. FM where the drivers are less obvious. Such techniques for assessing the peripheral/central pain sensitization mechanisms in patients with FM and other patients with musculoskeletal pain have been developed and provide the opportunity to quantify pain mechanisms such as temporal summation, descending inhibition, spreading sensitization, and additional modality-specific hyperalgesic reactions. Such tools can help to phenotype patients with FM based on the role of the various pain sensitization mechanisms involved and have recently been used as tools to predict pain outcomes after pharmacological or surgical interventions in various groups of musculoskeletal pain conditions. Relating clinical benefit of a given therapy with quantitative assessment of the pain sensitization mechanisms involved provides new opportunities for better diagnostics and hence for tailored and individualized management regimes. Although assessed differently in specific tissues for various musculoskeletal pain conditions, the underlying mechanisms share common underlying features. An example of similar mechanisms across chronic pain conditions could be cutaneous allodynia in neuropathic pain assessed by brush, which corresponds to pain evoked by weak muscle pressure in musculoskeletal pain and to pain provoked by a weak colonic distension in visceral pain. Another example can be facilitated temporal summation and impaired descending modulation across many different chronic pain conditions including fibromyalgia. This mechanistic understanding is of importance for developing better diagnostics and for implementing tailored pain management programs. The understanding that FM and other musculoskeletal conditions share common fundamental features has positioned FM as the one extreme

end as opposed to, e.g. a myofascial pain problem at the other end. This has provided some new insight into the development of the sensitization processes from one extreme to the other. Some of the current available mechanistic human pain biomarkers translate back to animals, providing new possibilities for bridging findings between pre-clinical and clinical studies. Data on the clinical applicability are increasingly available.

IS-12

The role of peripheral nociceptors in fibromyalgia syndrome

Nurcan Üçeyler
Department of Neurology, University of Würzburg, Germany

The pathophysiology of pain in fibromyalgia syndrome (FMS) is unknown. Patients mostly describe deeply localized pain in muscles and tendons with high variance in intensity and spatial distribution. Pain mostly starts at circumscribed regions and spreads over the entire body. Patients regularly report of typical additional core symptoms such as sleep disturbance, gastrointestinal problems, subjective cognitive impairment, and depressed mood, which in turn may increase pain. Analgesic treatment is challenging and often leads to side effects rather than being efficient. Hence, most FMS patients stop pharmacological treatment and turn to non-pharmacological therapies with better outcome.

In the last years FMS research has increasingly focused on small nerve fibers (thinly-myelinated A-delta and unmyelinated C fibers), which terminate in the epidermis and mainly conduct pain, thermal sensations, itch, and pleasant touch. Since the first description in 2013, several studies from different laboratories worldwide have been published describing hints for small fiber impairment in FMS patient subgroups. These alterations cover a reduction in fiber quantity as assessed in the skin and the cornea, an increase in small fiber sensory function thresholds, and a reduction in electrical conduction. In parallel, microneurography revealed spontaneously active nociceptors in FMS patients. The underlying mechanisms that lead to small fiber impairment in FMS patients are not understood and it is also unclear, if and how small fiber abnormalities may contribute to FMS pain. Also, these findings are not specific for FMS and do not prove or disprove the diagnosis.

Currently, small fiber assessment does not have a diagnostic impact in FMS patients. Lacking a validated objective biomarker, the diagnosis of FMS is still made following internationally accepted criteria that are based on the clinical presentation and symptom load. However, research on the pattern and underlying pathophysiology of small fiber pathology in FMS has intensified and more studies investigating well characterized large patient cohorts are needed to decipher the underlying pathomechanisms.

In this presentation, current data on small fiber pathology in FMS will be summarized and critically discussed with the audience mainly focusing on methodology, data interpretation, and potential diagnostic and therapeutic implications.

IS-13

“More brain than muscle” the fibromyalgia paradigm

Roberto Casale¹ & Alberto Rainoldi²

¹Opusmedica, PC&R Patient, Care & Research Network, Piacenza, Italy. ²Motor Sciences Research Center, Interfaculty School of Motor Sciences, University of Turin, Italy.

Using PubMed to go back in time, at the beginning of the publications of what at that time was called fibrositis and now defined as fibromyalgia, the muscle was always indicated as the pivot of the myriad of symptoms reported by fibromyalgic patients. Even sleep disturbances were referred to a lack of rest because of muscle pain, anxiety because of continuous pain in the muscle and even easier, fatigue was considered as the perfect condition that may follow continuous muscle pain. And when fibrositis was dropped out and myositis took its place, followed by muscle rheumatism and non-articular rheumatism, muscle remained the bad guy. In this period that we can define the “muscle era”, the pivotal point was to find out possible presence of alterations in the fibromyalgic muscle. All bioptic studies agreed on the presence of atrophy of type II fibers and of a phlogistic aspect. However, these features can be found regularly in the elderly, as well as in different pathologies and etiology: disuse and corticosteroids induced atrophy, corti-

cospinal tract alterations and other diseases. Neither optical nor electronic microscopy revealed any inflammatory or pathognomonic pattern. Both techniques have in fact shown how, from this point of view, the fibromyalgic muscle may appear “normal” or show borderline characteristics as discrete and non-specific alterations. The use of ultrastructural electron microscopy techniques didn’t substantially change the idea that what can be found, were only secondary non-specific alterations. On this cul de sac are also modern non-invasive techniques such as fMR, failed to provide proof and sound diagnostic markers, again showing in one of the most recent papers only unspecific alterations in intramuscular ATP, PCr and fat content reflecting a combination of inactivity/atrophy-related to pain and dysfunction of muscle mitochondria *i.e.* a lack of function in oxidative muscle fibers [Gerdle et al 2013]. In more recent years and once again starting from the muscle we have succeeded in identifying patterns of muscular activation typical of fibromyalgia and not referred to a disorder of the muscle itself but to a wrong or better to say, non-appropriate or dysfunctional motor command. This puts attention not on the effector organ rather than on the ability of the nervous system to match sensory information and to generate congruous motor output. These researches agreed with other lines of research where instead of looking at the periphery, researchers were looking into the CNS functioning with the more sophisticated technologies such as fMR. Indeed, this is the “brain era” in which the muscle doesn’t miss its important role but simply changes its role from the major and main actor to an important part of the interplay between sensory inputs and motor output in a continuous interplay. Moreover there are experimental evidences that indicate that when the bioelectrical phenomena known as localized muscular fatigue develop in the muscle, also in the central nervous system there are neuro-hormonal and excitability changes of the cerebral cortex, which suggest central factors that act upstream of the motoneuronal drive (Taylor JL, Gandevia 2008). In a simplistic and schematic representation: an incongruous motor output, triggered by a wide range of bio-psycho-social and person-related factors, generates an incongruous motor activation which generates incongruous sensory inputs to the brain which misinterpret the information and generates incongruous motor response (Casale & Rainoldi 2011). It turns that this abnormal sensory-motor coupling, if reiterated, can steadily modify the brain response to any motor task. This opens new questions on which type of rehabilitation is needed in fibromyalgia.

IS-14

ENFA: what is it for?

Souzi Makri

The European Network of Fibromyalgia Associations (ENFA), Cyprus.

ENFA (The European Network of Fibromyalgia Associations) was officially inaugurated as an Organization in September 2004 and was supported by the United Kingdom, Scotland, The Netherlands, Switzerland, Denmark, Norway and France.

Fibromyalgia affects an estimated 14 million people in Europe. It has a devastating impact on those who suffer from the disease and also for those careers and families who are trying to support them. Also it imposes a large economic burden on society and individuals. The mission of ENFA is to promote Fibromyalgia awareness to politicians, physicians, scientists and the general public on a European level.

As Fibromyalgia was adopted by the European politicians by way of accepting the written declaration 69/2008, ENFA’s efforts aim to achieve implementation of the declaration with the primary goal of placing Fibromyalgia as a key topic in the European Health Programme.

ENFA, has Organized some various events to raise awareness of this invisible disease among the general public and the patients. These include a lunch meeting hosted by the Cypriot Member of the European Parliament, Mr. Takis Hadjigeorgiou on 12th 2017 under the topic: “The position of the fibromyalgia patients in the society”.

The ENFA Conference 2018, was organized in partnership with ME, CFS & Fibromyalgia Alliance Malta – VO/818 and took place in May 2018 in Valetta, Malta. Titled ‘In every disability, there is an ability’, the conference was held under the distinguished patronage of Her Excellency Marie-Louise Coleiro Preca, President of Malta.

IS-15

Role of the patients associations on dealing with fibromyalgia patients: the Italian experience

Egidio Riva, Giuseppina Fabio, Piercarlo Sarzi-Puttini

Associazione Italiana Sindrome Fibromialgica (AISF-onlus), Italy

Background. The need of patients associations is quite relevant when you deal with chronicity; there are a variety of unmet needs that patients associations can take care of starting from patients proper information, visibility, political issues and funding among the others.

Clinicians face a rather difficult task in fibromyalgia: to guide patients on what may be a syndrome which will be present and influence in a relevant way the journey of their lives. Clinicians must preserve their patients’ hope and resilience while at the same time giving them accurate information. And patients with fibromyalgia face a difficult task: navigating a route while confronting a chronic and treatment-resistant disease. Communication between patients with fibromyalgia, their familial and social environment, and the treating clinicians may present many challenges. Communications between physicians and patients may improve; patients need easier access to information about their medical condition and their health care; patients associations can help to deliver patient-centered care, reflecting to what is important to them, and how to endorse relationships between health care professionals and patients that should be stronger, more trusting, and empathic.

Education and information. AISF (Italian Association of Fibromyalgia Syndrome) was founded nearly 15 years ago with the mission of obtaining the recognition of Fibromyalgia as a discrete entity and with the willingness of educating both the clinicians and the patients on recognising this diagnosis and treating properly the patients affected by this syndrome. One of our main activities is concentrated on spreading out the knowledge of the existence of this syndrome. Patients need to know the upcoming news and AISF takes care of an yearly National Congress where professionals open their knowledge in the various subjects of their specialties and answer to general and personal questions. A dedicated booklet “Manuale pratico per il paziente affetto da sindrome fibromialgica”, which is regularly updated and which probably will have this year an English edition as well, explains the main contents of symptoms, diagnosis, pharmacological and non-pharmacological treatments; 28 authors develop topics on Fibromyalgia on 13 chapters addressed to patients and to health care professionals. AISF takes care and issues complete scientific and information literature addressed to patients and professionals. A six-monthly paper, called “Caleidoscopio”, reports recent studies and specific informations on the activities organized by the local sections and an Internet account gives general information on all activities. General practitioners who take care of family based public health need to be updated about diagnostic procedures and appropriate therapies to be prescribed according to their personal knowledge and the informations derived by the specialists and by the evidence-based literature. AISF organizes Regional Courses for health care professionals to let them expand their knowledge on this topic.

Self help groups. AISF has 20 Sections spread out in the majority Italian Regions; their mission and action is supported by the main head office based in Milan. Sections are managed by voluntary referees: two patients and one Doctor mostly often specialized in Rheumatology or in Pain medicine. Sections take care of organization of periodical events dedicated to associated and non associated patients. Some of the conferences and meetings are organized for clinicians with different specializations but interested in chronic pain. AISF promotes the idea of self-management and creates self-help group among patients where it’s possible. Our main office and the local sections provide continuous personal informations through telephone calls and mail assistance to all patients who need for practical and psychological support. It is helpful when we may suggest where dedicated and specialised hospitals departments are located on the nearby for quick and easy assistance. Experienced patients are supporting other newly-diagnosed patients with suggestions and advices on how to do and how to manage their day by day life, to survive to their pain and to handle frequent misunderstandings by families and sometimes by clinicians that do not recognize this syndrome as a clinical entity or do not have enough scientific knowledge to deal with.

Political issues. One of the main controversies in Italy is to have Fibromyalgia recognised by Public Health Assistance Institutions; this will help scientific and pharmaceutical researches and will reduce the costs for the patients. AISF political activity is continuously and deeply dedicated to contacts with National and Regional Institutions looking for having the opportunity to request and to obtain the syndrome to be included by law into chronic diseases sponsored by the Italian Public Health System.

IS-16

The Israeli perspective – what we've learned over the last 2 decades

Sharon Gur

Asaf, Fibromyalgia and CFS Nonprofit Organization, Israel.

ASAF association for fibromyalgia, (FM) and CFS, was founded 20 years ago by a small group of young women with common background - all had Fibromyalgia. Back then, there was no information, no known cure and no support. We felt lost, and seeking support, we decided to work together in order to raise awareness to FM among doctors, medical teams and patients alike. Only few rheumatologists knew about FM and recognized it as illness. Family physicians were not aware of FM, there was no medical treatment offered, no research. We felt that no one cared.

Our foremost task was and still is, getting appropriate recognition, acceptance from the medical, state authorities and the society.

From this modest start and with hard work ASAF became the voice of the patients.

It is a Sisyphean process we call: From transparency to Visibility.

Approaching rheumatologists, pain physicians and family physicians in various occasions, arranging dedicated meetings, joining medical professional conferences and adamantly lecturing in order to explain and convince. We approached medical teams, nurses, and alternative medicine practitioners etc. trying to educate and gain support.

The journey was, and still is, a long one. Although specific medicines were finally introduced worldwide, but, at the beginning, they were not approved in Israel as part of the national healthcare insurance funded drugs.

Therefore, we advocated and eventually succeeded to make it possible for FM patients to purchase these medicines at a considerable discount.

A decade ago we encouraged a research aimed to explore the benefits of Cannabis use for FM patients and later approached the Ministry of Health, appealing to include FM patients among those who are given prescription to legally use Cannabis for pain relief.

We also realized that without recognition the patients had no rights under social security law. Insurance companies refused to cover claims of income protection insurance for FM patients.

10 years ago, ASAF approached the Social Security Institute in order to create a dedicated deficiency article in the disabilities list, so patients will get proper recognition and fair entitlement.

We had to appeal to the Supreme Court twice. Eventually it ruled in our favor. We are finally approaching an agreement with SSI. That will be a major change for the patients.

We approached the media numerous times, got articles in newspapers, interviews on the radio and on television shows and social media - Facebook etc. ASAF is a safe haven for patients – our message to them is: “you are not alone; we understand your suffering and wishes, we want and can help”.

Our mission is to empower the patients and encourage them to take full responsibility on their life. Our support groups enable patients and their families to be part of a larger group of people that suffer similar symptoms. An important tool is our phone help line, open to all patients and their families even before they were diagnosed.

ASAF reaches out to reclusive populations in Israel, such the orthodox Jews, share knowledge and offer assistance and comfort.

We encourage patients to follow up with doctors' recommendation on physical activity, which is most effective for FM patients.

We suggest trying hydrotherapy, CBT and T'ai Chi. Part of our responsibility is to alert patients from treatments offered by charlatans.

Our yearly conference is dedicated to familiarizing patients and families with the newest innovations and allowing them to meet people with similar interest and struggle. Membership is open to all.

ASAF cooperates with other patients' organizations that complete our activities for the mutual benefit of all.

It is our life mission; all of us are volunteers and dedicate our time to our goals.

In the past 20 years ASAF helped thousands of patients. Let's do more, much more.

IS-17

Is it all in your genes? (genetics of fibromyalgia)

Dan Buskila¹, Piercarlo Sarzi-Puttini²¹Soroka Medical Center, Israel. ²Rheumatology Unit, ASST Fatebenefratelli-Sacco, University of Milan, Italy.

Fibromyalgia (FM) is a common chronic widespread pain disorder persisting for more than 3 months that presents diagnostic challenges for clinicians (1,2). FM is commonly accompanied by additional symptoms, such as fatigue, sleep disturbance, cognitive dysfunction, and depression.

Previous studies have clearly demonstrated a strong familial aggregation of chronic pain, leading researchers to conclude that up to 50% of the development of chronic pain may be explained by heritability (3, 4). Pellegrino *et al.* (5) found that 26 (52%) of the enrolled parents and siblings exhibited clinical evidence of FM, and an additional 11 (22%), without apparent symptoms of FM, exhibited abnormal muscle consistency on palpation. Similar observations in terms of familial aggregation among FM patients were also reported in two studies by Buskila *et al.* (6-8)

Psychological factors such as depression and personality traits also demonstrate familial aggregation among FM patients.

Similar to other complex CNS disorders, FM is considered to result from an interaction between genetic factors and environmental factors (3, 4). Thus, genetics per se appear to explain only part of pathogenetic puzzle of FM.

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IS-18

The times they are a'changin': epigenetics of chronic pain

Frances MK Williams
King's College London, UK

Chronic widespread musculoskeletal pain (CWP) is the cardinal symptom of fibromyalgia. The definition emphasizes axial pain, as well as the presence of pain in the upper and lower quadrants, and the right and left sides of the body. The chronic pain syndromes (CPS) are a poorly defined constellation of syndromes with ongoing pain that show overlap in presenting symptomatology such as fatigue, sleep disturbance, anxiety, depression, headache, and functional bowel disturbance. Chronic pain syndromes (CPS) are highly prevalent in the general population, and increasingly the evidence points to a common etiological pathway. CWP has a reported prevalence in the general population of approximately 15%. CWP not only causes profound individual suffering and disability in activities of daily living but is also associated with high health care utilization and increased health care costs. CPS are a serious challenge to health care providers because of their unclear and complex multifactorial pathophysiology, psychological element, and poor response to therapy. Knowledge about the causes of chronic pain remains very limited but current research suggests that the pathology and its somatic expression are influenced by genetic susceptibility - epigenetic factors are also implicated.

IS-19

"Fear and awe": how important is stress after all?

Kati Thieme
Institute of Medical Psychology at Philipps – University Marburg, Germany.

The interaction of pain and fear as an etiological factor has been observed in patients with chronic pain, in psychosocial (1-5), psychophysiological (6, 7), psychophysical (8) endocrine (9, 10), genetic (11, 12) and central responses (13, 14), however inconsistent results suggest a heterogeneity in stress responses of chronic pain. Biopsychological mechanisms such as classical (15) and operant learning (16, 17) of different stress responses will be discussed.

The theoretical base of the stress influence on diseases was proposed by Lacey & Lacey "The principle of relative [stress] response specificity [is] formulated as follows: For a given set of autonomic functions (hence the term *relative*), subjects tend to respond with idiosyncratic pattern of autonomic activation in which maximal activation is shown by the same physiological function, whatever the stress." ((18), p 50).

Our study with 120 female fibromyalgia patients examined the relationship of psychophysiological response patterns with psychological characteristics and comorbid mental disorders (7). Surface electromyographic data, systolic and diastolic blood pressure (BP), heart rate (HR), and skin conductance levels were recorded continuously during baseline, stress, and relaxation tasks. Cluster analysis revealed 4 subgroups of patients who differed on pain intensity, cognitive, affective, and behavioural responses to pain and stress (Table I):

Table I. Relationship of stress response pattern and psychological responses

SG	Prev	Physical			Pain	Cognitive Interference	Affective Anxiety	Depression	Behavior	
		BP	SCL	EMG					Pain Behav.	Physical Activity
I	46%	high	-	-	high	high	high	-	high	low
II	41%	low	-	-	low	low	-	high	low	high
III	9%	high	high	-	high	high	-	-	high	-
IV	3%	low	-	high	-	-	high	high	-	-

BP: Blood Pressure; EMG: Electromyogram; Pain Behav: Pain Behavior; Prev: Prevalence; SCL: Skin Conductance Level; SG: Subgroups; '-': non-significant.

FM patients with hyperreactive BP (I) and increased electrodermal stress response (III) displayed the highest number of pain behaviours as expression of fear, in contrast to patients with hyporeactive BP (II). The results suggest that the stress response in patients with high BP and high sudomotor response may be related to operant learning that reinforces pain behaviour expression (7). Several studies show that baroreceptor response operantly

modified by phasic BP changes (19, 20). It is assumed that a long-term stress associated with adrenergic dysregulation (10) increases both systolic and diastolic BP and a reduction of BP and pressure variability in the carotid sinus. Since baroreceptors are activated only by changes of pressure intensities, reduced BP variability leads to a diminished baroreflex sensitivity that provokes a reduced regulatory activity of the dorsal medial nucleus tractus solitarius (dmNTS) reflex arcs (Fig. 1) that regulate pain, blood pressure and fear (21, 22). The diminished solitary pathway and the disruption of emotion and emotional modulation of pain and nociception may contribute to chronic pain (14).

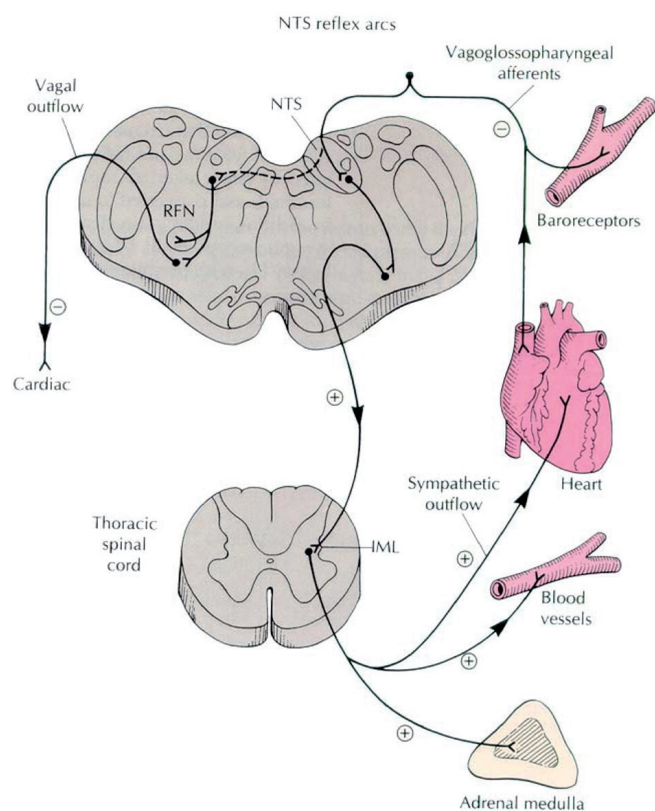


Fig.1. NTS reflex arcs.

These findings contrast with those from patients with a hypotensive stress response that show reduced sympathetically mediated profiles at rest and in response to stress. This pattern is consistent with a relative enhancement in baroreceptor buffering capacity, which mediates a reduction in pain perception and diminished psychological and functional distress (7). Patients with hypotensive stress responses display an overlap of thermoregulation and pain modification with lower body temperatures, lower metabolic rates, and lower circulating cortisol/corticosterone in response to stress (23).

The identification of the mechanisms that contribute to these group differences will further our understanding of the mechanisms involved in the development and maintenance of chronic pain and suggest differential treatment strategies (16, 24-26).

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IS-20

Re-tuning the brain: neuromodulation for fibromyalgia

Roberto Casale

Opusmedica, PC&R Patient, Care & Research Network, Piacenza, Italy.

The concept of neuromodulation is commonly referred to the chronic therapeutic electrical stimulation of the central nervous system or special nerves with an implanted stimulating device. In a more broad way INS (International Neuromodulation Society) defines neuromodulation as "the process of inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral or autonomic nervous systems. It is the science of how electrical, chemical, and mechanical interventions can modulate the nervous system function" (Krames, ES., *et al.* 2009). The use of electrical currents is the most common form of neuromodulation to interact with the brain, spinal cord, peripheral nerves, plexuses of nerves, the autonomic system, and muscles, while chemical neuromodulation uses direct place-

ment of chemical agents to neural tissues through utilization of technology of implantation such as epidural or intrathecal delivery systems. In this presentation we will not put attention on neuromodulation as described above rather than to a more basic science paradigm such as plasticity. Indeed any form of “modulation” is based on the specific property of the nervous system to be modified in both ways for bad and for good (Costigan, M., Scholz, J., & Woolf, C. J. 2009).

Spasticity for the motor system and chronic pain for the sensory system are examples of maladaptive response of the nervous system. In many cases they can be present and intermingled expression of this maladaptive plasticity (Finnerup, NB. 2017).

If we consider any therapy as the attempt to restore the homeostasis, pushing or pulling, blocking or activating, inhibiting or exciting any given “altered” function or activity within the body we have to enlarge the concept of neuromodulation to any form of physical, pharmacological as well as psychological intervention as an attempt to re-modulate a given function or neural activity. This attempt is done in rehabilitation when the maladaptive motor and sensory responses are the effect of a lesion and therefore our ability to act on plasticity is limited by the lesion itself but also in more subtle and apparently inexistent malfunctioning of motor and sensory systems as we see in fibromyalgia. Now we realised that fibromyalgia is the terminal of a sequence of inadequate responses to physical, psychological and social stressful events (May, A. 2011) without signs of lesion, leading to a more and more generalised maladaptive responses involving any aspect of the bio-psycho-social paradigm. Indeed there are no signs of anatomical lesion in nervous system of persons affected by fibromyalgia, however a consistent bulk of evidences are pinpointing the existence of functional dysregulation not only in the sensory system but also in motor cortical areas (Saavedra LC, Mendonca M, & Fregni F 2014). This leads to the maintenance of a vicious circle involving sensory afferences, cortical sensory-motor coupling and non-adequate motor responses. Being fibromyalgia a severe form of maladaptive plasticity, any interventions should be tailored as also any form of therapy can be “interpret” in a maladaptive context. Although therapies such as the hyperbaric oxygen therapy (Casale *et al.* 2019), transcranial magnetic stimulation (Macfarlane, GJ *et al.* 2017) or other therapies are showing promising results “re-tuning” the metabolism - *i.e.* the activity of different cortical areas- however factors such as resilience and the inner ability to overcome stressor events can be considered in the light of a still not acceptable percentage of persons affected by fibromyalgia non responding to any effort to re-tuning our brain.

IS-21

Towards novel classification of complex brain-related syndromes: lessons from brain imaging

Neil Basu

Senior Clinical Lecturer of Rheumatology, University of Glasgow, UK.

Disorders such as fibromyalgia and chronic fatigue syndrome represent some of the most clinically challenging conditions in Medicine. Their excess biological and phenotypic heterogeneity is a primary driver of this. A situation which is further conflated by their prevalent co-existence with other, mechanistically distinct, disorders. Numerous initiatives have sought to characterise and ultimately classify these syndromes with varying degrees of success and controversy. These have almost entirely been ‘top-down’ in approach *i.e.* derived from either expert consensus or phenotypic data. With historically limited knowledge of pathogenesis, it has been challenging to adopt a biologically based ‘bottom-up’ approach to classification. However, advances in brain imaging, which at long last have begun to deliver mechanistic insights into these syndromes, offer a significant opportunity. The possibility to classify patients into homogenous subgroups will greatly support aetiological research - until now true signals have likely been masked by methodological artefacts generated from studying centralised syndromes as single entities rather than focusing on potentially mechanistically distinct subtypes. Clinically, the ability to firstly parse out co-existing centralised features in peripherally dominated chronic diseases will support the judicious use of existing therapeutics. In the future, mechanism based sub-classification will help triage patients towards optimal interventions, in

keeping with the ideals of personalised medicine. In order to meet such ambitions, close collaborations with data scientists will be essential. Evidence is accruing that machine learning methods can successfully integrate rich MRI data streams in order to answer clinically relevant questions. Ultimate implementation of such algorithms into health care services has yet to be realised but is certainly feasible.

IS-22

Non-pharmacological treatment for fibromyalgia: complementary/alternative treatment may be your first choice...

Valerie Aloush

Fibromyalgia Clinic, Department of Rheumatology, Tel Aviv Sourasky Medical Center, Israel.

Fibromyalgia (FM) is a complex syndrome characterized by chronic widespread pain, sleep disturbances, fatigue and cognitive impairment, associated in some cases with anxiety and depression. FM affects quality of life in many aspects (personal, familial, social and professional) and remains a therapeutic challenge. Comprehensive treatment of this condition aims not only to alleviate pain but rather needs a holistic approach to address both physical and psychological symptoms; to treat pain and functional consequences of pain. In this regard, non-pharmacological interventions have been shown to be effective, most of them with low cost and high tolerability. Education is the first required step to ensure adherence and compliance to treatment program. Understanding fibromyalgia, its causes, natural history, and treatment options leads to better coping and improved outcomes. Validation of the diagnosis of FM also helps reducing health-related anxiety.

Low-intensity aerobic exercise training, starting gradually, has been shown to improve health-related quality of life (HRQOL), decrease pain intensity and improve physical function. Aquatic training is beneficial for improving wellness, symptoms, and fitness in adults with fibromyalgia. Exercise training (exercise performed against a progressive resistance) may improve function, pain, tenderness and muscle strength in women with FM.

Meditative movement therapies (MMT) - involving core elements of specific movements, meditative instruction and breath regulation- are considered as a complex intervention integrating concepts of mind and body, with physical, emotional and spiritual aspects. In recent years, there is abundant literature reporting benefits of MMT in various chronic pain conditions, including fibromyalgia. Qi Gong and Tai Chi have shown significant improvement regarding pain, sleep disturbances, fatigue, depression and HRQOL. Better outcomes are obtained when MMT is practiced daily, which may be challenging for FM patients. One recent study has shown that Tai Chi improves cardiac autonomic function, sympatho-vagal balance, pain, fatigue, strength and flexibility in women with fibromyalgia. Another study shows that Yoga may modulate abnormal pain processing in fibromyalgia, demonstrated by improvements in heat pain tolerance and pressure pain threshold. Balneotherapy (BT) (treatment based on thermal mineral water from natural springs) and hydrotherapy (HT) (normal water) are additional alternative interventions usually recommended in the management of FM. Studies of BT and HT in FM patients have shown improvement on pain and HRQOL, with no significant effects on depressive symptoms. How these therapies may improve FM symptoms is not fully understood, but effects on pain alleviation may be explained by hydrostatic pressure and effects of temperature on the nerve endings, as well as by muscle relaxation.

Cognitive Behavioral Therapy (CBT) aims to reinforce self-efficacy in managing symptoms of FM and plays a central role in the non-pharmacological management of FM. CBT improves physical functioning and pain, and reduced catastrophizing, by improving pain-related brain responses, as demonstrated in functional MRI studies. Other complementary and alternatives therapies that have demonstrated clinical benefit on symptoms of FM include hypnosis/ guided imagery, biofeedback and acupuncture. Brain neuromodulation constitute promising therapeutic options for FM patients, although current use is still limited by low availability and high costs. Optimal management of FM patients requires an integrated multidisciplinary approach beyond pharmacologic therapy, including education, exercise, psychological and complementary interventions, that must be tailored according to symptoms, patient's preferences and financial resources in order to ensure adherence to the treatment program as well as for improving outcomes.

IS-23

Medicating fibromyalgia in 2019: any news in the pipeline?

Piercarlo Sarzi-Puttini, Alberto Batticciotto, Daniela Marotto, Fabiola Atzeni ASST Fatebenefratelli-Sacco University Hospital, Milan; Rheumatology Unit, Ospedale del Circolo Varese; Rheumatology, Department of Medical Sciences and Public Health Assl Olbia, Olbia; Rheumatology Unit, University of Messina, Messina, Italy.

Fibromyalgia syndrome (FM) continues to pose an unmet need regarding pharmacological treatment and many patients fail to achieve sufficient relief from existing treatments (1). Recently published guidelines recommend the adoption of a symptom-based approach to guide pharmacologic treatment. Emerging treatment options for FM may be best differentiated on the basis of their effect on comorbid symptoms that are often associated with pain (e.g. sleep disturbance, mood, fatigue) (2). None of the currently available drugs are fully effective against the whole spectrum of FM symptoms, which seem to benefit from multidisciplinary management (3).

Various drugs have been recommended in the different guidelines, but none have been approved by the European Medicines Agency, and only three by the Food and Drug Administration (FDA): the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine and milnacipran, and pregabalin, which acts via the $\alpha 2\delta$ subunit of voltage-gated calcium channels. However, a significant number of patients do not respond adequately to these drugs or experience intolerable side effects (3).

The existence of subgroups of FM patients has been suggested by many studies and the heterogeneity of the condition may be responsible for the limited efficacy of pharmacological treatments (4, 5).

In observational, prospective, and longitudinal studies, patients frequently require and take multiple prescription drugs, although monotherapy would clearly be the optimal approach to treating FM (6, 7). However, there is no evidence that patients actually benefit from drug combinations: only few trials have investigated the combination of pregabalin and antidepressants, as well as combined treatment with amitriptyline (8).

The new formulations of older drugs include a controlled-release (CR) formulation of pregabalin, an extended-release (ER) formulation of gabapentin, and the sublingual TNX-102 tablet of low-dose cyclobenzaprine. Although evidence is scarce the once-daily formulations of these drugs are promising therapeutic options that should also improve patient compliance (9).

However, Tonix's sublingual oral cyclobenzaprine (TNX-102) was disappointing. Tonix evaluated TNX-102 in at least four FM trials and seven other studies. The trials indicated that TNX-102 did have its benefits, but it failed to reduce pain significantly in at least 30% of the FM patients taking it.

Mirogabalin is a gabapentinoid with significantly higher potency than pregabalin. In the three, 13-week, double-blind, global, phase 3 ALDAY clinical trials evaluating mirogabalin for the treatment of pain associated with FM, mirogabalin did not meet the primary efficacy endpoint to demonstrate a statistically significant reduction in the weekly average of worst daily pain score from baseline to Week 13. In Japan, the company submitted a marketing application only for treatment of peripheral neuropathic pain.

Ambroxol is a secretolytic substance, but may also potentially influence several pathophysiological mechanisms involved in fibromyalgia. First, ambroxol interferes with oxidative stress and influences cytokines and inflammation. Second, ambroxol blocks sodium channels, especially the tetrodotoxin-resistant (TTX-r) channel subtype Nav1.8, which is expressed particularly in spinal ganglion cells and in nociceptive, sensory neurons. Nevertheless, at this point the evidence basis for ambroxol is not strong enough for clinical recommendation (10).

There is no evidence that pure opioids are effective in fibromyalgia but there is some evidence that opioids with additional actions on the norepinephrine-related pain modulatory pathways, such as tramadol, can be clinically useful in some patients. Novel actions of low-dose opioid antagonists may lead to better understanding of the role of opioid function in fibromyalgia (11).

Even though current evidence is too scarce and weak to support the use of cannabinoids in FM, it would be interesting to investigate their potential role. The existing data are limited to the synthetic cannabinoids, nabilone, and dronabinol, but future studies should also investigate the role of the efficacy and long-term safety of other synthetic or natural cannabinoids (12). Evidence-based interdisciplinary guidelines give a strong recommendation for aerobic exercise and cognitive behavioral therapies. Drug therapy is not mandatory. Only a minority of patients experience substantial symptom relief with duloxetine, milnacipran, and pregabalin or with a combination of different drugs (13).

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IS-24

Cannabis for fibromyalgia: the great green elephant in the room

Silviu Brill

Director of Institute of Pain Medicine, Tel Aviv Medical Center, Israel.

In recent years, cannabis had been approved for medical use in more than 30 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.

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-25

Blueprint for “future fibromyalgia” conference

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

Fibromyalgia remains a project under construction. While decades of research as well as clinical experience have added greatly to our current understanding and appreciation of fibromyalgia, the true nature of the disorder and the scope of the problem remain elusive. Diagnostic criteria continue to evolve, reshaping both the clinical spectrum as well as the epidemiology and cultural understanding of fibromyalgia as a nosological entity. At the same time, cutting-edge research technologies continue to be developed, constantly opening new windows and new perspectives into the pathogenesis of fibromyalgia and chronic pain in general. Functional neuroimaging, next generation sequencing and epigenetics, as well as novel tools for inducing neuroplasticity, all may reshape fibromyalgia as we know it over the coming years.

Fibromyalgia continues to hold an unusual place among rheumatological disorders. While the major clinical symptoms of fibromyalgia, *i.e.* widespread musculoskeletal pain, fall squarely into the field of rheumatology, probably encompassing many of the very patients who would have been described in past generations as suffering from “rheumatism” of one kind or another, it has become ever more obvious that the underlying pathogenic mechanisms involved in initiating and perpetuating the fibromyalgia syndrome are connected more closely to dysfunctional processing within the central nervous system than to “rheumatological” tissues such as synovium and cartilage. Thus, fibromyalgia should better currently be addressed in similar strategies as are being applied to other complex CNS disorders, including depression. In this aspect it is noteworthy to pay attention to the inspirational “Research Domain Criteria” (acronym RDoC) which is being developed and implemented by the National Institute of Mental Health (1). This ambitious project is striving to integrate emerging findings from hitherto diverse fields of research such as genetics, physiology, network analysis and psychology in order to create a new matrix for classifying and diagnosing patients suffering from mental disorders. This approach, which conceptually may eventually replace the criteria – based taxonomies such as the DSM, aims at eventually reaching true individualized precision medicine. It is appealing to vision, that other complex conditions involving the CNS such as fibromyalgia, will eventually similarly be addressed. In such a system an individual patient would actually not necessarily need to be given an ICD – based label such as fibromyalgia, but would rather undergo extensive genetic (and epigenetic) profiling, including pharmacogenetic evaluation, as well as functional neuroimaging aimed at identifying abnormal patterns of connectivity; physiologic pain processing could also be incorporated such as assessment of conditioned pain modulation (CPM) and other patterns of pain processing. Psychological and cognitive assessment would also be incorporated as well as psycho-social evaluation. Ultimately, this process would culminate in a very personalized plan of treatment, combining optimal pharmacological agents together with non-pharmacological tools all aimed at alleviating pain, minimizing disability and restoring function.

This description may yet sound somewhat utopian at the current point in time. Currently, fibromyalgia patients are diagnosed based on criteria which change at a rather alarmingly rapid pace and often the diagnosis appears to be made by physicians not very well acquainted with the diagnostic criteria to begin with. Both over – diagnosis and under diagnosis are abundant and many misconceptions remain among both laymen as well as in the medical community, regarding what fibromyalgia is and what it is not. Patients are all too often frustrated to encounter lack of knowledge as well as disrespect and disbelief, all of which naturally impede clinical rapport and reduce any prospect for significant improvement. These predicaments can only gradually be overcome through better education and increased awareness.

It is in this perspective that one must regard the establishment of ongoing academic frameworks for dissemination of up-to-date scientific and clinical information regarding the fibromyalgia syndrome. While fibromyalgia has hitherto mainly been discussed and debated on the sidelines of major scientific venues centered on either rheumatology or pain, it has often been relegated to somewhat back scene setting within these forums. Establishing an ongoing tradition of scientific conferences focusing on fibromyalgia, which will showcase recent advances in this complex field and highlight areas of ongoing debate, is sure to attract broad attendance by both clinicians and researchers; moreover involving fibromyalgia patients within this endeavor is a highly productive stratagem which may help in increase patient engagement and decreasing the sense of alienation felt by many patients as well as in encouraging collaboration between patients and researchers for

reaching optimal results. In the aftermath the first international congress on controversies in fibromyalgia, held in Vienna, Austria in March 2019, the organizers hope to initiate an ongoing tradition of similar events to be held in additional locations helping to sketch at least the initial outlines of a roadmap for achieving the ambitious project that lays ahead, in order to bring relief to the immense number of individuals currently suffering from the fibromyalgia syndrome.

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IS-26

Is there a role for prevention or early diagnosis in fibromyalgia?

Piercarlo Sarzi-Puttini, Alberto Batticciotto, Daniela Marotto, Fabiola Atzeni

ASST Fatebenefratelli-Sacco University Hospital, Milan; Rheumatology Unit, Ospedale del Circolo Varese; Rheumatology, Department of Medical Sciences and Public Health Assl Olbia, Olbia; Rheumatology Unit, University of Messina, Messina, Italy.

It is well known that fibromyalgia is prevalent, difficult to manage, and associated with high costs, in health care and society in general. The current diagnostic and treatment pathway for patients with fibromyalgia (FM) is complex, and early and effective identification and appropriate treatment of FM remain a challenge in current clinical practice (1). Ideally, FM management involves a multidisciplinary approach with the preferable patient pathway originating in primary care but supported by a range of health care providers, including referral to specialist care when necessary (2). Recently published guidelines recommend the adoption of a symptom-based approach to guide pharmacologic treatment. Emerging treatment options for FM may be best differentiated on the basis of their effect on comorbid symptoms that are often associated with pain (*e.g.* sleep disturbance, mood, fatigue) (3).

Acute pain is of sudden onset and expected to last less than 3 months. Chronic pain is defined as ongoing or recurrent pain, lasting beyond the usual course of injury healing or more than 3 to 6 months. The development of chronic pain results from complex interactions between biological, psychological, and social factors. There is increasing evidence that the transition from acute to chronic pain (particularly FM) is associated with permanent neurophysiological transformations (*i.e.*, central sensitization, gliopathy, and an emotional shift in the brain circuitry involved in nociception) and genetic and epigenetic factors (4, 5). A variety of different conditions can play a role in the transition from acute to chronic pain: demographic aspects (*e.g.*, female gender and low socio-economic status), injury-related (*e.g.*, lower limb injury and compensable injury), autoimmune or neoplastic diseases, small fiber neuropathies, surgery (*e.g.*, mastectomy, thoracotomy, and amputation), psychological risk factors such as anxiety, depression, pain catastrophizing and pain-related fear. Because of the link between FM and exposure to stress, and because both the neuroendocrine and autonomic nervous systems could cause many of the symptoms of FM, these factors have been fairly extensively studied; however, these factors are now generally thought to play a role in some individuals, but not to be central pathogenic factors in all individuals with these conditions (6, 7).

The prevalence of FM varies from 2 to 5%, depending on the population sampled and the method of evaluation (8). The incidence of FM was determined in a population-based sample of Norwegian women between the ages of 20 and 49 years who were followed for 5.5 years. The incidence of FM among women who began the observation period without any complaints of musculoskeletal pain was 3.2%, corresponding to an average annual incidence of 583 cases/100,000 women between 20 and 49 years of age. For those with any self-reported pain at the beginning of the study, the incidence was 25% and risk factors for the development of FM included pain for 6 years or more, self-assessed depression, lack of professional education, and the presence of 4 or more associated symptoms, such as disturbed bowel function, unrefreshing sleep, paresthesia, and subjective swelling (9). In another cohort of 1,198 early arthritis patients followed by rheumatologists, the incidence of FM was 6.77/100 person-years in the first year after diagnosis of arthritis, and declined to 3.58/100 person-years in the second year. Pain severity and poor mental health predicted FM risk (10).

Why prevention is so difficult in potential FM patients? This is a list of some potential topics: 1) there is no biomarker; 2) we should treat any type of acute pain to prevent cronicity; 3) we do not know why central sensitiza-

tion occurs in some patients and not in others; 4) can we improve resilience or is it only genetically and/or environmentally determined? 5) what is the role of psychoaffective and/or personality problems in these patients?

We do not have an answer to these questions and we can only treat patients early both with non pharmacological or /and pharmacological armamentarium. We can teach the patient how to handle fibromyalgia (perceived self-efficacy in pain management and pain acceptance) but not how to get rid of it or even better how not to develop the syndrome in presence of risk factors. Long-term outcome data for FM are limited. Although available studies indicate that symptoms of FM often persist, many patients are able to identify strategies over time that can moderate symptoms (7).

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O-1 Neuro-Biological Underpinnings of Fibromyalgia and Centralized Pain

Autonomic dysfunction and fibromyalgia

Gisele Pickering, Nicolas Macian, Alexanne Achard, Jean-Michel Cardot, Bruno Pereira
Clinical Pharmacology, CPC/CIC Inserm 1405, University Hospital and Medical Faculty, France.

Background. Autonomic dysregulation is thought to contribute to the pathophysiology and symptoms of patients with fibromyalgia (FM), but there is a paucity of information on the non-invasive assessment of sudomotor function in FM, and on the links with central modulation of pain.

Objectives. Identify sudomotor function in FM patients vs controls, correlations with comorbidities and with the functionality of descending inhibitory pathways.

Methods. The study included 50 right-handed female FM patients (51±8 years old; disease duration 30±9.8 months) and 50 matched controls. The primary endpoint was electrochemical skin conductance (microSiemens (μS)) on hands and feet measured with Sudoscan (Impeto Medical, France). Secondary endpoints included anxiety, depression, social criteria, quality of life, sleep disorders (HAD, Beck, EPICES, Pittsburgh, SF12 questionnaires). A subgroup of 25 patients had Cold Conditioned Pain Modulation testing (CPM30 sec).

Results. Hand conductance was lower in patients (71.8±10.2 vs 74.7±10.1 μS, $p=0.003$), on the dominant hand, $p=0.03$. Patients were significantly impaired on all secondary parameters. No correlations were observed.

Conclusion: This study shows that sudomotor/autonomic function is significantly impaired in FM females especially on the dominant hand. This marker is however independent of the duration of disease. It does not correlate with central inhibition functionality, suggesting the additivity rather than causality of peripheral and central events in FM disease.

Reference

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O-2 Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

Correlation between fibromyalgia severity score and fitness for work: a cross-sectional study

Ayala Krakov^{1,2}, Shlomo Moshe^{1,2}

¹Occupational Medicine, Maccabi Healthcare Services, Israel.

²School of Public Health, Sackler Faculty of Medicine - Tel Aviv University, Israel

Background. Fibromyalgia significantly affects the quality of life, professional, social and personal performance of patients, causing disability. Several studies have found that fibromyalgia patients have decreased work fitness and are eligible for disability allowances, and that decreased work performance correlates with the severity of fibromyalgia symptoms.

Objectives. To examine the correlation between the diagnosed fibromyalgia severity score and the patient's fitness for work.

Methods: In this cross-sectional study patients' fitness for work was evaluated by an occupational physician and the ACR diagnostic criteria questionnaire. The data was then collected and statistically analyzed for correlation.

Results. We examined the correlation between various components of the questionnaire and found no correlation between loss of working capacity and any part of the questionnaire.

Discussion. In contrast with what is described in literature, we found no correlation between the severity of the condition as measured by the questionnaire and loss of working capacity.

The reason may lie with the limitations of our research:

- Homogeneity of the subject population
- The subjects were not selected randomly, but were people who had come to the occupational health clinic for a fitness of work evaluation
- Small sample size
- Socio-demographic variables, such as family support and the patient's relationship with their employer, were not taken into consideration since they could not be measured objectively.

Conclusion. In order to examine the issue further, more research with larger samples and more heterogenic populations is needed.

O-3 Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

Reconciling research fields in fibromyalgia: a proposed integrative model

Ana Margarida Pinto^{1,2}, Mariana Luís¹, Filipe Palavra^{3,6}, Afton Hassett⁴, Rinie Geenen⁵, José António Pereira da Silva^{1,6}

¹Rheumatology Department, Coimbra Hospital and University Centre, Portugal. ²Psychological Medicine Department, Faculty of Medicine, University of Coimbra, Portugal. ³Centre for Child Development, Neuropaediatric Unit, Coimbra Hospital and University Centre, Portugal. ⁴Department of Anesthesiology, University of Michigan, USA. ⁵Department of Psychology, Utrecht University, The Netherlands. ⁶i.CBR - Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine, University of Coimbra, Portugal.

Background. Current research in fibromyalgia (FM) seems to adhere to one of two separate paradigms – neurophysiological vs psychological, failing to provide an integrated account of the main findings related to both fields. This lack of integration hinders not only progress in our understanding of FM, but also the effectiveness of potential interventions.

Objectives. The main objectives of this study were to: a) review literature in order to identify and summarize main domains and features of FM; b) develop an integrative, multi-level model informed by the available evidence; and c) shed light upon the dynamic interplay between body and mind.

Methods. A model was developed based on an extensive review of the available literature and clinical insights from the interdisciplinary team. The model was repeatedly refined by observations and recommendations of experts in the field.

Results. We propose that FM is fueled by the chronic hyperactivation of the threat/defense system (due to multiple factors, including early-traumatic experiences and dispositional features). This leads to multiple biases that bolster the perceived salience and dangerousness of everyday events and cross-amplifies alarm signals, such as pain. At the core of this self-sustaining process is hyperactivity in the salience neural network.

Conclusion. Although further research is needed to test and fine-tune the proposed model, it seems promising as a guide for future research and clinical management of FM. Studies investigating the efficacy of psychosocial interventions designed to diminish the dominance of the threat-system and promote soothing mechanisms seem warranted.

O-4 Genetics, Pharmacogenetics and Epigenetics

Single-base resolution analysis of DNA methylation in fibromyalgia women compared with their healthy sisters

Maria Carla Gerra¹, Inge Søkilde Pedersen², Davide Carnevali³, Alberto González-Villar⁴, Yolanda Triñanes⁴, Marina Pidal-Miranda⁴, Lars Arendt-Nielsen¹, María Teresa Carrillo-de-la-Peña⁴.

¹Department of Health Science and Technology, School of Medicine, Center for Sensory-Motor Interaction (SMI), Aalborg University, Denmark.

²Molecular Diagnostics and Department of Clinical Medicine, Aalborg University Hospital, Aalborg University, Denmark.

³Department of Chemistry, Life Sciences, and Environmental Sustainability (UNIPR), University of Parma, Italy.

⁴Department of Clinical Psychology and Psychobiology, University of Santiago de Compostela, Spain.

Background. Fibromyalgia (FM) is a pathological condition characterized by chronic widespread pain and comorbid symptoms. Its multifactorial nature makes complex the diagnosis, the identification of effective therapies and the understanding of causative mechanisms. Biomarkers detection could contribute to improve its controversial management.

Objectives. The present pilot study aims to investigate DNA methylation in targeted genome regions of eight FM women compared to their healthy sisters. Epigenetic biomarkers could clarify the relationship between experienced stress and FM development.

Methods. Methylation status was tested in leukocytes DNA by bisulfite sequencing of 240.134 kbp (Agilent SureSelect^{XT}Target Enrichment for Illumina Multiplexed Sequencing), including CpGs promoters of genes previously found associated with FM or related symptoms. Chronic pain, sleep problems and depression were explored utilizing FIQ, WPI, SS scale, VAS, PSQI and BDI.

Results. No significantly differentially methylated regions comparing FM

patients and their sisters were found; few differentially methylated cytosines were identified with p-value 0.05, but none of them survived the correction for multiple comparisons.

Conclusion. This is the first study profiling DNA methylation patterns at single-base resolution in targeted regions of FM patients and their sisters. The similar trend in DNA methylation does not support that FM is associated to epigenetic changes and invites to carefully consider previous epigenetic findings. Nevertheless, given the small sample size, further genome-wide researches correlating genetics with potential stressful life events might reveal new perspectives in FM pathogenesis.

Reference

REN K, BAIG: An Overview of Epigenetic Correlates of Human Chronic Pain Conditions. Vol 7. Elsevier Inc.; 2019.

O-5 Treatment of Fibromyalgia

Fibromyalgia and chronic fatigue clinic: The Mayo Clinic experience

Christopher Aakre, Connie Luedtke, Ryan Eastman, Tony Chon. Department of Medicine, Mayo Clinic, USA.

Background. Fibromyalgia and chronic fatigue cause significant reductions in quality of life. Interdisciplinary programs focused on patient education, non-pharmacologic and pharmacologic approaches are effective initial steps to reduce symptom burden.

Objectives. In this report, we describe Mayo Clinic's experience with an outpatient interdisciplinary Fibromyalgia and Chronic Fatigue Clinic (FCFC).

Methods. Mayo Clinic - Rochester FCFC, established in 1999, serves local and non-local patients. Initially, the program spanned multiple-days; over time the program was compressed to address time- constraints of non-local patients. The current program entails: 1) a 60 minute RN evaluation, 2) a 90 minute physician consultation for diagnosis confirmation and patient education; and 3) two half-day small-group sessions led by RNs with specialized training in fibromyalgia and chronic fatigue management. Each small group contains between 10-20 participants, including one guest per patient. Referral to Pain Rehabilitation is available for patients with refractory symptoms after initial management.

Results. The FCFC is staffed by 10 fibromyalgia-focused RNs and a rotating group of 16 general internal medicine physicians and one physician assistant. From November 2017 through October 2018, 1786 patients were seen in consultation and 1173 patients attended the small group education and management class.

Conclusion. Our comprehensive outpatient consultation and one-day treatment program is effective for delivering fibromyalgia/chronic fatigue education and initial management principles and identifying patients who would benefit from more intensive interventions.

O-6 Treatment of Fibromyalgia

Ba-Duan-Jin alleviates pain and fibromyalgia-related symptoms in patients with fibromyalgia: results of a pilot randomized controlled trial

Juan Jiao¹, Russell Irwin², Wang Wen³, Wang Jing^{1,4}, Zhao Ya-yun¹, Zhang Rou-man¹, Quan Jiang¹.

¹Rheumatism Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China. ²Consulting, Fibromyalgia Research and Consulting, USA.

³Consulting, JCW Education Consulting, USA. ⁴Clinical evaluation center, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China.

Background. Fibromyalgia is a chronic debilitating musculoskeletal pain syndrome. Currently, there has been a growing interest in the development of non-pharmacological therapies. Ba-Duan-Jin is an ancient Chinese exercise for health promotion yet easy to learn. To evaluate the effectiveness of Ba-Duan-Jin in managing fibromyalgia symptoms experienced by Chinese patients.

Methods. In this randomized, usual therapy-controlled study, patients with fibromyalgia practiced Ba-Duan-Jin for one hour, twice a week for 12

weeks. The primary outcome measure was change in the Visual Analogue Scale for pain (pain VAS). Secondary outcomes included the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Assessment of Fatigue (MAF), the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI), the Perceived Stress Scale (PSS), the Tender Points Count (TPC). These measures were assessed at Baseline and after 4, 8, and 12 weeks. The Patient Global Impression of Change (PGIC) was collected at week 12. The Mann-Whitney U test was performed using the intention-to-treat population.

Results. A total of 62 fibromyalgia patients were randomized to the Ba-Duan-Jin or the control groups. For the Ba-Duan-Jin group, significant improvement in pain VAS, FIQ, MAF, PSQI, and TPC were documented at weeks 4 ($P \leq 0.046$) and continued at week 8 ($P \leq 0.003$). At week 12, all of the outcome measures including BDI and PSS exhibited significant improvement ($P \leq 0.004$), and PGIC ratings were significantly better ($P = 0.001$). No significant changes in the control group were observed.

Conclusion. This study suggests that Ba-Duan-Jin exercise has the potential to be a valuable non-pharmacological intervention among Chinese fibromyalgia patients.

O-7 Treatment of Fibromyalgia

Hospitalisation in fibromyalgia: in-patient treatment characteristics, costs and geographical variation in England

Anushka Soni^{1,2}, Andrew Segerdahl², Stephanie Santos-Paulo², Kassim Javaid¹, Rafa Pinedo-Villanueva¹, Irene Tracey².

¹Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford, UK.

²Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, UK.

Treatment of fibromyalgia occurs primarily in the out-patient setting, but historical data suggest significant direct medical costs may arise from hospitalisation. We aimed to describe present-day in-patient care associated with fibromyalgia and myalgia within the English National Health Service.

This observational study used aggregate data for April 1st 2014 to March 31st 2018 inclusive from Hospital Episode Statistics Admitted Patient Care, which provides data for all hospital admissions across all the clinical commissioning groups (CCGs), in the NHS in England. Hospital admissions were described in terms of patient demographic, the class, number, duration and cost of admissions, and procedures conducted, over the last four financial years. Geographical trends of hospitalisation were also visualised. An estimated 46,050 patients were admitted during the study period. The majority were female (22,525.00/31,250.00, 72%), with peak age between 45 and 55 years. Day case care was most prevalent (60%), with elective admissions representing the largest overall economic burden. Procedures often incorporated radiological input for diagnostic or therapeutic purposes, and/or therapeutic infusions or musculoskeletal injection therapy. Marked variation in annual costs was seen across the country ranging from under £25,000 in some CCGs to over £100,000 in others; this persisted after normalising for overall inpatient activity in each CCG.

This study highlights the potential disparity between current treatment recommendations, which are predominantly delivered in an out-patient setting, and current practice. Furthermore marked geographical variation, which may be related to factors such as socioeconomic status or provision of pain management programmes across the country, has been demonstrated.

O-8 “Transparent Pain”: How Society Deals with Fibromyalgia

Gender stereotypes and lack of social legitimization of fibromyalgia in Spain

Erica Briones-Vozmediano

Department & Faculty of Nursing and Physiotherapy, University of Lleida, Spain.

Background. Fibromyalgia (FM)’s lack of recognition is still common in policies, the professional and clinical fields, and the affected people’s social circle.

Objectives. To explore how FM is socially constructed as a health problem in Spain.

Methods. Review and analysis of health policies, parliamentary initials, newspapers and personal interviews with women and men diagnosed with Fibromyalgia and health professionals.

Results. The emergence and social visibility of FM as a health problem is linked to gender stereotypes. This in turn has an influence on how FM is socially considered, how health professionals approach such patients in the clinical encounters, and how patients experience the consequences of the disease. Health policies have not yet taken the emergence of this recently diagnosed disease into account. The existence of a gender-biased patient health care attention could result in a lack of effort in diagnosis and unbalanced concessions in applications for unfitness for work and disability allowances. Health professionals are aware of the lack of legitimization existing on a social level, and, above all, prejudices among the health professional collective. Women affected by FM experience such rejection as a barrier to effective health coverage, and men feel ashamed for suffering a woman’s disease.

Conclusion. The increase of training and sensitization of health professionals is needed to improve the management of FM patients, together with the implementation of specific policies for FM.

Reference

BRIONES-VOZMEDIANO E: The social construction of fibromyalgia as a health problem from the perspective of policies, professionals, and patients. *Global Health Action* 2016; 9: 31967.

P-1 Neuro-Biological Underpinnings of Fibromyalgia and Centralized Pain

Immunopsychiatry in fibromyalgia and chronic fatigue syndrome

Egil A Fors², Solveig Klæbo Reitan^{1,3}, Nina Groven¹.

¹Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Norway.

²Department of Public Health Sciences and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Norway.

³Department of Psychiatry, St. Olav's Hospital, Norway

Background. Fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS) patients often experience similar symptoms as those seen in inflammation. Depression is often associated with FM and CFS and peripheral inflammation. Low-grade inflammation can be measured in blood by hsCRP.

Objectives. Explore the relationship between low-grade inflammation (hsCRP) and depression, and study whether hsCRP differs between FM, CFS and healthy controls.

Methods. The association between hsCRP and depression (HADS) were assessed by Spearman's rho in adult, females diagnosed with FM ($n=7$) or CFS ($n=49$) according to the ACR1990 and Fukuda criteria, respectively, and healthy controls ($n=54$). Student-t-tests were applied in pairwise group comparisons of low-grade inflammation (hsCRP) compared to healthy controls and controlling for age and BMI. The Kruskal-Wallis and Mann-Whitney U tests were used to compare depression scores between the three groups.

Results. There were no significant correlation between hsCRP and depression scores. Depression and hsCRP scores in FM and CFS were significantly higher than in the control group ($p=.000$ and $p=.003$, respectively) but did not differ from each other. The differences remained significant after controlling for age and BMI.

Conclusion. We found no significant correlation between hsCRP and depression, however FM and CFS had slightly elevated levels of hsCRP compared to healthy controls, but no difference between themselves

Reference

GROVEN N, FORS EA, IVERSEN VC, WHITE LR, REITAN SK: Association between cytokines and psychiatric symptoms in chronic fatigue syndrome and healthy controls. *Nord J Psychiatry* 2018 Jul; 31: 1-5.

P-2 Neuro-Biological Underpinnings of Fibromyalgia and Centralized Pain

Lack of vitamin D among fibromyalgia patients

Pirjo Lindfors¹, Kari Nurmi⁴, Henna Karvonen³, Sami Leppämäki².

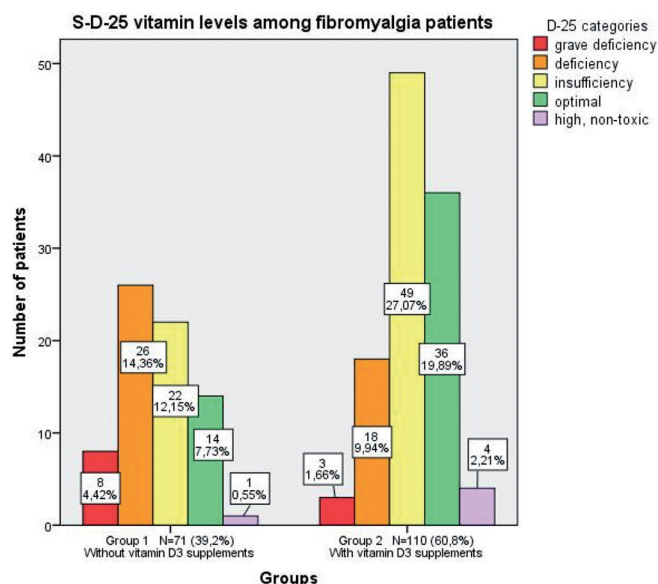
¹Clinicum, Department of Public Health, Helsinki University, Finland. ²Department of Psychiatry, Helsinki University Central Hospital, Finland. ³Department of Clinical Nutrition, Helsinki University Central Hospital, Finland. ⁴Faculty of Education, Helsinki University, Finland.

Background. Lack of vitamin D has been shown to be connected to fibromyalgia, but the evidence is controversial.

Objectives. The aim was to study the vitamin D levels (S-D-25) among fibromyalgia patients.

Methods. In a retrospective study we analyzed the laboratory samples of all fibromyalgia patients ($N=181$) from two central hospital pain clinics that had had their S-D-25 measured in the beginning of the treatment during 2008 and 2016.

Results. The majority of the tested were women 87.3 % (158). The mean age of the tested was 47.5 years. 39.2 % (71) of them were not taking vitamin D supplements. Their mean S-D-25 was 54 nmol/l indicating insufficiency. 11.3 % had grave deficiency with S-D-25 between 7 and 24 nmol/l. 36.6% had deficiency (25-49 nmol/l), 31.0% had insufficiency (50-74 nmol/l) and 19.7% had an optimal level (75-135 nmol/l). All patients with a slightly darker skin color had S-D-25 comparable to rickets or osteomalasia. 60.8 % (110) had been taking vitamin D supplements before testing. Their mean vitamin D level was 73 nmol/l. 2.7 % of them had grave deficiency, 16.4 % deficiency, 44.5 % insufficiency, 32.7 % optimal levels and 3.6 % had high, but not toxic levels (135-224 nmol/l). The tests were taken any time of the year, also during the three summer months.



Conclusions. Most fibromyalgia patients have an insufficient vitamin D level. Levels should be investigated and supplementation tailored accordingly.

Reference

HOLICK MF, CHEN TC: Vitamin D deficiency. *Am J Clin Nutr* 2008; 87(4): 1080-1086.

P-3 Neuro-Biological Underpinnings of Fibromyalgia and Centralized Pain

Brain mechanisms involved in emotional influences on working memory dysfunctions in fibromyalgia patients: an fMRI study

Francisco Mercado¹, Vanesa Soto³, Paloma Barjola¹, Irene Peláez¹, Ivan Panyavin³, Roberto Fernandes¹, David Ferrera³, Francisco Gómez², Antonio Oliviero³.

¹Psychobiology, Faculty of Health Sciences, Universidad Rey Juan Carlos, Spain.

²Embryology and Human Anatomy, Faculty of Health Sciences, Universidad Rey Juan Carlos, Spain. ³Neurophysiology, National Hospital for Paraplegics, Spain

Working memory dysfunction has been considered as one of the most disturbing symptoms in fibromyalgia (FM), since it could provoke a functional impact even more important than pain itself. Recent neuroimaging studies have showed abnormal brain activation in fibromyalgia patients when they were performing in a working memory task. However, underlying dysfunctional brain mechanisms related to emotional influences on working memory processes are still unknown up to date. A total of 33 women (sixteen fibromyalgia patients- FM- and seventeen healthy volunteers -HV-) took part in the experiment. Neural activity related to working memory processes was measured while participants performed in an n-back task involving a sequence of letters. Two difficulty levels were set (1-back and 2-back). A block design was used where each experimental condition was also determined by its emotional meaning (emotional context: positive, negative, painful and neutral). BOLD signal showed a decrease within dorsolateral prefrontal cortex (BA9) in FM patients. This result was only found for the 2-back task condition. Additionally, an increase in BOLD signal was found for FM patients when either a painful or negative context was presented. Present results indicated that experimental conditions with high-demand of working memory resources (2 back) could explain the lower activity of prefrontal regions supporting proposals where these cortical regions would be involved in the main cognitive dysfunctions of FM patients. Finally, negative emotional contexts modulated brain activation of visual regions. Nevertheless, further research is needed to fully understand and delimitate this impairment.

P-4 Neuro-Biological Underpinnings of Fibromyalgia and Centralized Pain

Is fibromyalgia associated with Hyposmia? Relations between olfactory and cognitive functioning

Cecilia Peñacobá, Lucía Sanromán, Sheila Blanco, Soledad Pérez-Calvo, Lilian Velasco.

Medicine and Surgery, Psychology, Preventive Medicine and Public Health and Medical Microbiology and Immunology, Rey Juan Carlos University, Spain.

Background. Fibromyalgia is a commonly encountered chronic pain disorder characterized by widespread pain and tenderness, which is often accompanied by affective and cognitive symptoms.

Previous research has found impaired olfactory function and cognitive deficits in patients with fibromyalgia. The relationship between cognitive and olfactory functioning has not been studied in fibromyalgia patients.

Objectives. 1) to analyze the differences between cognitive and olfactory functioning in a sample of women with fibromyalgia in comparison to women without a chronic pain disease, 2) to analyze the relations between cognitive ("objective measure" by WAIS and "subjective measure" by The Memory Failures of Everyday -MFE-) and olfactory functioning ("objective measure" by CCCRC score and "subjective measure" by "subjective measure").

Methods. A transversal study was conducted with fibromyalgia patients (n=146) and women without a chronic pain disease (n=122). Descriptive analysis, t de Student test and chi-square tests were conducted.

Results. There were significant differences in perceptive organization and processing speed, and in odour identification, odour threshold and total CCCRC score, the lower scores were for fibromyalgia patients. Among the fibromyalgia patients there were significant differences in the verbal scale, the manipulative scale, the total scale and processing speed between normosmic and hyposmic patients. There is a significant negative relationship between subjective complaints and olfactory function.

P-5 Neuro-Biological Underpinnings of Fibromyalgia and Centralized Pain

Muscle activity, pain and anxiety in fibromyalgia

Teemu Zetterman^{1,2}, Ritva Markkula¹, Juhani V. Partanen³, Teemu Miettinen¹, Ann-Mari Estlander¹, Eija Kalso^{1,4}

¹Pain Clinic, Helsinki University Hospital, Finland. ²Health Centre, City of Vantaa, Finland. ³Clinical Neurophysiology, HUS, Imaging Centre. ⁴Clinicum, Helsinki University, Finland

Background. The pathophysiology of fibromyalgia (FM) involves changes in pain processing in the central nervous system (CNS). (1) Also, FM patients have displayed both hypo- and hyperactivity and disturbed regional activation cycle within muscles. (2-4) The research is still lacking on whether central nervous system changes might be caused or aggravated by peripheral pain signals from the muscles.

This is the first stage of our extensive study of muscle activity and muscle metabolism in FM. Here, we explore how psychological factors and cognitive stress affect muscle function in FM.

Methods. 51 women aged 18 – 65 years with FM were recruited from both primary and secondary care health care with 31 healthy female age-matched controls.

Data on background and psychological factors including the State-Trait Anxiety Inventory (STAI) were collected. The subjects underwent a surface electromyography (sEMG) recording in a seated position with five four-minute phases of alternating relaxation and induced stress (mental calculation). Finally, maximal isometric contractions of the recorded muscles were performed to detect the maximum sEMG amplitude (sEMGmax) for each subject to determine the sEMG-sEMGmax ratio (%EMG).

Preliminary results. The FM patients showed 2.57 -fold elevation in %EMG in comparison to controls ($p = 0.001$). Pain intensity correlated to %EMG ($r = 0.373$, $p = 0.001$). Both pain intensity and %EMG correlated to state anxiety (STAI-A) ($r = 0.669$, $p = 0.001$ and $r = 0.494$, $p = 0.001$ respectively).

Conclusions. The results provide support for previous findings that both anxiety and muscle function are likely to mediate pain sensation in FM.

P-6 Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

Development and Validation of the Simple Fibromyalgia Screening (SIFIS) Questionnaire for improving the recognition of fibromyalgia in daily practice

Fausto Salaffi, Marco Di Carlo, Giacomo Beci, Sonia Farah, Martina Schettino.

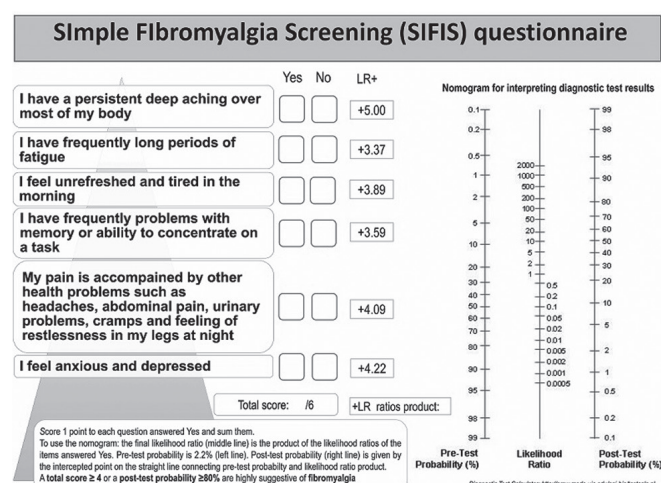
Università Politecnica delle Marche, Dipartimento Scienze Cliniche e Molecolari, Rheumatological Clinic, Ospedale "Carlo Urbani", Italy.

Introduction. To develop and validate a new self-administered screening tool, called Simple Fibromyalgia Screening (SIFIS) questionnaire, for the detection of FM in daily practice.

Method. The development of the SIFIS followed five principal steps: identification of a specific patient population, item pool development, item reduction, test of the provisional questionnaire, and validation study. The item generation was carried out by a review of the literature. Thirty three items were identified, and a survey was performed among 139 physician specialists. The frequency importance product allowed to select the most six significant items. Validation study was conducted, aiming to calculate the post-test probability of presence of FM, by applying the Bayesian Analysis Model method.

Results. 230 patients filled the SIFIS questionnaire. Likelihood ratios for individual parameters varied between 3.37 and 5.00. Of the six items of the SIFIS, the best positive likelihood ratio (LR+) was found in item 1 (LR+ 5.00), exploring persistent pain, and in item 5 (LR+ 4.09) and item 6 (LR+ 4.22), two questions exploring inflammatory pain accompanied by other health problems and mood (anxiety and depression), respectively. Fatigue (LR+ 3.37), sleep disorders (LR+ 3.89) and fibrofog (LR+ 3.59) gave similar results. The presence of four of six items gave a post-test probability $\geq 80\%$ (range from 81.8% to 87.1%). To calculate the final score a mobile APP was successfully created.

Conclusion. The SIFIS questionnaire is a useful tool that can be used as potential screening classification surrogate to the ACR criteria in daily practice. This tool needs further validation.



P-7 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Patients' and practitioners' views and experiences of chronic widespread pain (fibromyalgia) and its management in the UK and Libya

Sedik Abokdeer, Professor Nicola Adams, Jenni Naisby.
Department of Sport Exercise and Rehabilitation, Sedik Abokdeer, UK.

Background. Fibromyalgia syndrome is a common chronic pain associated with a significant financial burden on healthcare providers. Factors such as pathophysiology, variability in diagnosis and clinical management approaches made the decision about the existence, as distinct clinical entity is debatable (Wolfe, *et al.*, 2010).

Objectives. This research aimed to capture patients and practitioners views of fibromyalgia and its management.

Methods. The convergent parallel study involved two phases. Phase I involved 12 semi-structured interviews with FM patients. They were recruited from the fibromyalgia self-help group in the North East region of England. Data were analysed using Framework analysis. Phase II comprises of a national health and medical professionals survey the British Pain Society and medical professionals in Libya. Data were analysed using SPSS 8 software.

Results. The findings showed a lack understanding by health and medical professionals and the general public of management of the condition and the emotional and physical impact of FM. Lack of understanding often led participants to avoid going back for further medical treatment. The quantitative analysis reported an increased number of diagnosed FM patients. Treatment approaches in both countries were similar and focused primarily focused on exercise and education, with CBT being more common in the UK. Participants exhibited a similar opinion about the psychological impact of FM. A significant difference ($p=0.05$) in the opinion about the active management approaches should aggravate pain temporarily in order to achieve functional gains.

Conclusions. The results indicate the high physical and emotional impact of fibromyalgia.

P-8 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Comparison of fibromyalgia prevalence in axial spondyloarthritis and psoriatic arthritis and its relationship with disease activity and functional status

Ivanka Marinović¹, Jadranka Morović-Vergles², Jure Aljinović¹, Mirela Stipić¹, Izabela Baničević¹, Dušanka Martinović Kaliterna³.

¹Department of Physical Medicine and Rehabilitation with Rheumatology, Clinical Hospital Center Split, Croatia.

²Department of Immunology and Rheumatology, Clinical Hospital Dubrava, Croatia.

³Department of Clinical Skills, School of Medicine in Split.

Background. Fibromyalgia (FM) is very common clinical problem in inflammatory rheumatic diseases. Concomitant fibromyalgia may influence on disease activity, functional status and quality of life, and its recognition is important for the management of these diseases.

Objectives: The aim of this study was to determine the frequency of FM in patients with axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) and to evaluate the effect of fibromyalgia on the outcome measures of these diseases.

Methods. This two-center cross-sectional study included patients aged ≥ 18 years, who were diagnosed with axSpA, PsA and FM by the rheumatologist. Patients with axial form of psoriatic arthritis were excluded. Clinical assessments included BASDAI and BASFI for axSpA group, HAQ-DI and DAS28 for PsA group. VAS and the Beck Anxiety Inventory (BAI) were performed for both group.

Results. The study included 22 axSpA patients and 22 PsA patients. Out of 44 patients, 20 (45.5%) were males and 24 (54.5%) were females, with a mean age of 51 ± 11.7 . Fibromyalgia was present in 18.18% of axSpA patients and in 22.73% of PsA patients ($p=0.500$). No difference in the prevalence of FM was found between male and female ($p=0.332$). BASDAI and DAS28 scores were higher in patients with coexisting FM ($p=0.001$). Patients with FM had higher values of BASFI ($p=0.001$) and HAQ-DI indexes ($p=0.003$), higher VAS pain score ($p=0.001$) and higher BAI anxiety score ($p=0.007$).

Conclusion. Patients with axSpA and PsA with concomitant FM had higher disease activity, a worse functional status, more severe pain and higher levels of anxiety.

P-9 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Fibromyalgia: a descriptive study on the cognitive and behavioural profile

Cristina Fonte³, Vittorio Schweiger^{1,2}, Valentina Varalta³, Alvisè Martini¹, Massimo Parolini¹, Marialuisa Gandolfi^{3,4}, Enrico Polati^{1,2}, Nicola Smania^{3,4}, Alessandro Picelli^{3,4}

¹Azienda Ospedaliera Universitaria Integrata (AOUI) of Verona, Pain Therapy Centre, Italy. ²University of Verona, Department of Surgery, Dentistry, Paediatrics and Gynaecology, Italy. ³Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Neuromotor and Cognitive Rehabilitation Research Centre (CR-RNC), Italy. ⁴Azienda Ospedaliera Universitaria Integrata (AOUI) of Verona, UOC Neurorehabilitation, Italy.

Introduction. Fibromyalgia (FM) is characterized by widespread pain, fatigue, cognitive deficits, sleep disorders, anxiety, depression and others somatic disorders. Although different etiological and pathopsysiological hypothesis, this syndrome is still an obscure pathology.

Objectives. First aim is to draft a cognitive-behavioural profile of FM patients. The second is to explore a possible relationship between cognitive, psychological and motor performances in these patients.

Methods. We recruited 10 FM patients from the Pain Therapy Centre of AOUI of Verona. Inclusion criteria were: female, age between 20-65 years old, no evidence of psychiatric or rheumatologic disease or dementia. Patients were assessed, with a specific cognitive battery (TMT, PASAT, Digit Span, Span Reversal, Rey Auditory Verbal Learning Test, Corsi's Block Tapping Test, Listening Span Test), a behavioural battery (STAI-Y1 e Y2, Brief Cope, Young Schema Questionnaire) and Timed Up and Go.

Results. Data show 60% of patients with pathological scores at least in one attention test and in one memory test. In addition 60% feel moderate state anxiety and 70% of them also feel moderate trait anxiety. 80% of women reveal significant depression but only 20% show dysfunctional coping strategies. The maladaptive behavioural schema more present are: tendency to self-sacrifice, excessive standards, feeling socially excluded and neglected, excessive vulnerability and submission. The results underline significant correlations between attention deficits and psychological aspects such as state anxiety, feeling of failure and submission.

Conclusion. This study reveals that FM patients have a common cognitive-behavioural profile and there is a correlation between several psychological symptoms and cognitive deficits.

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

The clinical characteristics, symptom severity and quality of life in patients with fibromyalgia in China – a pilot study

Juan Jiao, Ya-yun Zhao, Hong Xiao, Quan Jiang.
Rheumatism Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China.

Background. There was not much epidemiology information of fibromyalgia in China.

Objectives. To observe clinical characteristics, fibromyalgia-related symptom severity and quality of life (QOL) in Chinese fibromyalgia patients.

Methods: One hundred twenty-four patients with fibromyalgia were included, and their demographic characteristics, social variables were collected. The FIQ, pain VAS, the Multidimensional Fatigue Inventory (MFI), the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI) and the Perceived Stress Scale (PSS), and SF-36 were also completed. They were divided into three-age group of young (≤ 39 years), middle-age (40-59 years), and older (≥ 60 years).

Results. The means of age, symptom duration, and FIQ total score among those 124 patients was 49.4 years (SD 10.8), 47.8 months (SD 65.9), and 49.7 (SD 19.1), respectively. The majority were women (107, 86.3%). A

percentage of 30.6, 46.8, 98.2, and 80.6 patients reported mild pain, no or minimal depression, normal or a little higher perceived stress, and good or normal sleep quality, respectively. There were 32 (25.8%), 73 (58.9%), and 19 (15.3%) patients in the young, middle-aged, and older groups. Pairwise comparison found the young and middle-age patients were associated with worse mental QOL ($P \leq 0.017$).

Conclusion. The demographic characteristics were similar in Chinese fibromyalgia patients from those abroad. The symptom severity was relatively mild and the psychological status was good in Chinese fibromyalgia patients. Patients younger than age of 60 years had severer fibromyalgia symptoms and worse QOL scores, especially in the aspects of mental health.

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

Comorbidity of fibromyalgia with rheumatic diseases

Przemysław Keczmer¹, Agnieszka Krawczyk-Wasielewska¹, Sławomir Jeka², Bogdan Batko³, Wojciech Romanowski⁴, Mateusz W. Romanowski⁵, Ewa Mojs⁶, Włodzimierz Samborski¹

¹Chair of Rheumatology and Rehabilitation, Poznań University of Medical Sciences, Poland. ²Clinical Department of Rheumatology and Connective Tissue Diseases, Nicolaus Copernicus University, Collegium Medicum, Poland. ³Rheumatology Clinic, J. Dietl Specialist Hospital, Poland. ⁴Rheumatological Centre, Rheumatological Centre, Poland. ⁵Chair of Rehabilitation and Physiotherapy, Poznań University of Medical Sciences, Poland. ⁶Chair and Department of Clinical Psychology, Poznań University of Medical Sciences, Poland.

Background. Fibromyalgia (FMS) is one of the most common causes of generalized pain and can coexist with other rheumatic diseases.

Objectives. The purpose of this study was to evaluate the prevalence of FMS in patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA).

Methods. The study included 69 patients with RA diagnosed according to the ACR/EULAR 2010 criteria and 38 patients with spondyloarthritis (17 ankylosing spondylitis and 21 Psoriatic Arthritis) diagnosed according to the modified New York criteria and CASPAR criteria respectively. A total of 107 participants completed the 2016 fibromyalgia survey questionnaire.

Results. The study included 69 patients with RA (15 males and 54 females with mean age 53.94 ± 12.85 years). Second group counted 38 patients with SpA (19 males and 19 females with mean age 47.52 ± 15.21 years). FMS was diagnosed in 24.6% (17 out of 69) RA patients predominately in females 13 (76.5%) versus male 4 (23.5%). The prevalence of FMS in SpA group was 18.42% (7 out of 38) predominately in females 5 (71.4%) versus male 2 (28.6%).

Conclusion. FMS is a frequent comorbidity in patients with RA compared to SpA. FMS prevalence is relatively higher in females in rheumatic diseases patients. Concomitant fibromyalgia may often complicates patient's management and may have influence on qualification criteria to biologic therapy.

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

Validity and reliability of the 2010 ACR preliminary diagnostic criteria for fibromyalgia syndrome in Turkish patients

Çağrı Atik², Yeşim Kurtaiş Aytür¹

¹Physical Medicine & Rehabilitation, Ankara University Faculty of Medicine, Turkey.

²Physical Medicine & Rehabilitation, Atatürk State Hospital, Turkey

Objective. To investigate the reliability and validity of 2010 American College of Rheumatology (ACR) Preliminary Diagnostic Criteria.

Methods. 100 FS patients diagnosed by 1990 ACR classification criteria with expert opinion and 100 controls, diagnosed with chronic inflammatory arthritis, were enrolled in the study. All participants were assessed by 2010

ACR criteria and for other characteristics besides Fibromyalgia Impact Questionnaire (FIQ) and Beck Depression Inventory (BDI). All assessments were done two times, one week apart by the same assessor. Necessary statistics were performed.

Results. There were no statistical differences between FS and control groups regarding demographics. VAS-pain, fatigue, sleep, number of tender points, FIQ, BDI and, WPI and SSS scores were significantly worse in FS group. The agreement between 1990 and 2010 ACR criteria for diagnosis was good. The sensitivity and specificity of 2010 ACR were 97% and 66%, respectively, and ROC analysis showed the diagnostic values of WPI and SSS to be statistically significant in FS. The consistency of 2010 ACR criteria was significantly high between assessments. Positive correlations were observed between FIQ, WPI and SSS.

Conclusion. This study demonstrated the validity and reliability of the 2010 ACR preliminary diagnostic criteria for FS in a group of Turkish patients, but the low specificity may hinder its use. This finding supports the use of new criteria after testing in a similar way in a similar population and the importance of clinicians' clinical decision.

P-13 Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

Frequency of fibromyalgia syndrome in patients admitted to a university hospital outpatient clinic with musculoskeletal complaints - preliminary results

Aysun Genç, Gülperi Isazade, Seçilay Güneş, Yeşim Kurtaiş Aytür.
Physical Medicine & Rehabilitation, Ankara University Faculty of Medicine, Turkey.

Background. Fibromyalgia Syndrome (FS) is thought to be underdiagnosed frequently in patients presenting with chronic musculoskeletal pain.

Objectives: In this study, it was aimed to determine the frequency of FS in patients admitted to a university hospital PM&R department with musculoskeletal complaints.

Methods. In this cross-sectional study all patients who agreed to participate, filled out a survey including demographics and clinical characteristics of their complaint including duration, site, pain level, WPI (Widespread Pain Index) and SSS (Symptom Severity Scale) of ACR 2016 FS diagnostic criteria, and quality of life (EuroQoL-5D-5L). Data was analysed by descriptive and frequency analysis and independent sample comparisons.

Results. 185 patients (82% female, mean age 46; 17-87 yr) out of 230 completed the survey. Mean duration of symptoms was 15 mo (1-120 mo) with a mean value of VAS-pain 6.2 cm. 54 (29%) patients had generalized pain (at least 4 out of 5 regions) of which 40 (21%) fulfilled ACR 2016 criteria. When the probable FS patients and the rest were compared, VAS-pain, WPI, SSS, and EQ-VAS scores were significantly worse in the FS group. Also, FS group had significantly worse sleep and fatigue scores as assessed by Likert-type scale.

Conclusion. In this preliminary study, the percentage of probable FS patients were found to be high in this study population. ACR 2016 criteria seem to discriminate the specific characteristics of FS patients well. Yet, the sensitivity and specificity should be further tested with clinician's further assessments in a larger study population.

P-14 Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

A preliminary investigation into diagnostic and clinical differences and similarities between fibromyalgia and ME/CFS

Kristy Themelis, Neil A Harrison, Kevin Davies, Jessica Eccles.
Brighton and Sussex Medical School, University of Sussex, UK.

Background. Fibromyalgia (FM) and Myalgic encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) share some clinical symptoms including fatigue, pain, sleep, and cognitive disturbances. A large proportion of ME/CFS patients experience widespread pain, sleep dysfunction as well as cognitive deficits. The aim of this preliminary study was to determine diagnostic and clinical differences and overlap of FM and ME/CFS.

Methods. Patients with a clinical diagnosis of Fibromyalgia and/or ME/

CFS were recruited through advertisements and patient support groups. Participants were assessed on symptom duration, symptom severity, and clinical diagnostic criteria for FM and CFS/ME.

Results. Of the 34 patients recruited; 7 had an initial diagnosis of FM, 17 had ME/CFS, and 10 patients had both diagnoses. 94% of people with a diagnosis of FM with or without ME/CFS and 53% of people diagnosed with ME/CFS only, met the Canadian Consensus Criteria, the 1994 Fukuda Symptom Criteria for ME/CFS, scored 36 points or higher on the Fatigue Severity Scale, and met the 2010 FM Diagnostic Criteria upon screening.

Conclusions. There is preliminary evidence that patients with FM share diagnostic and clinical overlap with ME/CFS. More than half of the participants with a clinical diagnosis of ME/CFS met the diagnostic criteria for FM. Further research will be conducted using a larger sample size to investigate not only the diagnostic and clinical overlap, but also the distinguishing and overlapping neurophysiological processes. A better insight into the overlap and distinction between these conditions has the potential to improve the understanding and treatment of these complex conditions.

P-15 *Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia*

Stability of fibromyalgia symptoms

Ann Vincent¹, Loren Toussaint².

¹Internal Medicine, Mayo Clinic, USA. ²Psychology, Luther College, USA.

Participants and procedure. 858 patients with fibromyalgia who previously participated in a survey were mailed a second identical survey two years after the initial study. Questionnaires included FIQ-R, MFI, SF36, BPI, POMS, and MASQ subscales. A total of 450 patients returned the survey.

Results. Paired-samples t-tests showed that there was a statistically significant change in FIQ-r, the MFI, SF36, BPI, POMS, and MASQ subscales. The symptoms subscale of the FIQ showed a mean decrease of 1.3 points. The MFI general fatigue and physical fatigue subscales both decreased by .48 and .58. There was an increase in the bodily pain subscale by .99 points as well as the vitality subscale by 1.56 points. The BPI showed a decrease in daily interference of pain subscale by .2 points. The POMS subscales suggest an increase in vigor and a decrease in confusion by about .4 points. Finally, the MASQ subscales showed a decrease in language ability and verbal memory by .47 and .45 points respectively.

Conclusion. Although a few statistically significant changes were observed over the two year time span most changes were quite small in size $d_s \leq .20$ and not clinically significant. Overall, the results of this study suggest that fibromyalgia symptoms are largely static over a two year time span. On average little change is present, but large standard deviations in change suggest that individual-level changes may vary substantially. Future research should seek to understand individual differences in change and attempt to identify individual characteristics that promote long-term improvements.

P-16 *Genetics, Pharmacogenetics and Epigenetics*

TRPM6 gene polymorphisms are highly frequent in patients with fibromyalgia

Giulia Andolina, Andrea Aricò, Daniela Caccamo.

Department of Biomedical Sciences, Dental Sciences, and Morpho-functional Imaging, Polytechnic Hospital University of Messina, Italy.

Background. Magnesium (Mg) deficiency occurs in fibromyalgia (FM) patients (1). Hypomagnesemia is related with muscle weakness and cramps (2), as well as systemic low-grade inflammation and increased substance P levels, responsible for fibromyalgia-related chronic pain (3). Moreover, Mg inhibits NMDA receptor activation, that is associated with spontaneous pain onset. Mg supplementation shows an analgesic action in the therapeutic management of chronic pain (4-6). Mg²⁺ absorption and homeostasis are modulated by TRPM6 channels. Notably, TRPM6 gene polymorphisms have been shown to induce hypomagnesemia (7).

Objectives. To investigate the association of TRPM6 rs2274923, rs11144089 and rs9919062 polymorphisms with FM.

Methods. Genomic DNA was isolated from peripheral blood of 92 FM patients and 82 controls. Allelic discrimination using Real-time PCR was carried out to assess the TRPM6 genetic background.

Results. Genotyping for rs9919062 showed that the mutated AA genotype was significantly more frequent in FM than CTR (44.5% vs 29.3%, $p=0.042$), and increased the risk for FM development (OR=1.94; 1.03-3.64; $p=0.038$). Other genotypes had a lower frequency in FM patients than in CTR (GG 17.8% vs 21.9%, GA 40% vs 48.8%). Genotype distributions for TRPM6 rs2274923 and rs11144089 did not show significant differences between the two groups.

Conclusions. Screening for TRPM6 gene polymorphisms should be carried out prior to Mg supplementation in FM patients.

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P-17 *Genetics, Pharmacogenetics and Epigenetics*

Identification of genetic determinants for central pain sensitization in fibromyalgia patients

Yvonne Gloor¹, Médéric Mouterde², Alain Matthey¹, Estella Poloni², Jocelyne Chabert³, Aurélien Simona¹, Luc Bovet¹, Marie Besson¹, Valérie Piguet¹, Christine Cedraschi¹, Gisèle Pickering⁴, Eva Kosek⁵, Georg Ehret⁶, Jules Desmeules¹.

¹Division of Clinical Pharmacology and Toxicology, Geneva University Hospital, Switzerland. ²Department of Genetics and Evolution, Faculty of Science, University of Geneva, Switzerland. ³Clinical Investigation Unit, Geneva University Hospital, Switzerland. ⁴Clinical Pharmacology Center, CIC Inserm, Faculty of Medicine, University of Clermont-Auvergne, France. ⁵Department of Clinical Neuroscience, Osher Centrum, Karolinska Institutet, Karolinska University Hospital, Sweden. ⁶Division of Cardiology, Geneva University Hospital, Switzerland.

Background and objectives. Fibromyalgia syndrome (FMS) covers a spectrum of chronic pain conditions characterized by widespread pain and increased sensitivity to nociceptive stimulus. Central sensitization is thought to be one of the key mechanisms underlying FMS. This process can be described as a loss of the natural balance between transmission of pain stimuli to the CNS and the central pain inhibitory feedback mechanisms. While familial aggregation could suggest a potential genetic component in FMS development, isolation of genetic determinants has proven difficult due to the multi-factorial nature and complexity of the syndrome. We aim to identify some of these determinants.

Methods and results. We used a customized Infinium CoreExome-24 BeadChip from Illumina to genotype 555'356 human genetic polymorphisms in 302 FMS patients and healthy controls. All samples call rates exceeded 99 % and the genotype completeness exceeded 99% in 97.8% of the SNPs. Following quality control, 98.1% of the SNPs were cleared for further bioinformatic analysis, combining genome-wide and candidate gene approaches and using the nociceptive flexion reflex as a primary stratification determinant.

Conclusions. The characterization of our cohort will be used to confirm suspected genetic predisposition and identify new genetic determinants of FMS based on objective measurements of central sensitization. Follow-up work combining genomic, transcriptomic and proteomic techniques will aim to gain a better understanding of the various pathophysiological mechanisms underlying the disease and allow the development of optimized personalized treatments for FMS patients. International collaborations will allow replication of our findings in two independent cohorts.

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P-18 Treatment of Fibromyalgia**Cannabinoid treatment in fibromyalgia**

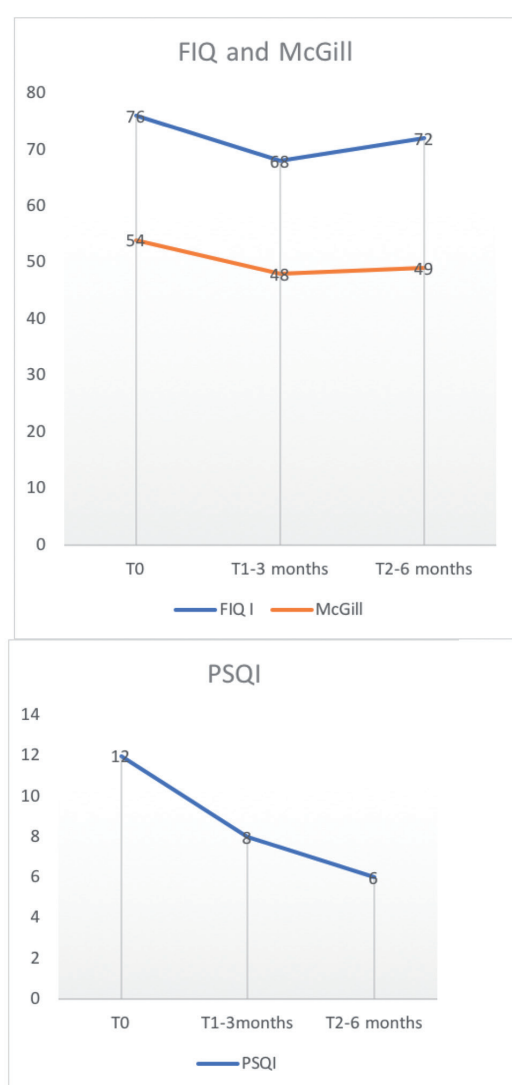
Andrea Garone, Alvise Martini, Elisabetta Arrigoni, Vittorio Schweiger, Massimo Parolini, Enrico Polati.
Pain Medicine Department, AOUI Verona, Italy.

Aim of the study. Therapy with cannabinoids has shown a beneficial effect in the treatment of different pathological conditions. We wanted to observe if they are able to improve quality of life and to control pain also in fibromyalgic patients.

Method. We reviewed outcomes of 15 patients followed by our center affected by fibromyalgia, which started cannabinoids as an add-on therapy. We proposed three questionnaires (FIQ, McGill pain questionnaire, PSQI), to which patients were asked to answer on a basis of three months, for an observation period of six months. All patients were treated by cannabinoid in oil extraction and doses may vary from patient to patient with the aim to achieve the maximum tolerable daily dose in two administration.

Results. We collected data from 15 patients. From the analysis of the results we saw a 13,15% drop down of the mean value of the FIQ and 14,15% decrease of the McGill pain questionnaires in the first 3 months of observation, with a consequent stabilization of the pain's perception to T2. Analysis of the results of PSQI showed a 41% improvement of the mean value at T2.

Conclusion. Cannabinoids have shown to increase sleep quality while their effect on pain or quality of life is still uncertain. Our main limitation is the small sample and moreover our patients have a lot of difficulties in getting a stable supply of the chosen cannabinoid. Anyway, a bigger sample is needed for a definite conclusion.

**P-19 Treatment of Fibromyalgia****Monitoring and adherence to a healthy physical activity program in fibromyalgia patients: preliminary results**

Marie-Eve Isner-Horobet², Sophie Haby-Ougier², Eric Salvat², Magali Schultz^{1,2}, Christophe Enaux², Lecocq Jehan^{1,2}.

¹Physical and Rehabilitation Medicine Department, University Institute of Rehabilitation Strasbourg University, France, France. ²Physical and Rehabilitation Medicine Department, University Institute of Rehabilitation Strasbourg University, France, France.

Introduction. The aim was to assess the quality of life of fibromyalgia patients after a program of physical activity (PA) sessions. The first part was to monitor treatment compliance and the subjects' feelings throughout the program.

Material and method. Monocentric, comparative, parallel group study. PA took place, either in a hospital or in an association for 16 weeks, twice a week. Study parameters: fibromyalgia-impact-questionnaire (QIF), quality-of-life-questionnaire (SF-36), PA-questionnaire (GPAQ), Beck's-depression-inventory, stress-test, 2-minute walk test. Study of observance and feeling: weekly telephone call.

Results. 23 subjects (87% female) were followed and completed the program. 3 subjects left the study after the first week and were not included in the analysis. Overall compliance in both groups was 67.8%. Reasons for absences from sessions were medical in 52.0%, personal in 27.8%, professional in 14.2% and organizational in 5.9%. Factors found limiting compliance were pain and sleep disorders, initial physical activity program considered too intense, fears and beliefs related to the pathology. Feeling of subjects: increased pain at the beginning of the program but a positive effect during the study in the form of "well-being".

Conclusion. Despite an initial increase in pain, overall compliance is good regardless of the management structure. The continuation of this study and the analysis of the various parameters will make it possible to specify the clinical and biological factors involved in improving the quality of life of these patients.

P-20 Treatment of Fibromyalgia**Deterioration after surgery in patients with fibromyalgia**

Helena Jamnik, Ana Ščavničar.
Outpatient Department, URI Soča, Slovenia.

Background. according to our clinical practice, frequent cases of negative impact of multiple surgeries were observed in patients with fibromyalgia syndrome.

Objectives. to explore the observed phenomena in fibromyalgia patients, referred to interdisciplinary pain rehabilitation program.

Methods. cases of 97 consecutive fibromyalgia patients were analyzed in terms of such reports.

Results. 25 patients (26%) reported aggravation (aggravation group AG). As the critical surgery triggering deterioration they reported orthopedic surgery -17, median nerve decompression -2, gynecological-urological -4, other -2. 44% of AG reported chronic pain more than 10 years (vs. 37% of the rest - RG). 37% in AG experienced more than 5 surgeries of different types (vs. 20% in RG). Significant differences were found in vocational status: in AG 56% and in RG 36% were retired/unemployed, previous year mean sick leave was 11,5 (SD 6,15) and 5,07 (SD 4,6) months in AG and RG respectively (p 0,001). There were no significant differences in sex (AG male 20%, female 80%; RG male 26%, female 74 %), age (AG mean 52,2 SD 7,69; RG mean 49,8, SD 9,66), average pain on NAS (AG mean 6,7 SD 1,69; RG mean 7,2, SD 1,57), painDETECT (AG mean 22,3 SD 7,92; RG mean 21,6, SD 7,13), WPI and SSS were in AG 9,4 (SD 4,56) and 8,1 (SD 2,39), in RG 11,1 (SD 4,9) and 8,9 (SD 1,98) respectively.

Conclusions. based on medical histories of patients with fibromyalgia future research is needed to explore outcomes of multiple surgeries in this patients' group.

P-21 Treatment of Fibromyalgia

Dramatic reduction of pain in fibromyalgia patients with a long-term gluten-free and lactose-free diet. Results of a monocentric study in 204 consecutive patients

Laurence Juhel Voog¹, Valérie Hégé², Jacques Gaillard³.

¹Internal Medicine, Private Hospital Pole Santé Sud, France. ²General Practitioner, Private Médical Office, France. ³Pain Center, Private Hospital Pole santé Sud, France.

Background. Fibromyalgia is a difficult to treat painful condition without standard treatment (1). The link between gluten and pain in fibromyalgia was evoked in a few recent studies (2, 3, 4).

Objectives. To evaluate the reduction of pain with gluten-free and lactose-free diet in a fibromyalgia population.

Methods. Two-hundred and four consecutive fibromyalgia patients were treated between January 1st and December 31st 2017 in our center. For all patients ACR 2010/2011 diagnostic criteria were positive (6) and Anti transglutaminase antibodies (IgA) were negative. Diet was conducted by a dietitian. In November 2018, they received a questionnaire. The main objective was to evaluate the reduction of pain under this diet on a scale (0-100%).

Results. Median duration of diet was 1 year. Gluten-free diet was strict for 60% of patients and lactose-free for 54%. Sixteen patients stopped the diet for different reason (cost; difficulty to follow; failure).

110 (54%) answers were received.

51% had pain reduction of 50% or more ul.

30% had pain reduction of 70% or more.

49% had pain increased when taking lactose or gluten again, 24% only for gluten and 5% only for lactose.

66% reported that there was a clinical link between abdominal bloating and pain.

Conclusions. Gluten-free and lactose-free diet is feasible in a fibromyalgia population. Gluten and lactose-free diet have a dramatic effect on pain reduction. We hypothesize that there is a link between intestinal fermentation and fibromyalgia symptoms.

P-22 Treatment of Fibromyalgia

A systematic, international review of recent research on multidisciplinary treatments for patients with fibromyalgia: research outcomes of policy-based recommendations

Anna Núria Llädser Navarro¹, Maria Pilar Montesó Curtó², Carlos Lopez Pablo³, Lina Cristina Casado Marin², Lluís Rosello Aubach⁴, Loren L Tousseint⁵, Nuria Llädser Navarro¹.

¹Internal Medicine Unit, Verge de la Cinta Hospital, ICS, IISPV, Spain. ²Department of Nursing, Rovira i Virgili University, Spain. ³Department of Pathology, Verge de la Cinta Hospital, ICS, IISPV, Spain. ⁴Department of Rheumatology, University Hospital of Santa Maria, Spain. ⁵Department of Psychology, Luther College, USA.

Background. Fibromyalgia is a pathology that causes physical, psychological, and social problems. For this reason, it requires treatment that involves all of these elements.

Objective. To determine the types of multidisciplinary treatment that are used to manage fibromyalgia.

Methods. In this systematic review, we searched the following databases: CINAHL, PubMed, Scopus, Cuidatge, Cuiden, ENFISPO, IBEC and IME. The inclusion criteria were: original primary articles, involving adults with fibromyalgia, and use of multidisciplinary treatment.

Results. Of the 356 articles found we selected 13 to analyse and summarize. There is great diversity in studies and treatments because there are many tools and methodologies currently available for women with fibromyalgia. We created 4 different categories: (1) Multidisciplinary Treatment Focusing on Health Education and Cognitive Behavioral Therapy (CBT), (2) Multidisciplinary Treatment that Includes Dietetics, (3) Multidisciplinary Treatment Adapted to the Patients' Characteristics and (4) Multidisciplinary Treatment Based on Physical Exercise.

Conclusion. Based on this review, multidisciplinary treatment that includes guidelines for physical exercise, health education programs, CBT, and pharmacotherapy is necessary. Catalan interventions had a high quality since they applied the basic elements of MT but they also included hidrokinestherapy that was not used in any other study outside of Catalonia. Therefore, we think that the articles made in Catalonia, where MTs are created based on the characteristics of the participants.

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P-23 Treatment of Fibromyalgia

Combretum A and Combretin B, two new triterpenes cycloartane-type reduces muscle and cutaneous hyperalgesia in chronic muscle pain in rats

Marius Mbiantcha¹, Khalid Rauf², Mehreen Arif², Hamza Dar².

¹Animal Biology, Laboratory of Animal Physiology and Phytopharmacology, Cameroon. ²Pharmacy, COMSATS Institute of Information Technology, Pakistan.

The present study evaluated effects of Combretum A and Combretin B, two new triterpenes cycloartane-type isolated from the leaves of *Combretum fragrans* in rat model of muscle-induced hyperalgesia. Cutaneous hyperalgesia of the paw (withdrawal threshold to von Frey filaments) was measured after induction of hyperalgesia and after treatment with Combretum A and Combretin B (saline, 25 and 50 mg/kg, *p.o.*). In the non-inflammatory model, 2 unilateral injections of acidic saline into the gastrocnemius muscle produced bilateral cutaneous and muscle hyperalgesia 24 hours after the second injection. Combretum A and Combretin B (25 and 50 mg/kg, *p.o.*) significantly increased the compression withdrawal thresholds of the muscle and the mechanical withdrawal threshold of the paw bilaterally when compared with vehicle. Therefore, Combretum A and Combretin B reduce both muscle and cutaneous hyperalgesia that occurs after muscle insult in animal model of muscle pain at doses that do not produce ataxia.

P-24 Treatment of Fibromyalgia

Chronic widespread pain and physical activity in fibromyalgia: a systematic review

Kabir Isah Mayana, Yeliz Prior.

School of Health and Society, University of Salford Manchester, UK.

Background. Fibromyalgia (FM) is characterised by chronic widespread pain (CWP). Guidelines for the management of FM identifies exercise as the primary intervention. However, low exercise tolerance is a barrier for individuals with FM to adhere to such interventions.

Objective. To systematically review the literature to identify the mechanisms which drive the relationship between physical activity and CWP in people with FM to provide target for behavioural interventions.

Methods. Following the Prisma guidelines, the review aimed to capture all studies published to date, via a computerised search of Cochrane library, Medline Ebsco, Web of Science, Pedro, British Nursing Index, CINAHL, and Psych INFO databases. Interventional and observational studies investigating associations between physical activity and CWP in people with FM, published in English were included from earliest to November 2018. Quality assessment was assessed by two researchers independently using the Joanna Briggs checklists.

Results. Fourteen studies (7 cross-sectional: 7 RCTs) met the inclusion criteria and were reviewed using a narrative synthesis due to the heterogeneity of outcome measures used. The quality ratings ranged from moderate to low. The relationship between physical activity behaviour and CWP was unclear. Most studies did not consider the role of personal, contextual and environmental factors. Sleep disturbance and sedentary behaviour was strongly associated with increased pain and fatigue.

Conclusion. There is a paucity of research considering the mechanisms which the relationship between physical activity and CWP in people with FM. There is a need to further explore this relationship from a biopsychosocial perspective to target behavioural interventions.

P-25 Treatment of Fibromyalgia**Differentiating profiles in adherence to walking behavior in women with fibromyalgia after the application of a brief motivational-volitional intervention**

Cecilia Peñacoba¹, María A. Pastor-Mira², Sofía López-Roig², Fermín Martínez-Zaragoza², Ana Lledó², Lilian Velasco¹.

¹Medicine and Surgery, Psychology, Preventive Medicine and Public Health and Medical Microbiology and Immunology, Rey Juan Carlos University, Spain. ²Health Psychology, Miguel Hernández University, Spain

Background. Fibromyalgia is characterized by generalized and diffuse chronic musculoskeletal pain, which additionally presents symptoms such as fatigue, sleep problems, emotional and cognitive problems. Physical exercise has proved to be an essential part of the multicomponent treatment recommended for these patients. Nevertheless, some studies have shown that patients tend to present low adherence to different exercise recommendations, including walking.

Objectives. The aim of this study was to test the efficacy of a group motivational plus implementation intentions intervention (MIIC) in promoting adherence to an unsupervised walking exercise program applied to a sample of 275 women with fibromyalgia. We also analyze the differentiating profiles of patients who are more successful in adhering to walk after the application of the program.

Methods. We designed a triple-blind, randomized, longitudinal study with measures at short (seven weeks post-intervention), medium (12 weeks) and long term (36 weeks). MIIC intervention is compared to an implementation intentions condition by alone (IIC) and to an active control condition (CC).

Results. The MIIC intervention has effects on the adherence to the short-term walking behavior, although it is necessary to improve its medium and long term. Likewise, the intervention has improvements in the physical function of the participants.

Conclusion: Based on these results and the limitations of the research, new strategies and approaches are provided to improve the MIIC intervention program. Supported by MINECO PSI2011-25132).

P-26 Treatment of Fibromyalgia**Understanding and promoting subjective happiness in chronic pain**

Ana Margarida Pinto^{1,2}, Carlos Costa¹, Mariana Luís¹, Ana Telma Pereira², Mariana Marques^{2,3}, António Macedo^{2,3}, José António Pereira da Silva^{1,4}.

¹Rheumatology Department, Coimbra Hospital and University Centre, Portugal.

²Psychological Medicine Department, Faculty of Medicine, University of Coimbra, Portugal.

³Psychiatry Department, Coimbra Hospital and University Centre, Portugal.

⁴CBR - Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine, University of Coimbra, Portugal.

Background. Happiness, *i.e.* the satisfactory fruition of life, should be the ultimate goal of medical intervention.

Objectives. 1. to examine if fibromyalgia (FM), rheumatoid arthritis (RA) patients and healthy controls (HC) differ on happiness levels, depression, affect and personality traits; 2. to ascertain the relative predictive effect of each of these variables on happiness.

Methods. All participants completed a battery of self-report measures, using the validated Portuguese versions. Between-group differences were assessed through one-way independent ANOVA. Hierarchical Regression analysis evaluated if disease, depression (entered first) and dispositional variables (entered last) significantly predicted happiness.

Results. 195 females were included [68 FM, 55 RA, 72 HC]. FM patients significantly differed from RA and HC on most measures. Overall, no differences were found between RA and HC. The hierarchical regression Model 1 was significant ($F(2,192) = 72.187; p.001$) and explained 42.3% of happiness's variance, both disease and depression being significant predictors. When personality traits and positive affect were entered (Model 2), the predictive power of disease became close to non-significance. Depression remained highly significant despite a marked reduction in beta weight. Model 2 was significant [$F(5,189) = 36.608; p.001$] and explained 49.2%. All dispositional variables entered in the model significantly predicted happiness.

Conclusion. FM patients are less happy than RA and HC. Results suggest that this is not an intrinsic feature of the disease itself, but is probably mediated by differences on personality traits, affect and depression. These need to be assessed and considered in management, if subjective well-being is the core target.

P-27 Treatment of Fibromyalgia**There is inter-individual variability in which symptoms are relieved in patients with fibromyalgia treated with low dose naltrexone (LDN)**

Karin Bruun Plesner¹, Kirstine Amris³, Palle Toft², Henrik Bjarke Vaegter¹, Morten Rune Blichfeldt-Eckhardt¹.

¹Odense University Hospital, Pain Research Group, Pain Centre South, Denmark.

²Odense University Hospital, Department of Anesthesiology and Intensive Care, Denmark.

³Copenhagen University Hospital, Department of Rheumatology, The Parker Institute, Denmark.

Background and aim. The use of low dose naltrexone (LDN) as off-label treatment for pain is growing, although the evidence is sparse, with only 3 small clinical trials, demonstrating an effect in fibromyalgia patients. In the clinical setting, LDN does not always seem to affect pain, but other fibromyalgia-related symptoms instead. This study explored which symptoms are most commonly relieved by LDN in patients with fibromyalgia.

Methods. The study was carried out as a dose-response study using the "Up-and-down" method. The level of 10 common fibromyalgia symptoms was rated on a 0-10 NRS, corresponding to the symptom part of the Revised Fibromyalgia Impact Questionnaire (FIQR), at baseline and after 2 and 3 weeks of treatment.

Results. 25 evaluable patients were included, 11 of these were classified as responders. Most responders had improvement of more than one symptom. The symptoms most commonly reduced with more than 30% after 3 weeks were 'tenderness' and 'waking un-refreshed' - whereas pain was the symptom least frequently reduced.

Conclusions. The decrease in tenderness could reflect an improvement of the hyperalgesic state seen in FM patients and we hypo these that this together with improvement of energy and sleep might lead to increased activity, which could blunt the expected improvement of pain. We suggest that future clinical trials exploring the effect of LDN on FM incorporate measures of 'tenderness' and measures of daily functioning or daily activity, to explore the hypothesis that LDN influences primarily on hyperalgesia, fatigue, sleep and daily functioning and secondarily on pain.

P-28 Treatment of Fibromyalgia**The effects of Vibrotactile stimulation on symptom relief in fibromyalgia: a randomized controlled trial**

Jesus Pujol¹, Elizabeth Corredor¹, Daniel Ramos-López¹, Laura Blanco-Hinojo¹, Guillem Pujol¹, Héctor Ortiz², Gerard Martínez-Vilavella¹, Josep Blanch³, Jordi Monfort³, Joan Deus^{1,4}.

¹MRI Research Unit, Hospital del Mar, Spain. ²Department of Project and Construction Engineering, Universitat Politècnica de Catalunya, Spain. ³Department of Rheumatology, Hospital del Mar, Spain. ⁴Department of Clinical and Health Psychology, Autonomous University of Barcelona, Spain.

We tested the effect of vibrotactile stimulation on symptom relief in fibromyalgia patients with a randomized, double-blind, sham-controlled, crossover clinical trial. Seventy-seven female patients were randomized and data from 63 valid cases were analyzed. Active intervention involved extensive body stimulation with gentle mechanical vibrations administered during 3 h at night for 3 weeks, and the placebo effect was controlled using identical instruments to simulate an alternative treatment option. The primary outcome measure combined pain, fatigue and complaints of poor cognition. Vibrotactile stimulation was significantly superior to sham in alleviating fibromyalgia symptoms globally. Changes in the global symptom score for sham showed mean \pm SD of $25.7\% \pm 30.7\%$ and vibrotactile stimulation $45.2\% \pm 33.9\%$, $t = 3.4$ and $p = 0.001$. However, univariate analyses showed that the effect was not universal. Benefits were perceived on unpleasant somatic sensations such as generalized pain and fatigue, but not on poor cognition, anxiety and depression. Vibrotactile stimulation was notably well tolerated and sleep quality significantly improved despite the vibrations being administered at night. The extent of symptom improvement may be sufficiently relevant to suggest a potential role for vibrotactile stimulation as symptomatic treatment in fibromyalgia. Moreover, the ease with which it can be administered during sleep, with no other action required than turning on the system at bed time, may eventually facilitate long-term compliance, which is a relevant limiting factor for the success in treating chronic disorders.

P-29 Treatment of Fibromyalgia**Physiological responses of fibromyalgic patients to a waving vibes therapy**

Juan Ribas, Alba Parras.
Medical Physiology and Biophysic, University of Seville, Spain.

Aims. To ascertain the physiological effects produced by a waving vibes therapy on a population of fibromyalgic patients.

Background. Vibrations have been used for therapy purpose during decades. Whole body vibratory platform is the most known but their effects have not been proved in fibromyalgic patients. We propose a new vibration therapy (andullation) to be applied to these patients

Methods. Twelve patients clinically diagnosed of fibromyalgia and twelve non-fibromyalgic patients were treated with a vibratory mattress for 30 min at day during 5 days. The mattress provided vibrations of distinct amplitude and frequency passing along the body surface from heel to the head and vice versa while patients stayed in a decubitus supinus position. Control subjects rest on the mattress but did not receive the vibration therapy.

Results. Pain thresholds showed a trend to increase after the treatment. VAS decreased 35% (from 4,8 (2,1) to 3,1 (2,3), mean (SD)) from the initial conditions to the last session of waving vibes therapy. Well-being score significantly increased by 32,4% (from 6,95(2,6) to 4,7(2,4)).

Discussion. Our devices apply a set of vibration of distinct amplitude and frequency distributed over the mattress in a horizontal position. The wave of vibration spread under the body surface of the subject avoiding the adaptation of mechanical receptors to the stimulation.

Conclusion. The waving vibes therapy (andullation) was able to increase the well-being condition as well as pain VAS and trended to increase the pain threshold in fibromyalgic patients.

P-30 Treatment of Fibromyalgia**Oxygen ozone therapy to control astenia and pain in fibromyalgia and chronic fatigue syndrome**

Giovanni Ricevuti¹, Marianno Franzini², Luigi Valdenassi³.

¹Department of Drug Science and Internal Medicine, Master in Geriatrics and in Oxygen Ozone Therapy, University of Pavia, IRCCS Salvatore Maugeri Foundation, Geriatrics, Italy. ²SIOOT, University of Pavia, Italian Scientific Society of Oxygen Ozone Therapy, Italy. ³Master in Oxygen Ozone Therapy, SIOOT Italian Scientific Society of Oxygen Ozone Therapy, University of Pavia, Italy.

Background. Fibromyalgia and CFS are two important diseases disabling many subjects with fatigue and muscle pain.

Objectives. We evaluated the effectiveness of local and systemic oxygen ozone therapy in controlling pain and fatigue. Oxygen ozone therapy has an immunomodulation and anti-inflammatory effects and therefore also antiaesthetics and analgesics.

Methods. 22 subjects with asthenia and muscular pain were identified in fibromyalgia (11 pts) and CFS (11pts) patients according to the ACR definition and the Fukuda criteria. The fatigue was evaluated with the FSS, Pain with the VAS scale, Frailty with the SHARE-FI, the Health Forms and the Quality of Life with the SF-36, Oxidative stress with the DROMS test of the Diacron company. We treated the patients with O₂O₃ on painful points and with auto hemo infusion, according to the Italian Society SIOOT protocols, twice a week for one month. After 8 treatments we have clinically re-evaluated and tested the patients.

Results. All patients showed an improvement in clinical status in the test execution. DROMS test showed and improvement of oxidative stress.

Conclusion. Oxygen Ozone therapy seems to be useful in the treatment of patients with fatigue and astenia and pain as in Fibromyalgia and in Chronic Fatigue syndrome. The treatment did not present complications.

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P-31 Treatment of Fibromyalgia**Probiotics can be a useful therapy in chronic fatigue syndrome patients**

Chiara Cusa¹, Letizia Venturini², Enrica Capelli³, Lorenzo Lorusso⁴, Marcello Romeo⁵, Colomba Falcone⁶, Giovanni Ricevuti⁷.

¹Internal Medicine, ASST Pavia, Italy. ²Internal Medicine, University of Pavia, Italy. ³Dipartimento di Scienze della Terra e Dell'Ambiente, University of Pavia, Italy. ⁴Department of Neurology, ASST Lecco, Merate Hospital, Italy. ⁵Master in Nutrizione Umana, Università di Pavia, Italy. ⁶Internal Medicine and Therapeutics, Cardiology, University of Pavia, Italy. ⁷Department of Drug and Science and Internal Medicine, Master in Geriatrics and in Oxygen Ozone Therapy, University of Pavia, IRCCS Maugeri Foundation, Geriatric Section, Italy.

Background. CFS/ME is a multisystems condition in which immune functions, mitochondrial function, cardiovascular and endocrine systems are compromised.

Objectives. The aim of the present study was to conduct a randomized clinical trial to evaluate the effectiveness of certain combinations of probiotics to modulate immune functions in controlling the symptoms of CFS/ME.

Methods. 26 subjects with CFS (Fukuda criteria) were randomized for classical and probiotics treatment for 3 months. Four different mixtures of probiotics (Bromatech s.r.l, Milano, Italy) were employed for treatments. Before and after probiotics treatment the fatigue was evaluated with the Chadler Fatigue Scale, Pain with the VAS scale, Frailty with the SHARE-FI, the Health Forms and the Quality of Life with the SF-36, the assessment of psychological status with Beck Depression Inventory scale (BDI-II), Oxidative stress with the DROMS test of the Diacron company.

Results. Considering the clinical features, after probiotic therapy we observed an improvement of the subjective state of health and of the indices of quality of life; a decreased of physical and mental fatigue and an improved mood were also observed. DROMS test showed an improvement of oxidative stress.

Conclusion. Probiotic therapy seems to be useful in the treatment of patients with Chronic Fatigue syndrome. Probiotics Treatment may be practicable and safe.

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P-32 Treatment of Fibromyalgia**The use of sub-anesthetic Ketamine (infusion and/or lozenges) in the treatment of fibromyalgia**

Olfat Zekry.
Pain Clinic, Royal Prince Alfred Hospital, Australia.

Ketamine is a non-competitive antagonist of N-Methyl-D-Aspartate (NMDA) receptors. Ketamine helps to minimise excessively painful responses. Antagonizing these receptors improves opioid receptor sensitivity, reduces opioid tolerance and suppresses opioid-induced hyperalgesia. Fibromyalgia (FM) is a chronic rheumatic disease of significant and great clinical impact. However, the treatment for FM has limited efficacy. Recent studies have found raised levels of glutamate in the insula, hippocampus and posterior cingulate cortex regions of the brain. This has led to the focus of the usefulness of glutamate blocking drugs in the treatment of FM.

I will discuss Janine, a 52 years old female who was treated successfully for Fibromyalgia with Ketamine infusion followed by Ketamine lozenges. The outcomes indicate that a sub-anesthetic inpatient ketamine infusion offers a promising therapeutic option for long-term relief of chronic non-malignant pain.

In addition, there is evidence that sub-lingual ketamine lozenges after an inpatient ketamine infusion have a role in the cessation / reduction of the pain medications in patients with Fibromyalgia.

Further research is required to assess whether the benefits outweigh the risks and costs. Until definite proof is obtained ketamine administration should be restricted to patients with therapy-resistant severe Fibromyalgia.

Evidence supports the use of ketamine for chronic pain, but the level of evidence varies by condition and dose range. Most studies evaluating the efficacy of ketamine were small and uncontrolled and were either unblinded or ineffectively blinded. Adverse effects were few and the rate of serious adverse effects was similar to placebo in most studies, with higher dosages and more frequent infusions associated with greater risks. Larger studies, evaluating a wider variety of conditions, are needed to better quantify efficacy, improve patient selection, refine the therapeutic dose range, determine the effectiveness of nonintravenous ketamine alternatives, and develop a greater understanding of the long-term risks of repeated treatments.

P-33 “Transparent Pain”: How Society Deals with Fibromyalgia

Beliefs, opinions and views of health professionals on patients with chronic pain

Martina Bürger Lazar, Nika Bolle.
Outpatient Rehabilitation Service, University Rehabilitation Institute, Republic of Slovenia, Slovenia.

Background. Patients and healthcare providers still commonly think of pain as a symptom caused mainly by tissue injury. Historically, pain without an obvious proof of anatomical or neurophysiological origin was labelled as psychopathological. Moral judgements and questioning the legitimacy of the patient's pain and coping responses is still a significant problem for those with chronic pain.

Objectives. At our Outpatient rehabilitation service, between 2016 and 2018, we conducted educational workshops on chronic pain for 132 health professionals (physicians, nurses, psychologists, physiotherapists, occupational therapists and speech therapists). In addition to educating health professionals on chronic pain, the workshop's purpose was also to identify their beliefs, opinions and views on patients with chronic pain.

Methods. Attended participants were asked a question: “When you think of a patient with chronic pain, what thought or image goes through your head?” The participants individually and anonymously wrote their answer on a piece of paper.

Results. We divided the answers into various content categories: “Physical attributes”, “Yammering”, “Difficult patient”, “Lack of evidence of pain”, “Suffering”, “Personality and moral integrity”, “Mental disorder” and “Older women”.

Conclusion. Based on the written responses of health professionals, we can conclude that health professionals need: more expertise on chronic pain, familiarity with the guidelines for evidence based interdisciplinary chronic pain treatment, identification and understanding of their own prejudices against patients with chronic pain, which could help them develop sensitivity and empathy to give patients the validation of their pain and respect of their moral and personal integrity.

P-34 “Transparent Pain”: How Society Deals with Fibromyalgia

Fibromyalgia and pain management in systemic lupus erythematosus

Ljudmila Stojanovich, Natasha Stanisavljevic N, Djokovic Aleksandra, Gordana Bogdanovic, Marija Zdravkovic.
Internal Medicine, Bezhanjska Kosa, University Medical Center, Belgrade University, Serbia, Serbia.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause characterized by multi-system manifestations. Lupus is known as “the great imitator”, because its symptoms mimic many other illnesses. Many people with SLE have secondary fibromyalgia, and individuals occasionally present with widespread pain as the initial manifestation of SLE. Other organ system involvement can be painful, such as serositis (pleuritis or pericarditis). Avascular necrosis (AVN) is a frequent complication both of SLE and its treatment, as glucocorticoid therapy raises the risk for AVN. A key challenge is determining the source of the patient's pain. Sometimes the pain is clearly related to active SLE, and treatment of the active inflammation relieves the pain. These treatments can include hydroxychloroquine, NSAIDs, glucocorticoids, and immunosuppressive therapies, such as belimumab. If the disease is well controlled and pain persists, then multimodal treatments should be recommended. These treatments can include, in step-wise fashion, analgesics such as acetaminophen, NSAIDs, tramadol, and opioid analgesics. Prevalence of FM in Caucasian SLE patients was high compared to the general population, and was significantly higher in those in later stages of disease. SLE patients with depression showed a strong risk of developing FM.

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Author index

A			F			M		
Aakre Christopher	O-5		Fabio Giuseppina	IS-15		Marinović Ivanka	P-8	
Ablin Jacob	IS-2, IS-25		Falcone Colomba	P-31		Markkula Ritva	P-5	
Abokdeer Sedik	P-7		Farah Sonia	P-6		Marotto Daniela	IS-23, IS-26	
Achard Alexanne	O-1		Fernandes Roberto	P-3		Marques Mariana	P-28	
Adams Nicola	P-7		Ferrera David	P-3		Martínez-Zaragoza Fermín	P-25	
Aljinović Jure	P-8		Fonte Cristina	P-9		Martini Alvise	P-18, P-9	
Aloush Valerie	IS-22		Fors Egil A	P-1		Martinović Kaliterna		
Amital Howard	IS-6		Franzini Marianno	P-30		Dužanka	P-8	
Amris Kirstine	P-27					Matthey Alain	P-17	
Andolina Giulia	P-16		G			Mayana Kabir Isah	P-24	
Arendt-Nielsen Lars	IS-11, O-4		Gaillard Jacques	P-21		Mbiantcha Marius	P-23	
Aricò Andrea	P-16		Gandolfi Marialuisa	P-9		Mercado Francisco	P-3	
Arif Mehreen	P-23		Garone Andrea	P-18		Miettinen Teemu	P-5	
Arrigoni Elisabetta	P-18		Geenen Rinie	O-3		Mojs Ewa	P-11	
Atzeni Fabiola	IS-23, IS-26		Genç Aysun	P-13		Monfort Jordi	P-28	
Atik Çağrı	P-12		Gerra Maria Carla	O-4		Montesó Curto Maria Pilar	P-22	
			Gloor Yvonne	P-17		Morović-Vergles Jadranka	P-8	
B			Gómez Francisco	P-3		Moshe Shlomo	O-2	
Baničević Izabela	P-8		González-Villar Alberto	O-4		Mouterde Médéric	P-17	
Barjola Paloma	P-3		Groven Nina	P-1		N		
Basu Neil	IS-21		Guggino Giuliana	IS-8		Naisby Jenni	P-7	
Batko Bogdan	P-11		Güneş Seçilay	P-13		Nurmi Kari	P-2	
Batticciotto Alberto	IS-23, IS-26		Gur Sharon	IS-16		O		
Beci Giacomo	P-6		H			Oliviero Antonio	P-3	
Besson Marie	P-17		Haby-Ougier Sophie	P-19		Ortiz Héctor	P-28	
Blanch Josep	P-28		Harrison Neil A	P-14		P		
Blanco Sheila	P-4		Hassett Afton	O-3		Palavra Filipe	O-3	
Blanco-Hinojo Laura	P-28		Häuser Winfried	IS-3		Panyavin Ivan	P-3	
Blichfeldt-Eckhardt Morten Rune	P-27		Hégé Valérie	P-21		Parolini Massimo	P-18, P-9	
Bogdanovic Gordana	P-34		I			Parras Alba	P-29	
Bolle Nika	P-33		Iannuccelli Cristina	IS-5		Partanen Juhani V.	P-5	
Botto Rossana	IS-4		Irwin Russell	O-6		Pastor-Mira María A.	P-25	
Bovet Luc	P-17		Isazade Gülperi	P-13		Pedersen Inge Søkilde	O-4	
Brill Silviu	IS-24		Isner-Horobeti Marie-Eve	P-19		Peláez Irene	P-3	
Briones-Vozmediano Erica	O-8					Peñacoba Cecilia	P-4, P-25	
Bürger Lazar Martina	P-33		J			Pereira Ana Telma	P-26	
Buskila Dan	IS-17		Jamnik Helena	P-20		Pereira Bruno	O-1	
C			Javaid Kassim	O-7		Pérez-Calvo Soledad	P-4	
Caccamo Daniela	P-16		Jehan Lecocq	P-19		Picelli Alessandro	P-9	
Capelli Enrica	P-31		Jeka Slawomir	P-11		Pickering Gisele	O-1, P-17	
Cardot Jean-Michel	O-1		Jiang Quan	P-10, O-6		Pidal-Miranda Marina	O-4	
Carnevali Davide	O-4		Jiao Juan	P-10, O-6		Piguet Valérie	P-17	
Carrillo-de-la-Peña María Teresa	O-4		Jing Wang	O-6		Pinedo-Villanueva Rafa	O-7	
Casado Marin Lina Cristina	P-22		Juhel Voog Laurence	P-21		Pinto Ana Margarida	P-26, O-3	
Casale Roberto	IS-13, IS-20		K			Plesner Karin Bruun	P-27	
Cedraschi Christine	P-17		Kalso Eija	P-5		Polati Enrico	P-18, P-9	
Chabert Jocelyne	P-17		Karvonen Henna	P-2		Poloni Estella	P-17	
Chon Tony	O-5		Keczmer Przemyslaw	P-11		Prior Yeliz	P-24	
Choy Ernest H.	IS-1		Kosek Eva	P-17		Pujol Guillem	P-28	
Clauw Daniel	IS-10		Krakov Ayala	O-2		Pujol Jesus	P-28	
Corredor Elizabeth	P-28		Krawczyk-Wasielewska			R		
Costa Carlos	P-26		Agnieszka	P-11		Rainoldi Alberto	IS-13	
Cusa Chiara	P-31		Kurtaiş Aytür Yeşim	P-12, P-13		Ramos-López Daniel	P-28	
D			L			Rauf Khalid	P-23	
da Silva José António Pereira	P-26, O-3		Leppämäki Sami	P-2		Reitan Solveig Klæbo	P-1	
Dar Hamza	P-23		Lindfors Pirjo	P-2		Ribas Juan	P-29	
Davies Kevin	P-14		Llädser Navarro Anna Núria	P-22		Ricevuti Giovanni	P-30 P-31	
Desmeules Jules	P-17		Lledó Ana	P-25		Riva Egidio	IS-15	
Deus Joan	P-28		Lopez Pablo Carlos	P-22		Romanowski Mateusz W.	P-11	
Di Carlo Marco	IS-7, P-6		López-Roig Sofia	P-25		Romanowski Wojciech	P-11	
Di Franco Manuela	IS-5		Lorusso Lorenzo	P-31		Romeo Marcello	P-31	
Djokovic Aleksandra	P-34		Luedtke Connie	O-5		Rosello Aubach Lluís	P-22	
E			Luis Mariana	P-26, O-3		Rou-Man Zhang	O-6	
Eastman Ryan	O-5		M			S		
Eccles Jessica	P-14		Macedo António	P-26		Salaffi Fausto	P-6	
Ehret Georg	P-17		Macian Nicolas	O-1		Salvat Eric	P-19	
Enaux Christophe	P-19		Makri Souzi	IS-14		Samborski Włodzimierz	P-11	
Estlander Ann-Mari	P-5					Sanromán Lucía	P-4	

Santos-Paulo Stephanie	O-7	T		Velasco Lilian	P-4, P-25
Sarzi-Puttini Piercarlo	IS-15, IS-17, IS-23, IS-26	Themelis Kristy	P-14	Venturini Letizia	P-31
Ščavničar Ana	P-20	Thieme Kati	IS-19	Vincent Ann	P-15
Schettino Martina	P-6	Toft Palle	P-27	W	
Schultz Magali	P-19	Torta Riccardo	IS-4	Wen Wang	O-6
Schweiger Vittorio	P-18, P-9	Toussaint Loren	P-15, P-22	Williams Frances MK	IS-18
Segerdahl Andrew	O-7	Tracey Irene	O-7	X	
Shoenfeld Yehuda	IS-9	Triñanes Yolanda	O-4	Xiao Hong	P-10
Simona Aurélien	P-17	U		Z	
Smania Nicola	P-9	Üçeyler Nurcan	IS-12	Zdravkovic Marija	P-34
Soni Anushka	O-7	V		Zekry Olfat	P-32
Soto Vanesa	P-3	Vaegter Henrik Bjarke	P-27	Zetterman Teemu	P-5
Stanisavljevic N Natasha	P-34	Valdenassi Luigi	P-30	Zhao Ya-Yun	O-6, P-10
Stipić Mirela	P-8	Varalta Valentina	P-9		
Stojanovich Ljudmila	P-34				