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IS-01

Year in review 2023

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Fibromyalgia (FM) remains a condition with a pathogenesis that is not completely understood, affecting a significant portion of the global population. Even in 2023, research on FM was notably active. Regarding FM etiopathogenesis, ongoing research focuses on small fiber neuropathy: some studies have documented its association with central sensitization, while others have revealed distinct sensory profiles in patients with FM and small fiber neuropathy compared to those solely with small fiber neuropathy. New insights have also been introduced regarding the pathogenetic role of the gut microbiota. Studies conducted on animal models have confirmed the significance of neuroinflammation at the level of dorsal root ganglia mediated by polymorphonuclear neutrophils. Additionally, dorsal root ganglia seem to play a crucial role in the pathogenesis of FM as they host satellite glial cells, which are targeted by pain-driving immunoglobulin G. These antibodies have been identified in a subset of patients exhibiting high symptom severity.

Mounting evidence underscores the link between COVID-19 and the persistence of FM symptoms after recovery.

In identifying potential biomarkers aiding FM diagnosis, research has also concentrated on studying the expression of specific circulating microRNAs. From a clinimetric perspective, studies have been conducted to evaluate the possibilities of interchanging the primary indices of disease severity, primarily for studies with substantial case numbers.

Recent discoveries have unveiled novel therapeutic strategies for FM, especially focused in non-pharmacological interventions. This includes a focus on non-invasive brain stimulation and exercise programs, all directed towards relieving symptoms and improving functionality in individuals affected by the condition.

IS-02

Fibromyalgia, hypermobility, and the quest for a ‘Syndrome X of Pain’

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Fibromyalgia leads to fatigue, sleep issues, and ‘central sensitisation’ where the nervous system overreacts to stimuli. Hypermobility Syndrome, characterized by flexible joints and pain, mirrors fibromyalgia’s widespread musculoskeletal pain. Understanding its multifactorial nature, including biomechanical stress and tissue fragility, is key for effective management. The notable prevalence of hypermobility in fibromyalgia patients suggests a potential interconnected etiology, possibly exacerbating each other’s symptoms, emphasizing the need for an integrated treatment approach. Traditional pain management strategies in fibromyalgia, such as aerobic exercise and strength training, must be adapted to avoid exacerbating joint instability in hypermobile patients.

In individuals with hypermobility, often associated with fibromyalgia, peripheral musculotendinous injuries are common due to diminished proprioception and tissue fragility. These injuries can become sites of peripheral sensitization, potentially exacerbating the central sensitization characteristic of fibromyalgia. This dual mechanism of sensitization may intensify the widespread pain typical in fibromyalgia, suggesting a complex interplay between peripheral injuries and central pain processes. Understanding this intricate relationship is crucial, in both diagnosis and management, considering the broad spectrum of pain generation and amplification mechanisms in these interconnected conditions.

In hypermobile individuals, a reduction in alpha muscle tone may be observed, likely due to impaired Golgi tendon organs function. This dysfunction can lead to inadequate muscle tone regulation. Alpha ascending nerve fibers, vital in pain modulation, also play a significant role in fibromyalgia, affecting cardiovascular system interactions and fatigue management. Their dysfunction or overactivation, highlights the critical balance they maintain in pain perception, cardiovascular regulation, and overall bodily homeostasis.

The intriguing overlap between fibromyalgia and hypermobility echoes the historical discovery of Syndrome X in the late 1980s by Dr. Gerald Reaven. Initially, Syndrome X described the relationship between hypertension and insulin resistance, a mystery in cardiovascular and metabolic health. Over time, this understanding evolved into what is now known as Metabolic Syndrome, highlighting the interconnected nature of these conditions.

This progression in understanding parallels our current exploration into a potential ‘Syndrome X of Pain’. This concept aims to encapsulate the complex interplay between fibromyalgia and hypermobility.

The exploration for a ‘Syndrome X of Pain’ is not merely academic. Unravelling this complex relationship could lead to innovative therapeutic strategies, much like the impact of Syndrome X on cardiovascular treatment. It promises a deeper understanding of the interconnectedness of human physiology, particularly in the realms of pain and neurosensory systems.

In summary, the correlation between fibromyalgia and hypermobility, and their potential shared pathophysiological pathways, opens a new frontier in medical research. The quest to define and understand a ‘Syndrome X of Pain’ could be the key to unlocking new approaches in the treatment and management of chronic pain disorders, offering hope and improved quality of life for millions suffering worldwide.

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IS-03

Mitochondrial pathology in fibromyalgia

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Fibromyalgia Syndrome (FMS) is a complex, debilitating disorder, marked by chronic widespread pain and a range of symptoms including fatigue, muscle pain, irritable bowel syndrome, joint pain, sleep disturbances, and more. Despite extensive research, the pathogenic mechanisms underlying FMS are not fully understood. Environmental stressors such as infections and physical trauma have been suggested as possible triggers, yet the specific pathways leading to FMS remain unclear.

Mitochondria, crucial for ATP production through oxidative phosphorylation (OXPHOS) and metabolic processes in the Krebs/TCA cycle, play a pivotal role in cellular energy production and metabolism. This central role has led to the hypothesis that mitochondrial dysfunction might contribute to the pathogenesis of FMS. Oxidative stress and inflammation, damaging mitochondria, have been implicated in FMS. Studies indicate a decrease in ATP and coenzyme Q10 levels, and an increase in ROS production in FMS patients, suggesting heightened cellular oxidative stress. These mitochondrial anomalies, including alterations in mitochondrial mass, downregulated mitochondrial biogenesis genes, and decreased respiratory complex activity, have been observed in both PBMCs and muscle tissue of FMS patients. Furthermore, symptoms such as fatigue and myalgia in FMS overlap with those seen in primary mitochondrial diseases.

This pilot study aims to investigate structural changes in the mitochondria of PBMCs in FMS patients compared to healthy controls using transmission electron microscopy (TEM). Our approach involved analyzing PBMCs from seven FMS patients and seven healthy individuals. Following informed consent, participants completed diagnostic questionnaires and provided blood samples for TEM analysis.

Results from the TEM analysis revealed distinct mitochondrial crista patterns in FMS patients, including a total absence of crista. These changes were correlated with the severity of widespread pain. Additionally, a high percentage of cells with “black particles,” potentially ribosome aggregates, was observed in FMS patient samples, suggesting a shared cellular stress response. This study thus uncovers novel morphological changes in mitochondria of FMS patients and highlights the potential role of mitochondrial dysfunction in FMS pathogenesis.

In conclusion, while it’s uncertain whether these mitochondrial changes are causative or secondary to FMS, they offer insight into the disease’s underlying mechanisms and present potential biomarkers for diagnosis and treatment targets. Further research is needed to elucidate the relationship between mitochondrial dysfunction and FMS, potentially leading to novel diagnostic tools and specific treatments for this challenging condition.

IS-04

Neuroimmunology of fibromyalgia and chronic pain

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Fibromyalgia is a chronic primary pain condition, the biological underpinnings of which are generally sought in maladaptive central nervous system plasticity.

This presentation will question this view. While there can be no doubt that pain is ultimately generated in the brain, there are indications of peripheral dysfunction in individuals living with fibromyalgia. For example, many people with rheumatoid arthritis display joint pathology that is primarily stromal in nature, with an overrepresentation of endothelial and fibroblast populations (Zhang *et al.*, 2023). This is likely to have an impact on nociceptive sensory neurons, since fibroblasts can directly activate and sensitise them (Chakrabarti *et al.*, 2020; Shinotsuka & Denk, 2022). It is therefore conceivable that rheumatoid arthritis patients diagnosed with fibromyalgia live with such local stromal cell pathology, which would not be affected by conventional disease-modifying anti-rheumatic drugs.

Additional evidence for the involvement of the peripheral immune and nervous systems in fibromyalgia comes from studies demonstrating that the condition can be transferred into mouse using patient sera (Goebel *et al.*, 2021) and that there are indications that individuals with fibromyalgia display signs of a small fibre neuropathy (Üçeyler *et al.*, 2013). In conclusion, the presentation will argue that we simply have not yet carried out enough translational studies in local tissues to be certain about the extent of peripheral drive in fibromyalgia.

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IS-05

CPM deficiency in fibromyalgia: key findings and novel treatment directions

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Conditioned pain modulation (CPM) is a powerful endogenous analgesic mechanism, occurring when the response to a nociceptive stimulus is inhibited by a second nociceptive stimulus delivered at a different body location (1). In healthy individuals, the application of a painful stimulus in the presence of another (conditioning) painful stimulus results in decreased pain response as measured across various paradigms, as well as decreased reported perceived pain (2). In patients with idiopathic pain syndromes (*e.g.* fibromyalgia, migraine, irritable bowel syndrome), evidence indicate that this neurophysiological mechanism is aberrant (3, 4). In recent years there is a growing interest in the study of CPM in fibromyalgia (FM) due to its contribution to the understanding of the pathophysiology of the disorder, as well as its potential as a treatment target.

The behavioral phenomenon of CPM in FM has been established over the last two decades, based on repeated behavioral findings, as well as systematic reviews and meta-analyses (4, 5). In recent years, studies examining the neurobiological underpinnings of CPM in FM are starting to emerge. These include neuroimaging results that indicate smaller periaqueductal gray (PAG) volume in FM patients as compared to healthy controls (HC), as well as correlation between CPM efficiency and PAG connectivity with cor-

tical areas (6). Another study investigated whether genetic variants in genes coding for six major structures in the opioid and serotonergic systems affect pain modulation in FM patients and HC. Regardless of pain phenotype, the OPRM1 (coding for the μ -opioid receptor) and 5-HT1a (coding for serotonin receptor) genes influenced pain modulation. FM patients displayed lower CPM than HC but no group differences were found in the effects of the tested genes on CPM (7). These evidence, although preliminary, help elucidate CPM mechanism in FM as well as propose potential targets for intervention. Some existing interventions have been shown to restore CPM in FM patients. For example, a single session of isometric exercise was shown to (temporarily) restore CPM in individuals with FM (as well as healthy controls) (8).

Finally, in the field of migraine (another idiopathic pain disorder), there is an FDA-approved, clinically-proven (9-13), CPM-targeted intervention, based on Remote Electrical Neuromodulation (REN). REN is a non-pharmacological technology that induces subthreshold non-painful conditioning electric stimulation in one body region (*i.e.*, the upper arm) to alleviate pain in distal body regions. A double-blind, randomized, sham controlled study examining REN intervention for the alleviation of FM pain and related symptoms is currently being conducted. The technology, previous findings, and study design are reviewed.

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IS-06

The potential of AI in fibromyalgia research

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Artificial intelligence can be used in various ways to improve the treatment of fibromyalgia. In my lecture, I will show several specific examples. Through unsupervised machine learning, clustering analyses can be performed to identify fibromyalgia phenotypes. Using generative AI, these phenotypes can also be visually represented as 'Digital Personas'. These

can be used, for example, in study design or function as 'Digital Twins'. Supervised learning is a classic discipline in machine learning, and it can be used to predict disease progression or, for example, the response to multimodal treatment programs. This can help plan interventions as an 'AI-supported shared decision process' together with the patient and treatment team. Self-management plays a particularly important role in fibromyalgia. Here, Digital Therapeutics (DTx) come into play, which include cognitive behavior therapy or physical exercise instruction and evaluation. Through so-called knowledge graphs, self-management programs can be automatically evaluated and visualized. Furthermore, gap analyses can be conducted and with the help of large language models such as ChatGPT, new conceptual frameworks can be created on how to better treat fibromyalgia with DTx.

IS-07

Central sensitization and nociplastic pain: how clinically useful are these concepts?

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Fibromyalgia has long been considered a central sensitization syndrome. Some years ago the term nociplastic pain was introduced in the scientific literature (1) and fibromyalgia is now considered a clear example of nociplastic pain. However, the concept nociplastic pain and its assessment have been criticised (2, 3) as well as the broad use of the concept central sensitization (4). In this presentation I will summarize the existing critique on the concepts central sensitization and nociplastic pain.

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IS-08

Non-invasive transcutaneous vagus nerve stimulation for the treatment of fibromyalgia

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The vagus nerve is a parasympathetic nerve that controls the enteric nervous system and the vascular and immune systems. Invasive and non-invasive electrical stimulation of this nerve induces pain relief, particularly in clinical conditions such as headache and rheumatoid arthritis. Vagal afferents towards the nucleus of the solitary tract, the central relay nucleus of the vagus nerve, are suggested as the main neurobiological mechanism that reduces pain intensity after vagal stimulation. Chronic pain symptoms of fibromyalgia patients might benefit from stimulation of the vagus nerve via normalization of altered autonomic and immune systems causing specific symptoms, but multi-session non-invasive auricular and cervical vagal stimulation effects on fibromyalgia have not been evaluated in randomized clinical trials. We have designed a parallel group, sham-controlled, randomized study to modulate the sympathetic-vagal balance and pain intensity in fibromyalgia by application of non-invasive transcutaneous vagus nerve stimulation (tVNS) over the vagal auricular and cervical branches. We are recruiting 136 fibromyalgia patients with chronic moderate to high pain intensity. Primary outcome measure in our study is pain intensity, and secondary measures are fatigue, health-related quality of life, sleep disorders, and depression. Heart rate variability and pro-inflammatory cytokine levels will be obtained as secondary physiological measures. We hypothesize that

multiple tVNS sessions (5 per week, for 4 weeks) will reduce pain intensity and improve quality of life as result of normalization of the vagal control of nociception and immune-autonomic functions. Since both vagal branches, auricular and cervical, project to the nucleus of the solitary tract, no significantly different results between both stimulation protocols are expected.

IS-09

Advancements in medications for fibromyalgia

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From a neurochemical point of view, fibromyalgia is characterized by an imbalance between pain-facilitating neurotransmitters, such as glutamate, and antinociceptive neurotransmitters, such as GABA and noradrenaline. The consequence of this imbalance is the generation of a central sensitized state that maintains itself through maladaptive neuronal plasticity.

Pharmacological treatments of fibromyalgia are predicated on the foundation of restoring a more balanced brain chemistry, but drug therapy is often only partially effective, also because potential drug targets are part of maladaptive plasticity and might be modified in number and function, as in the case of opioid receptors.

Antidepressants, especially TCA and SNRI, alpha2 delta ligands, antiepileptic drugs have been widely used in the treatment of fibromyalgia, with variable responses also related to the "type" of fibromyalgia. New approaches based on oxybate, cannabinoids, atypical antipsychotic, acetyl-L carnitine, have been conceived or under study.

The pharmacodynamic properties of each of these drugs will be analyzed in the perspective of the pathogenetic mechanisms that they could correct.

IS-10

Psychotherapy in fibromyalgia: the state of the art and new directions

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Introduction. Fibromyalgia is a chronic syndrome characterized by widespread pain, fatigue, sleep disturbances, and mood alterations, mainly affecting women. It represents a clinical challenge with a multifactorial complex pathogenesis. Most of the available guidelines suggest that FM should be approached with integrated protocols encompassing pharmacological and non-pharmacological treatments. However, although the number of studies has risen significantly in recent years, a clear indication of efficacy of psychological treatments on specific FM related outcomes (such as pain, fatigue, sleep, depression, anxiety, quality of life) is missing in literature.

Objective. To provide a brief and comprehensive summary of the recent evidence about the efficacy of psychological and psychotherapeutic interventions for FM on related outcomes.

Methodology. A systematic literature review on the last 10 years was conducted on relevant electronic databases such as PubMed, Web of Science, PsychInfo and Cochrane. Key words were: FM, Psychotherapy, Cognitive Behaviour Therapy, Non-Pharmacological Treatment, Counseling, Mindfulness, Psycho-education, Psychological treatment. A total of 356 relevant articles were retrieved and reviewed for the current work.

Results. In FM literature, the most commonly used psychological approaches are Cognitive-Behavioral Therapies (CBT), such as Acceptance and Commitment Therapy (ACT) and Mindfulness-Based Stress Reduction (MBSR) (Alvarado, 2022; Hong-Baik *et al.*, 2023; Skelly *et al.*, 2020). However, other effective approaches include biofeedback, hypnotherapy, psycho-educational programs, and psychodynamic interventions that focus on improving emotional identification and processing, such as Emotional Awareness and Expression Therapy (EAET) (Martinez-Calderon *et al.*, 2021; Santoro & Cronan, 2014).

The most frequently studied FM outcomes are perceived pain, sleep distur-

bance, fatigue, affective symptoms (such as depression and anxiety), functional deficits and cognitive impairment (Skelly *et al.*, 2020).

CBT, ACT and MBSR appear to have discordant results with respect to the efficacy of treated symptoms (Alvarado, 2022; Amutio *et al.*, 2018; Cabral *et al.*, 2021; Gómez-de-Regil & Estrella-Castillo, 2020; Hong-Baik *et al.*, 2023; Kundakci *et al.*, 2022). Specifically, a significant improvement in perceived pain, sleep disturbance, functional deficit and cognitive impairment [Strength of Evidence (SEO): moderate] was observed in intermediate treatments (6-12 months) (Skelly *et al.*, 2020). EAET showed little evidence in association with reduction in short-term pain intensity in FM patients (SEO: low) (Kundakci *et al.*, 2022; Lumley *et al.*, 2017). The effectiveness of bio-feedback, hypnotherapy was observed in pain relief and psychological distress reduction with controversial results (SEO: moderate). Psychoeducational programs, and psychodynamic therapies has been shown to improve pain management, disability, pain catastrophizing, anxiety, and depression in patients with fibromyalgia, providing them with tools to better understand and manage their condition (SEO: low) (Skelly, 2020; Green *et al.*, 2013; Zech *et al.*, 2017; Picard *et al.*, 2013; Martinez-Calderon *et al.*, 2021).

Conclusion. Multidisciplinary interventions, with the integration of different treatments, are shown to be effective in improving symptoms in the short term (1-6 months) (Martinez-Calderon *et al.*, 2021) Recent guidelines, including those from EULAR and NICE, emphasize the robust recommendation for multidisciplinary interventions (Macfarlane *et al.*, 2017; National Guideline Centre (UK), 2016). This review emphasizes the nuanced effectiveness of different therapeutic modalities and underscores the need for further research to optimize protocols and understand the long-term effects on FM management.

IS-11

The relationship between chronic pain and depression in fibromyalgia

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Mood depression reduces the pain threshold by promoting central sensitization. On the other hand, pain, through various mechanisms (chronic stress, demoralization, functional limitation, social isolation, etc.) can promote the appearance of depression. However, the relationship between depression and pain is not a simple co-morbidity but it must be considered as a co-pathogenesis (Torta *et al.* 2023). The shared mechanisms underlying both depression and pain are multiple. From the neurotransmitter point of view a deficit of 5HT and NE in the fronto-limbic circuits induces a mood depression but, at the same time, such a deficit in the inhibitory descending system (from the periaqueductal griseum to the spinal cord) involves a reduction of algic inhibition. Hyperactivation of the HPA system (hypothalamus-pituitary-adrenal axis) leads to several consequences, such as an increased release of pro-inflammatory cytokines (involved in mood, pain and cognition), a prevalence of sympathetic tone (characterizing both depression and algic states) and also an increased release of CNS glutamate (favoring both depression and pain). Neurosteroids are also reduced, resulting in a lowering of gabaergic tone and an increase in glutamatergic one. The induction of IDO (indoleamine 2-3 dioxygenase), caused by the increased release of pro-inflammatory cytokines, leads to a reduction of serotonin and melatonin (mood and insomnia) and an increase in glutamate (depression and pain). Several of these mechanisms are linked to neuroinflammation (Benatti *et al.*, 2016) and we found that high level of cytokines correlate with mood depression, cognitive dysfunction, pain and stress levels (Baudino, Torta *et al.*, 2012). The treatment of depression and pain must therefore be contextual and can be based on both pharmacological and non-pharmacological (psychological, physical and social) interventions. Among the pharmacological interventions, the most relevant, especially in a context of nociplastic pain, is represented by antidepressants, in particular dual ones, acting on both pain (PAG system) and mood (fronto-limbic system); by gabapentinoids, alpha-2 delta receptor blockers (acting on pain and anxiety); by some analgesics, such as tramadol and tapentadol (that act at the same time on mu opioid receptors and on reuptake inhibition of 5HT or NE) or cannabinoids, especially through the action of cannabidiol, which simultaneously act on the sense of well-being, anxiety, insomnia and pain (Sarzi-Puttini *et al.* 2021). From the psychotherapeutic point of view some interventions have been widely validated for their ability to act in parallel on mood and algic components. Cognitive behavioural therapy is effective, not only on the

emotional aspects, but also on pain, as demonstrated by neuroimaging studies in which there is a reduction in the thalamus activity and an enhancement of the inhibitory action of the fronto-limbic circuits. Other types of interventions such as mindfulness and hypnosis show the same clinical results, also with neuroimaging confirmations (Torta, 2023). Physical interventions, such as aerobic physical activity, which contributes to the strengthening of self-management and the reduction of fatigue, counteract the algic and depressive components (also through the stimulation of endogenous opioids). In conclusion, the vicious circle between mood and pain must necessarily be addressed with interventions that allow a comprehensive approach of the bio-psychosocial components to avoid the already detected risk that partial interventions do not achieve a significant improvement

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IS-12

The impact of environment on fibromyalgia symptoms

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Environment can be defined as a sum total of all the living and non-living elements and their effects that influence human life. While all living or biotic elements are animals, plants, forests, fisheries, and birds, non-living or abiotic elements include water, land, sunlight, rocks, and air. Moreover environment is defined as the situation that you live or work in, and how it influences how you feel.

Fibromyalgia is a chronic widespread pain syndrome accompanied by joint stiffness, fatigue, sleep, cognitive and mood issues. Despite extensive research, the underlying mechanisms of FM symptoms are still not fully understood. Applying the bio-psycho-social model of health is it possible to at least partially focus the influence of the different aspects of environment on the FM symptoms and their onset (1, 2). It is recognized that, beside a genetic predisposition, environment factors, like infant trauma, stress, depression, infections play a fundamental role in the onset and development of FM (3, 4), probably through an epigenetic (5, 6) modulation.

In fact, genome-wide association studies investigated genes potentially involved in FM pathogenesis highlighting that genetic factors are possibly responsible for up to 50% of the disease susceptibility. A gene-environmental interaction has been proposed as triggering mechanism, through epigenetic alterations. Epigenetic mechanisms have been observed to play an important role as mediators of long-term changes in central and peripheral nervous systems in chronic pain, including the impact of inflammation, neuroinflammation, neuroendocrine and oxidative stress balance (7).

All aspects of environment should be taken into consideration: age, gender, diseases, infections, sleep, mental and emotional health, belief and expectation, self-esteem, coping- and social-skills, interpersonal relationships, family, school, peer, social support dynamics, socioeconomic.

To face the complex nature of FM, interdisciplinary and multidisciplinary collaborations are fundamental. These include cooperation among researchers, clinicians, and patients, to develop a comprehensive understanding of the disease. Using a multi-system lens is a possible way to plan an effective strategy for prevention and treatment in FM.

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IS-13

Concomitant fibromyalgia in rheumatic diseases

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Fibromyalgia is characterized by widespread pain accompanied by somatic symptoms such as fatigue and sleep disorders. Fibromyalgia is particularly prominent in patients with rheumatic diseases. It is of great importance to recognize fibromyalgia as a source of pain and to separate it from the inflammatory process in order to properly treat the patient and prevent unnecessary changes of treatment. Databases indicate greater switching of biologics among patients with inflammatory arthropathies and concomitant fibromyalgia.

The prevalence of fibromyalgia in patients with rheumatic disease is about 20 to 30% of patients. A north American database of approximately 6000 patients identified a 21% prevalence of fibromyalgia in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and osteoarthritis. Similar rates have been described in spondyloarthritis (SpA), including psoriatic arthritis (PsA) and other connective tissue diseases. It should be noted that, like in primary fibromyalgia, secondary fibromyalgia is more common in women.

Different studies have shown that the intensity of pain and disability is higher in patients with rheumatic disease such as RA and PsA and concomitant fibromyalgia. This fact may have a profound impact on the evaluation of disease activity in patients with inflammatory rheumatic diseases.

The treatment of RA and SpA is based on the treat to target concept. In the last 2 decades, the treatment of these diseases has been revolutionized by the introduction of biologic agents and targeted agents. The treat to target strategy aims at reaching a state of remission or low disease activity. When evaluating RA, common measures of disease activity are Disease activity score-28 (DAS-28) or Simplified disease activity score (SDAI). Both measures include the number of swollen and tender joints out of 28, patient's disease activity assessment and a measure of inflammation such as ESR or CRP. Assessment of the disease activity by the patient may be influenced by many factors such as the objective state of inflammation but also by the intensity of non-inflammatory pain, due to fibromyalgia. It has been unequivocally shown that the presence of fibromyalgia among RA and PsA patients significantly increases the various measures of disease activity. A patient with RA and fibromyalgia may demonstrate a lack of swollen joints along with multiple tender joints raising the levels of DAS to rates of moderate to high disease activity. The same has been shown in PsA where the difficulty is further increased by the presence of enthesitis which may be confounded by tender points or in axial spondyloarthritis which is assessed by subjective symptoms of back pain and morning stiffness.

In patients with inflammatory disease and concomitant fibromyalgia, it seems that any change in disease modifying drugs (DMARDs) should be based on more objective methods of evaluation such as ultrasound and not only rely on physical examination and patients reported outcomes.

In addition, the presence of fibromyalgia may represent a factor in the choice of the DMARDs. The JAK/STAT pathway is receiving increasing attention in the modulation of nociceptive responses given to its clear role in cytokine signalling. Therefore, inhibition of JAK/STAT pathway with specific JAK inhibitors has the potential to modulate pain in patients with RA and PsA. In conclusion, fibromyalgia is common among patients with rheumatic diseases. Identifying the phenomenon is of great importance in order to prevent misinterpretation of disease activity measures leading to unnecessary treatment. Proper identification of fibromyalgia in rheumatic patients will lead to a better understanding of patient's symptoms and appropriate treatment.

IS-14

Why should(*nt) the diagnosis of fibromyalgia be given (only) by a rheumatologist

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Fibromyalgia syndrome (FMS) is a chronic condition characterized by widespread musculoskeletal (MSK) pain, fatigue, and sleep disturbances. The complex symptomatology of fibromyalgia also involves autonomic disturbances, cognitive dysfunction, hypersensitivity to external stimuli, somatic symptoms and psychiatric disorders. Albeit, due to the omnipresent musculoskeletal symptoms, the disorder has transitioned over the past century to the primary care of the rheumatologist reaching the point where more than a third of rheumatology referrals are requests for the evaluation of suspected FMS or treatment thereof. Whereas the rheumatologist is proficient in ruling out other causes of MSK pain such as inflammatory and degenerative arthritis, myositis and vasculitis, he is deficient in the ability to assess the psychiatric aspects of the syndrome. Despite these shortcomings, making a diagnosis of FMS based on typical MSK complaints after ruling out only rheumatic conditions has become the norm. This is largely due to the fact that focusing on and treating the MSK domains of FMS is more acceptable to the patients as people tend to be more comfortable confronting a physical disease than a mental illness. In fact, suggesting psychological distress as the initial cause or propagator of FMS is no longer "Bon Ton". It is therefore hereby suggested that the diagnosis of FMS be performed by a joint team of a rheumatologist and a psychotherapist. The first will assess for the presence of inflammatory or degenerative causes for widespread musculoskeletal pain while the latter will evaluate past and current psychiatric morbidities. It is not improbable that in a sizable proportion of cases a psychiatric illness may explain the clinical syndrome in its entirety precluding a diagnosis of FMS. In such cases, giving a diagnosis of FMS is not only erroneous in its redundancy but also in removing the focus from psychological based therapies.

IS-15

The role of stress in fibromyalgia

Valerie Aloush MD

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Fibromyalgia, a chronic pain disorder characterized by widespread musculoskeletal pain, tenderness, and fatigue, presents a complex clinical challenge. The emerging body of evidence underscores a profound connection between fibromyalgia symptoms and the central nervous system (CNS). This association encompasses changes in pain processing within the brain and spinal cord, neurotransmitter dysregulation, and structural modifications in key brain regions involved in pain, emotional regulation, and stress modulation. Chronic or excessive stress, a natural physiological response to challenging situations triggering the body's "fight or flight" response, is recognized as a significant contributor to fibromyalgia. Epidemiological studies consistently demonstrate a correlation between stressful life events – such as traumatic experiences, major life changes, or chronic stressors – and the development of fibromyalgia. Longitudinal studies indicate that individuals exposed to high levels of stress are more susceptible to developing this condition. Psychosocial factors, including elevated levels of perceived stress, anxiety, and depression, are prevalent among individuals with fibromyalgia. This sets the stage for bidirectional relationships, where stress contributes to psychological symptoms, and psychological distress, in turn, exacerbates fibromyalgia symptoms.

Acknowledging the strong connection between psychological factors and fibromyalgia emphasizes the necessity of integrating mental health support into comprehensive care. Collaborative efforts between rheumatologists, pain specialists, and mental health professionals ensure a holistic approach to managing both the physical and psychological aspects of fibromyalgia, targeting psychological stressors alongside medical and physical treatments. Understanding the intricate interplay between fibromyalgia and the CNS, coupled with recognizing the impact of stress on the body, lays the groundwork for exploring specific mechanisms through which stress may contribute to the development and exacerbation of fibromyalgia symptoms.

IS-16

Multidisciplinary approach in fibromyalgia treatment

Winfried Häuser

Speaker: Winfried Häuser is a specialist in general internal medicine, psychosomatic medicine and pain medicine, and author of systematic reviews of pharmacological and non-pharmacological treatments of FMS. His H-index is 71.

In my lecture, I refer to the 2017 recommendations of the European League Against Rheumatism (EULAR) for the management of FMS and the 2017 German guidelines on the diagnosis and therapy of FMS and my personal experiences in collaborating with people with FMS since 30 years.

If we consider a multidisciplinary approach to FMS, we have to keep in mind that:

- The management of FMS substantially depends of the resources of the particular health care system and that there are great differences between countries, even in so-called first world countries in the treatment options available for people with FMS.
- As in most other diseases, we can differentiate different severities of FMS (mild, moderate, severe). Guidelines recommend a graduated approach in the management of FMS depending on the severity.

Multicomponent or combined therapies are defined by the combination of at least two treatment modalities (exercise, physical therapies / physiotherapy, psychological and pharmacological therapies). We know from patient surveys that most people with FMS use a multicomponent self-management approach. Multicomponent treatment does not necessarily imply a multidisciplinary treatment. A single GP, rheumatologist, psychiatrist or pain specialist can use a combined therapy, e.g. medication and psychological support and advice for aerobic exercise. Thus, mild and some moderate FMS-cases can be managed by a single disciplinary approach.

EULAR and the German guidelines recommend the referral to a mental health care specialist in case of anxiety, depression or maladaptive coping (e.g. catastrophizing). In most European countries, many FMS-patients are under a multidisciplinary, yet uncoordinated treatment, e.g. pain treatment by a GP and pain specialist and therapy of mental disorders by a mental health care specialist. Unfortunately, this multidisciplinary treatment is not interdisciplinary, because regular exchange between the disciplines require time and are not reimbursed by health insurance companies.

EULAR and the German guidelines recommend multimodal rehabilitation programs for severe cases of FMS defined by high impairment in daily function. Interdisciplinary programmes have to include (a) a common philosophy treatment in line with the biopsychosocial model of pain; (b) a treatment component where patients actively participate by means of tasks, training and/or exercise; (c) at least three different healthcare professionals from various disciplines that provided the interdisciplinary treatment; (d) a single facility where each patient received treatment. These programs are available and reimbursed by statutory health insurance companies in Scandinavia and Germany. Unfortunately, the evidence for combined and interdisciplinary treatment for FMS is not convincing. There is evidence from systematic reviews of RCTs that combined aerobic exercise with at least one psychological therapy was superior to control groups (waiting list, attention control treatment as usual) in reducing pain and disability in the long-run. However, combined aerobic exercise with cognitive behavioral therapies was not superior to aerobic exercise alone in 6 RCTs. A systematic review of cohort studies has shown that participation in an interdisciplinary programme was associated with considerable improvements in wellbeing that were generally maintained at follow-up in patients with chronic primary musculoskeletal pain. However, only a few studies with FMS-patients could be included in the review and no FMS-subgroup analysis was provided.

IS-17

Emerging technologies in fibromyalgia diagnosis and treatment

Jacob N. Ablin

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FMS is a complex medical condition characterized by chronic widespread pain, fatigue, and cognitive difficulties, commonly referred to as “fibro fog.” The condition’s elusive pathogenesis and multifaceted symptomatology have historically made diagnosis and treatment challenging.

The Role of AI and Machine Learning. AI and machine learning are revolutionizing the approach to FMS. These technologies are instrumental in pat-

tern recognition, enabling the identification of subtle indicators in patient data that might be overlooked by conventional methods. AI algorithms excel in analyzing extensive datasets, including genetic information, to aid in early and precise diagnosis. Furthermore, AI-driven models can predict treatment responses, helping to tailor personalized therapeutic strategies that reduce the often frustrating trial-and-error process in FMS treatment. AI is also invaluable in symptom monitoring, with capabilities to analyze data from wearable devices to track pain levels, sleep patterns, and physical activity.

Digital Therapies and Smartphone Applications. The FDA’s authorization of the Stanza mobile app, a smartphone-based digital therapy, marks a significant development in FMS management. The app provides ACT and CBT to assist patients in coping with psychological symptoms, such as anxiety and depression, often accompanying FMS. Clinical trials report notable improvements in depression, anxiety, and overall quality of life among Stanza users (Pain News Network, 2023). Other helpful smartphone applications include Evernote for memory and note-taking, “Where’s My Car?” for location tracking, “Tasks Free” for task management, “Manage My Pain” for pain logging, and Dictionary.com for aiding in word recall (NewLifeOutlook, 2014).

Wearable Technology in Pain Management. The advancement in wearable technology is exemplified by the FDA-approved Quell device, a novel non-pharmacological treatment option. This wearable neuromodulator stimulates sensory nerves, eliciting the body’s natural pain relief response, and has shown considerable promise in improving the quality of life in FMS patients (FierceBiotech, 2022).

Natural Language Processing (NLP) in Research and Patient Support. NLP is significantly impacting FMS research and patient support. By analyzing unstructured data in medical records and scientific publications, NLP helps in identifying emerging trends and potential research areas. It also plays a pivotal role in patient communication, with chatbots offering interactive support. NLP’s sentiment analysis of social media discussions offers insights into the patient community’s concerns and experiences.

Cognitive Training and Exercise Therapy. Cognitive training platforms like CogniFit provide exercises specifically designed to mitigate cognitive symptoms associated with FMS. These exercises aim to improve memory, attention, and processing speed, among other cognitive functions affected by “fibro fog” (CogniFit, 2024). Exercise therapy, as outlined by platforms like Hinge Health, is vital in managing FMS symptoms. Strategies such as energy pacing, goal setting, and adopting a “Movement is Medicine” mindset aid in incorporating physical activity into patients’ routines, despite the challenges posed by fatigue and pain (Hinge Health, 2024).

Emerging Treatments: HBOT and TMS. There is growing interest in the potential of Hyperbaric Oxygen Therapy (HBOT) and Transcranial Magnetic Stimulation (TMS) for FMS. Preliminary evidence suggests that these treatments may positively impact neuro-functioning in FMS patients. However, a detailed presentation of these technologies and their effects on FMS is beyond the scope of this abstract.

Conclusion. The integration of AI, digital therapies, wearable technology, NLP, and emerging treatments such as HBOT and TMS represents a transformative shift in the management of FMS. These technologies not only provide novel diagnostic and therapeutic avenues but also enhance the daily management of the condition. As we continue to embrace and develop these technologies, the potential to significantly improve the quality of life for individuals with FMS becomes increasingly tangible.

IS-18

Exploring the interplay between fibromyalgia, nutrition, and the microbiome

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Fibromyalgia, often accompanied by chronic fatigue syndrome (CFS), is a challenging chronic pain syndrome lacking a clear treatment consensus. This presentation investigates fibromyalgia’s connections with dietary choices and the microbiome, alongside emerging clinical trial findings.

The multifaceted nature of fibromyalgia, with symptoms overlapping other chronic illnesses, demands a multidimensional treatment approach. Widespread pain, fatigue, cognitive issues, mood disorders, and gastrointestinal problems are common, making diagnosis and management complex.

One of the intriguing aspects of fibromyalgia is the potential link between dietary choices and symptom severity. While there is no specific dietary therapy for fibromyalgia, several studies have suggested that nutrition plays a significant role in influencing symptom presentation and overall quality of

life for affected individuals. Researchers have explored how diet composition, food sensitivities, and micronutrient deficiencies may contribute to the manifestation and exacerbation of fibromyalgia symptoms. Understanding these dietary factors and their impact on the condition is crucial for tailoring effective treatment strategies.

Dietary interventions like prebiotics, probiotics, and personalized dietary plans show promise in modulating the gut microbiome and alleviating symptoms, suggesting a potential for personalized treatment strategies.

The gut microbiome has emerged as a key factor in fibromyalgia. Altered microbiome composition in patients raises questions about dysbiosis' role in heightened pain sensitivity and inflammation. The gut-brain axis, involving bidirectional communication between the gut and nervous system, is implicated in fibromyalgia's pathophysiology, necessitating further exploration into microbiome's influence.

Ongoing clinical trials focus on anti-inflammatory nutritional interventions, targeting the underlying inflammatory processes in fibromyalgia. Notably, Fecal Microbiota Transplantation (FMT) from fibromyalgia patients to germ-free mice has demonstrated induced pain hypersensitivity, suggesting a direct link between gut microbiota and fibromyalgia pain. A pilot study in humans showed reduced pain following FMT from healthy donors, highlighting FMT's therapeutic potential.

The presentation concludes with expectations for future research to uncover novel insights into fibromyalgia's etiology and innovative therapeutic approaches.

Key words: fibromyalgia, nutrition, microbiome, dysbiosis, chronic pain, dietary interventions, gut-brain axis, clinical trials, inflammation, multi-dimensional approach

IS-19

Innovative approaches in fibromyalgia management

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Fibromyalgia syndrome (FMS) emerges as an intricate and persistent pain condition, characterized not solely by widespread musculoskeletal discomfort but also marked by profound fatigue, disruptions in sleep patterns, and a myriad of other symptoms impacting various organs and systems (1). There are many therapies available for fibromyalgia, including pharmacologic therapies, exercise, electrotherapy, psychological therapies, and complementary and alternative treatments (2). Many systematic reviews have reported the outcomes of these therapies for patients with fibromyalgia; indeed, the therapeutic approach to managing patients with FMS is characterized by integrated and multidisciplinary interventions, acknowledging the diverse range of symptoms experienced by patients (3). The treatment of FMS can be divided into four pillars: patient education, fitness, pharmacological/non pharmacological treatment and psychotherapy. Suggested treatment strategy should take into account not only the latest EULAR recommendations (3) for FMS management but also real-life clinical experience and realistic patient expectations and goals (1).

Pharmacological intervention constitutes a pivotal aspect of this approach, recognizing that while it may not be a standalone solution, it can yield satisfactory results for a distinct percentage of patients. The US Food and Drug Administration (FDA) has approved 3 medications to treat FMS: pregabalin, duloxetine, and milnacipran. However, in a survey only 19% reported being very satisfied with their current treatment, whereas 28% were not very satisfied or not at all satisfied; fatigue, joint pain, and concentration difficulties were also not well managed (4), highlighting an unmet need for additional treatments that can adequately treat multiple symptoms of FMS. Among new pharmacological therapeutic options, we should include NMDA antagonists like ketamine, which is a non-competitive NMDAR antagonist, nitrous oxide and NYX-2925, identified as a NMDAR modulator, that has demonstrated promising effects in preclinical studies (5); TNX-102 SL which is a novel, low-dose, sublingual formulation of cyclobenzaprine designed to be taken at bedtime (6).

There is mounting evidence supporting cannabis use in chronic pain conditions [53]. An in-depth review has shown that cannabis has proven benefits in treating chronic pain [54]. However, there is only a handful of randomized trials in FM patients, even though cannabis was associated with beneficial effects on some FM symptoms (7-8). Cannabinoids can be synthesized in the laboratory or extracted from dried plant inflorescences, necessitating

a careful distinction between the two and critical evaluation of study outcomes regarding these preparations. With the rising global trend of cannabis use in chronic pain emphasizing FM, evidence is being gathered that supports cannabis use among FM patients (9). Naltrexone has garnered attention for its potential in FMS treatment. In particular, a paradoxical analgesic effect was observed with low-dose naltrexone (LDN) (10).

Combined therapeutic strategies also benefit from integrating drugs and nutraceuticals. It has been found that the fatty acid amide palmitoylethanolamide (PEA) and acetyl-L-carnitine (ALC) both have an effect on CWP (11), and one study has investigated the analgesic and anti-inflammatory effects of PEA in FM patients (12). PEA is an endogenous chemical that is thought to regulate inflammatory analgesic events and tissue reactivity by activating the cell surface cannabinoid (CB) 2-like receptor, the orphan G protein-coupled receptor (GPR)-55, and the nuclear receptor of the peroxisome proliferator-activated receptor (PPAR) family, and down-regulating mast cell degranulation autacid local inflammation antagonism (ALIA) mechanisms. ALC provides another approach to nociceptive pain therapy (13) as it increases the effects of nerve growth factor (NGF) while acting as an acetyl-group donor, and contributes to mitochondrial energy homeostasis and detoxification.

As in the case of other chronic conditions, fitness (14) is pivotal and should involve weight loss, aerobic and strengthening exercises as well as dietary modifications, all of which are important disease-modifying factors. Weight loss improves posture and well-being, and decreases both obesity-induced inflammation and peripheral nociceptive inputs. Aerobic exercise is strongly recommended as it can improve pain and physical function in patients with FMS, although the commencement of training can be difficult for some patients because of deconditioning and psychological factors. A recent meta-analysis evaluated the effect of physical exercise-based therapy (PEBT) on pain, impact of the disease, quality of life (QoL) and anxiety in patients with FMS, to determine the effect of different modes of physical exercise-based therapy, and the most effective dose of physical exercise-based therapy for improving each outcome (15). Thus, due to the low compliance of patients to recommendations for physical activity or a healthy lifestyle, physicians trend to medicalize the disease.

Psychological therapies (16) (e.g. relaxation, hypnosis, coping skills training, biofeedback, and cognitive behavioural therapy) may help people manage pain and its disabling consequences. Therapies can be delivered face-to-face by a therapist, via the Internet, by telephone call, or by computer programme. A systematic review and meta-analysis of 25 randomized controlled trials comparing the effect of all types of electrical neuromodulation (17) in patients with fibromyalgia was conducted showing that electrical neuromodulation is significantly effective in treating pain, depression, and functioning in patients with fibromyalgia.

In a recent review, the effectiveness of most therapies for fibromyalgia was not supported (4). Strong evidence supported only cognitive behavioural therapy for pain, as well as antidepressants and central nervous system depressants for pain and quality of life, but these associations were small.

In light of the multifaceted nature of FMS, a tailored and symptom-driven approach to pharmacotherapy emerges as crucial. Monitoring and prioritizing key symptoms pave the way for integrating various solutions, including nutraceuticals, into the treatment regimen. This comprehensive strategy aims at achieving individualized therapeutic outcome (18-20).

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IS-20

Patients organizations: the Italian experience

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In Italy Fibromyalgia is still an invisible disease. There is no biomarker, no diagnostic test that highlights it, no drug is approved. It is a disease with a high social and economic impact due to the direct and indirect costs of work and healthcare.

Patient Associations' main objective is to ensure this recognition, in order to give dignity to those who suffer from this condition, who very often are not even believed to be ill.

Thanks to their awareness-raising work, in the budget law, the State has allocated 5 million euros to be divided among all regions for the diagnosis, treatment and research of fibromyalgia.

One of these Patient Associations is Aisf-Odv (Italian Association of Fibromyalgia Syndrome).

It is non-profit social utility organizations. It is engaged both in activities of collective interest and in the protection of individual patients, working to ensure them a better quality of life in terms of medical, pharmacological and social assistance.

It was born in 2005 in Milan, but operates throughout the national territory; creates and develops dedicated programs for the improvement of fibromyalgia patients' lives. Aisf Odv created a nationwide Network able to directly support patients, listening to them and educating them to actively self-manage their condition: these interventions were shown to be particularly effective in many chronic conditions, especially in fibromyalgia, and self-management programmes have been at the core of many interventions 1,2. This is done through educational interventions about the disease (which are organized not only for patients, but also for healthcare professionals and Institutions), various workshops and activities. Examples of such activities are the Art therapy workshop, which helps patients transform their suffering with a greater and more correct awareness, movement activity projects and psychoeducational support groups. A recent ambitious project is to build up Reference Centres for the multidisciplinary management of fibromyalgia syndrome.

In Italy the real problem of fibromyalgia is an economic one. All political parties have proposed legislative measures, but the government struggles to secure the necessary economic resources to enact a specific law.

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IS-21

Patients organizations: the European experience

Gunilla Göran

European Network of Fibromyalgia Associations (ENFA)

In Europe, around twenty 20 million people with fibromyalgia live with a very low quality of life and with the highest sickness absence from work. Patients with fibromyalgia have significant differences in treatment in Europe. The understanding and knowledge of fibromyalgia is very low among healthcare professionals, patients are sent around in the healthcare which generates huge costs. There are no national guidelines for treatment. The quality of training of medical students varies and there are significant differences in social security rights for patients in European countries.

ENFA works for equal and fair access to health care for fibromyalgia patients. Request for a resolution from the European Commission to invite the national governments:

- 1) to pay attention and be aware of the needs of fibromyalgia patients.
- 2) to oblige national health authorities to include fibromyalgia among diagnoses with patient rights for consultation in specialist healthcare and to oblige municipalities and specialists to apply recommended diagnostics and treatment.
- 3) to approve legal matters devoted to the patient's financial support and treatment.

IS-22

Fibromyalgia respects no borders: the Brazilian experience

Caren Cunha

ANFIBRO, Brazil

Brazil is the 5th largest country in the world and the 9th world economy. It also has the biggest public health system (called SUS), in which 71% of Brazilians rely on. Being such a big country with its well known social economic issues creates different scenarios depending on the area or state someone lives. A Clinical Practical Guideline for treating widespread pain in SUS facilities was created in 2012, which includes Fibromyalgia.

Despite that, the time from the appearance of early symptoms to the definitive diagnosis of fibromyalgia according to Silveira *et al.* (1) is about 9.85 yrs. (more than 50% longer than Gendelman *et al.* (2) found in Israeli people: 6.42 yrs). The other Brazilians who rely on a private health system, almost 30% of Brazilian citizens, also have a very difficult time receiving paid leave from their job due to the fact Brazilian physicians in general do not recognize the fibromyalgia disabling potential.

Since 2019, ANFIBRO has been working together with the Italian fibromyalgia association LIBELLULA LIBERA. These two associations have jointly organized the first international fibromyalgia congress for patients which remains available for free on ANFIBRO's YouTube channel. We believe in the exchange of experiences between different realities in order to achieve our goals such as making Fibromyalgia to be recognized as a real and potential disabling disease.

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Treatment of Fibromyalgia

P-01

Evaluation of memantine in patients with fibromyalgia from the Multidisciplinary Center at Namur Godinne University Hospital

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Methods. Memantine, a non-competitive NMDA receptor antagonist, reduces the neurotoxic effect of glutamate, found in high concentrations in certain brain areas of patients with fibromyalgia and/or neuropathic pain. In our center, we prescribed it at a dose of 20 mg per day, according to a progressive schedule to fibromyalgia patients, not improved by the previous treatment implemented (duloxetine, pregabalin or other analgesic, exercise programs, health education and cognitive-behavioral therapies). The first findings reported by patients suggested an improvement in pain and quality of life. We carried out a qualitative and quantitative evaluation, using three questionnaires on D0 and D180:

1. the neuropathic pain symptoms inventory,
2. Fibromyalgia Impact Questionnaire,
3. Mac Nair Memory Complaint Scale.

Results. In this sample of 76 patients, 51 have been taking this treatment for 6 months and 11 stopped the trial because of adverse effects (dizziness, nausea, drowsiness and headache). Reducing doses helps improve these effects. The counting of the questionnaires at 6 months is still in progress. Qualitatively, more than 30% of patients report an improvement of more than 70% in quality of life.

Conclusion. The initial encouraging results invite us to continue the trials and their evaluations. This molecule, which has an excellent risk/benefit ratio, is a promising avenue in persistent complex pain.

P-02

Efficacy and safety of TNX-102 SL (sublingual cyclobenzaprine) for the treatment of fibromyalgia: results from the phase 3 randomized, double-blind, placebo-controlled RESILIENT trial

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Background. Fibromyalgia is a chronic pain disorder resulting from amplified sensory and pain signaling within the CNS.

Objective. To evaluate efficacy and safety of TNX-102 SL*, a bedtime sublingual formulation of cyclobenzaprine, for syndromal treatment of fibromyalgia.

Methods. Across 33 U.S. sites, RESILIENT enrolled 457 fibromyalgia patients; each received TNX-102 SL 2.8 mg for 2 weeks, followed by 5.6 mg for 12 weeks (n=231) or matching placebo (n=226). The primary endpoint was change from baseline at Week 14 in daily diary pain scores. Secondary endpoints included Patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire - Revised (FIQR) Symptoms and Function domains, PROMIS Sleep Disturbance and Fatigue, and daily diary sleep quality ratings. Safety was assessed by adverse events (AEs).

Results. Reduction in daily pain from baseline at week 14 was significantly greater with TNX-102 SL (LS mean change [95% CI], -1.82 [-2.04 to -1.59]) vs. placebo (-1.16 [-1.40 to -0.93]; p=0.00005), with a calculated effect size of 0.38. TNX-102 SL demonstrated significant improvement in PGIC, FIQR domains, PROMIS instruments, and daily sleep quality (all p≤0.001). Treatment-emergent AEs were reported in 58.9% TNX-102 SL, 36.7% placebo. Oral AEs were most common: oral hypoesthesia (23.8% TNX-102 SL vs. 0.4% placebo), product taste abnormal (11.7% vs. 0.9%), oral paresthesia (6.9% vs. 0.9%), and tongue discomfort (6.9% vs. 0%).

Conclusion. TNX-102 SL treatment significantly reduced daily pain and demonstrated broad FM symptom improvement, with an overall favorable safety and tolerability profile.

*TNX-102 SL has not been approved for any indication.

P-03

A model of psychological predictors of central sensitivity in fibromyalgia: effects on physical and psychological quality of life

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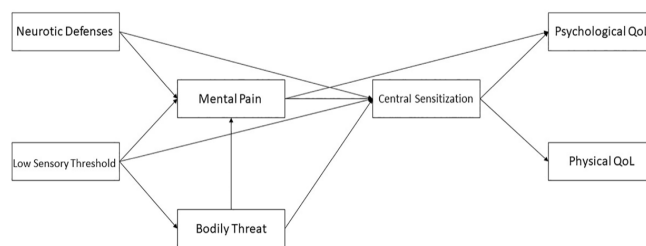
Background: Central Sensitivity (CS) is an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold inputs. It remains unclear in the literature what psychological factors influence CS in the case of fibromyalgia (FM).

Objectives: This study aims to investigate the impact of various psychological factors on CS in women with FM. The first aim explores the influence of temperament, personality, childhood trauma, defense mechanisms, and mental pain on CS. The second aim tests the most significant predictors of CS in affecting quality of life (QoL) through a path analysis.

Methods: 510 women with FM completed a self-administered protocol online between April and June of 2023.

Results: Higher levels of low sensory threshold (β=0.210), traumatic experiences of physical threat (β=0.141), neurotic defenses (β=0.124), and mental pain (β=0.241) emerged as the best predictors of increased CS in FM. A path diagram model was presented to explain the interplay between psychological factors, CS and QoL. The model showed a satisfactory fit (c²=27.200; df=10; p=0.002; GFI=0.984; NFI=0.949; CFI=0.967; RMSEA=0.061 [95% CI 0.034-0.090]) with large and medium effect sizes on physical (-0.576) and psychological (-0.190) QoL.

Conclusion: The study highlights the crucial role of psychological dimensions in influencing CS levels and their connections to QoL in FM patients. CS evaluation is suggested to improve the reference of eligible patients to psychological care.



QoL: Quality of Life

P-05

Use of tVNS as new therapeutic option in a cohort of patients with fibromyalgia syndrome: a pilot study

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Background. Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain. The etiology of fibromyalgia is not yet fully understood; however, data reveal that a dysfunction of the Autonomic Nervous System (ANS) could play a fundamental role. Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive technique that uses electrical stimuli to modulate the activity of the ANS. There is growing evidence that tVNS can improve nociception, mood and sleep quality.

Objective. The aim of this study is to evaluate the effectiveness of tVNS in reducing disease activity and improving sleep quality in fibromyalgic patients.

Methods. Our cohort underwent treatment with tVNS, consisting of 30-minute stimulation, 5 times a week for 4 consecutive weeks. Disease activity and sleep quality was assessed by clinimetric indices (VAS, FIQR, SSS, WPI, PSQI) at the beginning, after 2 weeks, and at the end of the treatment.

Results. 17 patients with FMS completed 4 weeks of treatment. After 2 weeks from the start of stimulation, an early reduction was found in both WPI

($p=0.002$) and total FIQR scores ($p=0.04$). After 4 weeks, patients obtained significantly lower scores in FIQR, both total ($p=0.001$) and Physical Function ($p=0.004$), Overall Health Status ($p=0.001$) and Symptoms ($p=0.001$), SSS ($p=0.001$), WPI ($p=0.002$) and PSQI ($p=0.001$) (Fig. 1 and Table 1).

Conclusion. Treatment with tVNS has been shown to reduce disease activity and improve sleep quality in our patient cohort; however, there were no significant differences in perceived widespread pain. These improvements were found both after 2 weeks and after 4 weeks.

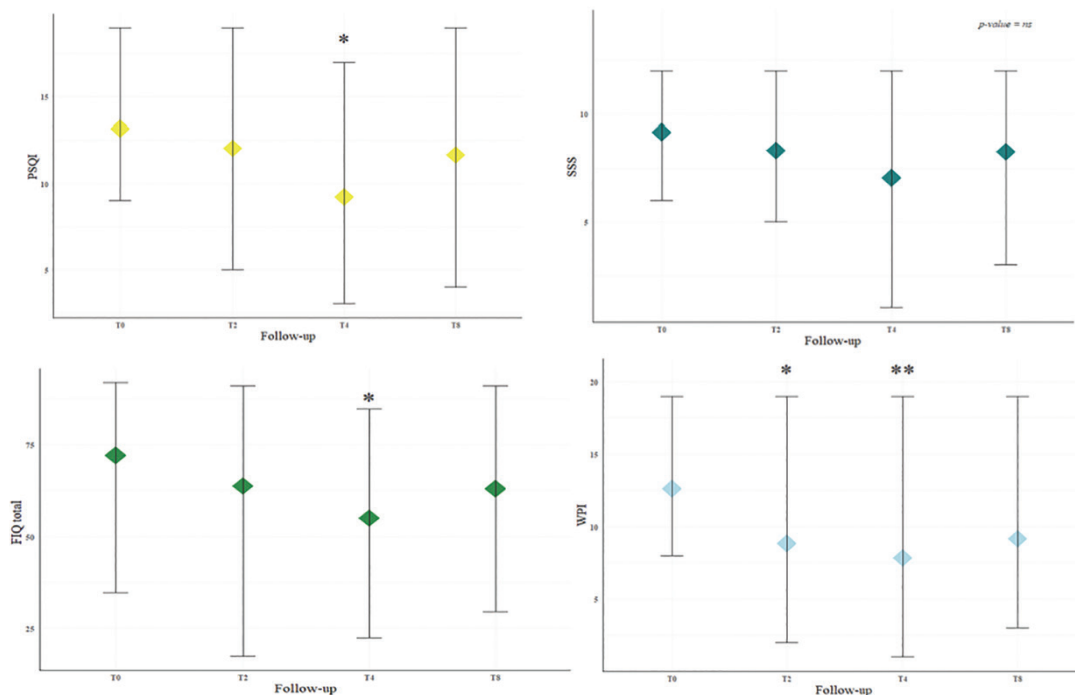
P-05: Table 1.

	Mean value	Z score	p-value§
VAS pain			
2 week - baseline	2.64 - 3.03	1.145	ns
4 week - baseline	2.14 - 3.03	-0.697	ns
8 week - baseline	2.19 - 3.03	-0.448	ns
FIQ general impact			
2 week - baseline	2.58 - 3.33	1.087	ns
4 week - baseline	1.89 - 3.33	-0.879	0.002
8 week - baseline	2.19 - 3.33	-0.207	0.04
FIQ symptoms			
2 week - baseline	2.53 - 3.44	0.701	ns
4 week - baseline	1.53 - 3.44	-1.145	< 0.001
8 week - baseline	2.50 - 3.44	0.443	ns
	Mean difference (IC 95%)		p-value§§
FIQ total			
2 week - baseline	-8.39 (-23.6, 6.82)		ns
4 week - baseline	-17.1 (-32.3, -1.8)		0.02
8 week - baseline	-9.08 (-24.2, 6.13)		ns
FIQ physical function			
2 week - baseline	-1.99 (-6.66, 2.67)		ns
4 week - baseline	-4.05 (-8.72, 0.61)		ns
8 week - baseline	-1.37 (-6.04, 3.29)		ns
WPI			
2 week - baseline	-3.77 (-7.40, -0.1)		0.03
4 week - baseline	-4.77 (-8.40, -1.1)		0.004
8 week - baseline	-3.44 (-7.07, 0.18)		ns
SSS			
2 week - baseline	-0.83 (-3.09, 1.42)		ns
4 week - baseline	-2.11 (-4.37, 0.14)		ns
8 week - baseline	-0.88 (-3.14, 1.37)		ns
PSQI			
2 week - baseline	-1.11 (-4.73, 2.51)		ns
4 week - baseline	-3.94 (-7.56, -0.3)		0.02
8 week - baseline	-1.50 (-5.12, 2.12)		ns

§ For multiple comparisons, the Nemenyi test was applied

§§ For multiple comparisons, the Tukey-Kramer procedure was applied

P-05: Fig. 1.



“Transparent Pain”: How Society Deals with Fibromyalgia

P-04

Sexual functioning and satisfaction in women with fibromyalgia confronted with other chronic pain conditions

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Background. Fibromyalgia (FM) is a prominent condition under the umbrella of Chronic pain (CP), adversely affecting various aspects of life, including sexuality. The challenge lies in discriminating sexual difficulties in FM and comorbid syndromes, often overlooked by both patients and clinicians.

Objective. The main aim is to compare sexual functioning and satisfaction of FM women with other CP conditions. The hypothesis anticipates differences between those exclusively diagnosed with FM, chronic headache (CH), vulvodynia (VU), compared to mixed diagnoses (MX; namely having FM in comorbidity with CH or/and VU) and a control group.

Methods. A total of 498 women completed an online protocol on sexuality between April and December 2023. A one-way MANCOVA having age as covariate was used to test differences among the five groups.

Results. FM, MX, and VU exhibited notably lower scores in sexual functioning and sexual satisfaction than controls and CH. While VU reported specific impairments in sexual desire and genital pain during penetration, FM showed a compromised profile in all aspects of sexual functioning (desire, arousal, and orgasm). Additionally, MX showed consistent difficulties in arousal and orgasm, reporting the highest level of distress than FM and other conditions.

Conclusion. CP significantly hampers the sexual experience in women, particularly in FM mixed diagnoses, possibly stemming from nociplastic pains. Clinicians urge to thoroughly investigate sexual experience in CP during routine consultations to improve the overall quality of life for these women.

Neuro-biological Underpinnings of Fibromyalgia and Centralized Pain

P-06

Investigating neutrophil-neuron interactions that modulate somatosensory processing and chronic widespread pain

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Our recent data shows a fundamental pro-nociceptive action of neutrophils derived from patients or mice with chronic widespread pain (CWP) when administered to naïve recipient mice. Neutrophils release extracellular vesicles (NDEVs) in response to numerous immunological stimuli, acting on and directly modulating target immune cells. We hypothesise that NDEV release and consequent actions of cargo enable neutrophils to sensitise sensory neurons and trigger nociceptive signalling.

To examine this, we have optimised a protocol to isolate NDEVs and have utilised flow cytometry, TEM and western blot analysis to characterise NDEV phenotype. To identify a specific pro-nociceptive capacity of NDEVs, we have isolated NDEVs from patients with fibromyalgia and pain-free controls to examine phenotypic and proteomic differences between cohorts.

We have successfully optimised a protocol of NDEV isolation from neutrophils whereby we see increased NDEV release following PMA stimulation. Our NDEV size profile and the presence of a phospholipid bilayer has been confirmed using TEM and western blot, identifying the transmembrane tetraspanin CD63. Phenotypic characterisation of NDEVs derived from patients reveals increased release when compared to pain-free controls, with equal size distribution. NDEV-mediated neuronal hypersensitivity may reflect a mechanism employed by neutrophils to trigger CWP in fibromyalgia. Pilot data also demonstrates neutrophil infiltration into the trigeminal ganglion, housing primary afferent nociceptors that innervate supracervical regions.

We have identified specific phenotypic differences between NDEVs derived from patients with fibromyalgia compared to pain-free controls. This altered phenotypic profile may reflect novel mechanisms through which neutrophils sensitise peripheral sensory neurons to produce CWP in fibromyalgia.

Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

P-07

Pain characteristics of patients with fibromyalgia: a comparison between gender and different emotional states

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Background. Generalized pain is the core symptom of fibromyalgia (FM). Few studies have described the different pain characteristics under various conditions.

Objective. To explore the pain characteristics of patients with FM of different gender and emotional states.

Methods. Three distinct instruments were used to assess the pain characteristics of 197 patients with FM: Numeric Rating Scale (NRS) for the severity of pain, Widespread Pain Index (WPI) for the number of pain regions, and Short Form-McGill Pain Questionnaire-2 (SF-MPQ-2) for the pain qualities. Zung Self-Rating Anxiety/Depression Scales were used to assess patients' emotional states. The differences in pain characteristics in FM patients of different gender and emotional states were analyzed.

Results. NRS was 7 (5–8), WPI was 13 (10–16), and the total score of SF-MPQ-2 was 2.36 (1.68–3.73) in all FM patients. Female patients reported more severe pain and numbness, less frequent chest pain and shooting pain than male patients did. Patients with FM and anxiety experienced more frequent and more severe punishing-cruel, fearful, sickening, and tender; more frequent jaw pain, and cold-freezing pain; more severe pain caused by light touch, and tiring-exhausting; less frequent lower leg pain than FM patients without anxiety did. Patients with FM and depression reported more frequent and more severe pain caused by light touch; more frequent tender; more severe tiring-exhausting, sickening, fearful, and punishing-cruel; less frequent and less severe piercing pain than FM patients without depression did.

Conclusion. Gender and emotional states significantly affected pain characteristics of patients with FM.

Classification, Diagnosis, Epidemiology and the Evolving Concept of Fibromyalgia

P-08

Pain and FM-like symptoms among Portuguese and Cape Verdean undergraduate students: are differences partly explained by race and psychosocial features?

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Background. Considering pain's significance and impact, it remains critical to identify potential modulators of its experience, with emphasis on biopsychosocial aspects whose profound influence is generally recognized but poorly understood. Such understanding is central to the FITSS model (1), which underscores the role of an over-responsiveness to threat and a hypo-responsiveness to safeness in amplifying pain and other somatic symptoms.

Objective. Characterize psychosocial features, pain pressure thresholds (PPT), and clinical symptoms between Portuguese and Cape Verdean students. Explore potential between-samples differences in threat-soothing balance and its association with pain sensitivity, fibromyalgiansess, psychological distress, and positive mental health (PMH).

Methods. A total of 118 Cape Verdean (n=67 women) and 116 Portuguese (n=61 women) undergraduate students were recruited. Participants' PPT was assessed using a dolorimeter while sociodemographic, clinical, and psychosocial variables were assessed through an online survey. Descriptive, correlational and Mann-Whitney analyses were used.

Results. Gender and between-samples differences were found, with women and Portuguese students presenting a greater threat-soothing imbalance, higher levels of threat, psychological distress, and fibromyalgiansess, and lower PPT and PMH. Gender and a greater activation of the 'threat-mode' were both significantly correlated with fibromyalgiansess, psychological distress, and PMH and correlated individually and respectively with threat-soothing imbalance and with PPT (only for Cape Verdeans).

Conclusion. Race/gender differences, and underlying mechanisms/correlates, constitute an important aspect that warrants further research. The results emphasize the need to explore how an overactivation of the 'threat-mode' influence pain/FM and to integrate the threat-soothing imbalance into the assessment and treatment of chronic pain/FM.

Key words: pain, fibromyalgiansess, racial and gender differences, threat-soothing imbalance

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P-09

From Emotions to Affect Regulation Systems: Development of the EASEL-3 Index

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Background. It is well-established that emotions are pivotal for one's overall welfare, and that, when dysregulated, they provide a diathesis for psychopathology (1-2). The 'three-circle model' (3) proposes the existence of three affect regulation systems – threat, drive, and soothing – responsible for managing threats, satisfy needs and attain valued resources/rewards, and support a sense of safeness and body restoration. When unbalanced, however, these systems may contribute to the emergence of physical and psychological symptoms, including fibromyalgia (4-5). Yet, the quantification of such imbalance has been hindered by the lack of a measurement system.

Objective. The study aims to address this gap by developing a new tool capable of estimating the degree of activation of each system.

Methods. Given the lack of a gold-standard, an expert survey methodology was used. A total of 70 experts from different backgrounds, grouped in three independent panels, were asked to estimate how much a pre-set of discrete emotions activated each one of the affect regulation systems.

Results. A high agreement among experts was attained regarding which emotions loaded in which system and how much they 'activated' it. Results were used to derive the Emotions-Affect Systems ELicitation index (EASEL-3) – a weighted estimation of the activation of the three systems.

Conclusion. The EASEL-3 constitutes a stepping stone in the development of a measurement system for quantifying the activation of the systems. While further validation and testing of it is warranted, the potential value and impact of the EASEL-3 in the assessment, classification and treatment of physical and mental disorders is promising.

Key words: emotions, affect regulation systems, expert survey, EASEL-3 index

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P-10

Geographical disparities in fibromyalgia severity: an Italian study

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Objective. Geographic origin may represent a variable capable of influencing health status. This study aims to verify the potential presence of differences of disease severity in Italian patients with fibromyalgia (FM) from different regional macro-areas.

Methods. This retrospective, cross-sectional study involved patients included in the Italian Fibromyalgia Registry. Three geographical macro-areas were identified, comprising patients from Northern Italy, Central Italy, and Southern Italy. Clinical differences (evaluated through Polysymptomatic Distress Scale [PDS], revised Fibromyalgia Impact Questionnaire [FIQR], and modified Fibromyalgia Assessment Status [FAS 2019mod]) among the geographical macro-areas were studied using one-way analysis of variance (ANOVA) and the Mann-Whitney test.

Results. A total of 6095 patients (5719 females and 379 males) were included, with 1957 from Northern Italy, 2979 from Central Italy, and 1159 from Southern Italy. All studied clinical indices showed a trend indicative of greater disease severity in Southern Italy, followed by Northern Italy and then Central Italy (mean values for PDS: 19.97±6.20 in Northern Italy, 18.61±7.12 in Central Italy, 23.01±5.66 in Southern Italy). These differences were statistically significant for the overall scores of all studied indices,

evaluated with ANOVA (all $p < 0.001$), and in the head-to-head comparisons, evaluated with Mann-Whitney test.

Conclusion. Geographic origin represents a demographic variable influencing the severity of FM in Italian patients.

Key words: fibromyalgia, disease severity, geographical variation, PDS, FIQR, FAS 2019mod

P-11

Fibromyalgia and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): overlapping conditions for men

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Introduction. There is significant overlap in the clinical features of fibromyalgia (FM) with those of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). This study aimed to examine this association by comparing the risk of prior FM between patients with CP/CPPS.

Methods. This study enrolled adult male patients with FM, diagnosed according to the 2016 ACR diagnostic criteria in a rheumatological setting. All patients were asked to complete the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI). The correlation (Spearman rho) between NIH-CPSI and indices of disease severity (revised Fibromyalgia Impact Questionnaire [FIQR], the modified Fibromyalgia Assessment Status [modFAS], and the Polysymptomatic Distress Scale [PDS]) was studied, and a multivariate analysis was then conducted to determine the variables correlated with the presence of CP/CPPS.

Results. A total of 36 individuals (25.3%) out of the 142 patients that were sampled had CP/CPPS, of whom 22 patients (15.5%) had moderate CP/CPPS and 14 patients had significant CP/CPPS (9.9%). The Spearman's rho revealed a significant correlation of NIH-CPSI and FIQR ($r=0.659$), modFAS ($r=0.883$), and PDS ($r=0.800$). Multivariate analysis revealed a positive relationship between CP/CPPS and variables of disease burden (FIQR, $p < 0.0001$; PDQ, $p < 0.0001$, widespread pain index [WPI], $p=0.0037$).

Conclusion. CP/CPPS are frequently associated in patients with FM symptoms. Urologists should be aware of the association between CP/CPPS and FM when treating patients.

Key words: fibromyalgia, chronic prostatitis/chronic pelvic pain syndrome, NIH-Chronic Prostatitis Symptom Index, disease severity

P-12

The effect of disease severity levels and pain catastrophizing subdomains on presenteeism-related productivity loss in female workers with fibromyalgia

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Objective. A decrease in health-related quality of life (HRQoL) is observed in fibromyalgia (FM) patients, and this decline is linked to a worsening of the condition and a reduction in job capacity. In order to discover potential new targets for preventive interventions, the aim of this cross-sectional study is to examine the mediating influence of pain catastrophizing subdomains and illness severity levels on work productivity loss due to presenteeism in women with FM.

Methods. The study used a cross-sectional design and had 303 female patients with FM. American College of Rheumatology (ACR) criteria for diagnosing FM from 2016 were used to confirm the diagnosis. All patients

filled out the revised version of the Fibromyalgia-Impact Questionnaire (R-FIQ), an assessment and evaluation tool that measures FM patient status, progress, and outcomes. The Pain catastrophizing scale (PCS) was used to measure chronic pain catastrophizing tendencies, and the Work Productivity and Activity Impairment questionnaire-FM (WPAI-FM) was employed to evaluate patients' employment status. FM patients were grouped into categories, based on their R-FIQ total score. Multiple regression and receiver operating characteristics (ROC) curve analysis were used to find out which factors were most likely to be linked to presenteeism.

Results. The patients' ages ranged from 1 to 21 years, with a disease duration of 5.08 (SD 6.12) years. The PCS score was ≥ 30 in 135/303 patients (44.55%). 181 of 303 FM patients (59.73%) were employed at the time of the evaluation. 106 patients (58.56%) worked full-time, while 75 (41.43%) worked part-time. The sample's overall productivity loss was 59.57%. Most respondents (74.5%) reported a high degree of presenteeism with an average level of 56.66%. On the other hand, absenteeism was uncommon, with just 3.8% of respondents reporting it. The overall sample's average level of absenteeism during the previous seven days was 11.43%. On average, among 181 workers, 14% had remission FM, 26% mild FM, 33% moderate FM, 28% severe FM, and 7% extremely severe FM. The PCS helplessness domain and R-FIQ symptom scores, with estimated values of 5 and 23.5 points, respectively were the factors most substantially associated with presenteeism.

Conclusion. PCS helplessness and R-FIQ symptoms domain were the factors most significantly associated with the presence of presenteeism-related productivity loss in FM patients. Overall, our findings have implications for health policy and emphasize the significance of identifying high-risk FM patients by monitoring pain catastrophism and severity of symptoms as indicators of presenteeism-related productivity loss in female workers with FM.

P-13

Study protocol for FIBROKIT: a new tool for fibromyalgia diagnosis and patient follow-up

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Background. Fibromyalgia (FM) is characterized by chronic pain, affecting about 4% worldwide population. Although its intricate pathophysiology complicates diagnosis, previous studies have suggested an association between the disease and oxidative stress, mitochondrial metabolism, intestinal microbiota and inflammation.

Objective. This randomized, prospective, low-interventional, double-blind and placebo-controlled clinical trial aims to develop a specific panel of FM biomarkers in blood and feces from patients, and the evaluation of their response to a six-month nutritional intervention.

Methods. Female FM patients and healthy women were contacted through online forms. Once filtered by inclusion criteria, both groups were involved into placebo (olive oil) and treatment (extra virgin olive oil) nutritional interventions for 6 months. Feces and blood samples were taken at the beginning, after 3 months, at the end of the nutritional intervention (6 months), and 6 months after the end of the nutritional intervention.

Results. A group of 210 FM patients and 40 control women were selected according to inclusion criteria. DNA was isolated from feces for further 16S rRNA gene sequencing using Illumina technology, while proteins were extracted from plasma samples to perform a nLC-MS/MS analysis. Health data from FM and control groups were collected through health questionnaires.

Conclusion. This is the first low-interventional investigation with more than 200 FM patients focused on exploring plasma proteome and intestinal microbiota roles in the pathology. The outcomes will contribute to the development of a robust panel of diagnostic biomarkers, and will shed some light on their modulation with non-pharmacological therapies such as nutrition.

P-14

Assessment of the association between the frequency of leisure activities and the intensity of pain and its impact on the lives of people with fibromyalgia

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Introduction. Fibromyalgia is the second most common rheumatologic disease in the world population, with few effective treatment available options. Leisure activities are commonly defined as those performed voluntarily for pleasure and unrelated to work-related obligations. The relationship between the frequency of performing leisure activities, pain, and its impact in fibromyalgia is not well understood. We aimed to investigate this relationship in patients with fibromyalgia.

Methods. This cross-sectional study was carried out through an online survey on Facebook groups of people with fibromyalgia. The frequency of performing leisure activities was assessed by a simple question. The average pain and the degree of interference of pain in the lives of participants were evaluated by the Brief Pain Inventory. The association between the frequency of performing leisure activities, pain intensity, and its degree of interference in the lives of participants was evaluated by robust multivariable linear regression with adjustment for at least 21 potential confounding factors.

Results. We included 2,176 participants with fibromyalgia. The practice of leisure activities was associated with a lower degree of pain interference in the lives of participants but not with a lower intensity of pain in the multivariable models. We did not find any interactions between frequency of participation in leisure activities and the frequency of engagement in physical activity regarding the levels of pain or its interference in the lives of participants.

Conclusion. Our results provide initial evidence that allow us to hypothesize a possible role for the practice of leisure activities independently from physical activity in the management of people with fibromyalgia.

P-15

Prevalence of rheumatic disease in patients with fibromyalgia

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Background. Fibromyalgia is a disorder characterized by musculoskeletal pain spread throughout the body and accompanied by fatigue and mood changes. These may be symptoms of other rheumatological diseases too. It is necessary to evaluate carefully each patient.

Objective. This study aims to identify the prevalence of rheumatic diseases in 151 female patients who have been diagnosed with fibromyalgia.

Methods. We evaluated the patients clinically, through physical examination, laboratory tests and radiological examinations, to determine if they have any rheumatological disease.

Results. 3.31% of patients were diagnosed with rheumatoid arthritis, 0.66% of patients were diagnosed with psoriatic arthritis, 12.58% of patients were diagnosed with systemic lupus erythematosus.

Conclusion. Regardless of the clinic characterized by musculoskeletal pain, the coexistence of fibromyalgia with other rheumatic diseases should be considered.

P-16

Fibro muscular dysfunction post Covid infection sequelae

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Fibromyalgia emerges as a myofascial straight muscle-triggering pain, primarily affecting females over 40, often combined with other conditions such as thyroid issues, functional bowel disorders, depression, anxiety, and disturbed sleep. The onset is preceded by trauma, stress, infection, and recent exposure to the COVID-19 pandemic.

The randomized placebo-controlled trial involves 44 post-COVID patients, showcasing a median age of 43 and various comorbidities like obesity, hypothyroidism, NASH, diabetes, and hypertension.

Two groups were formed: Group A, diagnosed with FM based on clinical criteria, and Group B, with concomitant maladies. Group A patients presented FM symptoms, including myofascial pain points (4/22), arm-neck-shoulder pain (9/22), leg pain (7/22), back pain (13/22), sleep disturbance (15/22), depression (17/22), and bowel changes (7/22). Lab analyses included CBC with Diff, SMA 18, TFT, ASMA, AMA, ESR, Cyclic Citrullin Peptide, RF, Desminated Gliadin Peptide, CRP, and HIV.

Group B exhibited a range of conditions but lacked distinctive FM symptoms, including thyroid hypothyroid (3/22), hypertension (2/22), diabetes (3/22), celiac disease (1/22), depression (4/22), anxiety (6/22), and IBS (2/22). Exclusion criteria comprised HIV, neuromuscular disease, collagen vascular disease, CVA, myasthenia, ALS, congenital muscular dysfunction, and hyperthyroidism.

The exclusion criteria ensured a focused study on FM development post-COVID, ruling out specific diseases. The study concludes with a unique correlation in Group A, linking post-COVID patients to the development of Fibromyalgic Dysfunction within six months, thereby shedding light on the pathology of FM as a long COVID sequelae.

P-17

Assessing childhood trauma, defense mechanisms, and alexithymia in single and comorbid syndromes among women with fibromyalgia and chronic pain

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Background. The central role of psychological factors in fibromyalgia (FM) and in other chronic pain (CP) syndromes is recognized in the literature. However, these factors' specific role in each chronic condition is still unclear.

Objective. This study aims to compare the impact of selected psychological factors (such as childhood trauma, defense mechanisms, and alexithymia) between FM and four other groups such as chronic headache (CM), vulvodinia (VU), mixed diagnoses (MX; consisting of FM in comorbidity with CM and/or VU), and a control group.

Methods. 1081 women (201 with FM, 220 with CM, 222 with VU, 327 MX, and 111 controls) completed a self-administered online protocol between June and November 2023.

Results. Significant differences were found among the five groups in the variables examined: childhood trauma ($R^2=0.055$; $F=9.209$; $p=0.001$), alexithymia ($R^2=0.085$; $F=13.243$; $p=0.001$), and neurotic defenses ($R^2=0.064$; $F=10.835$; $p=0.001$). The comparison shows that MX, compared with FM and the other conditions, is more characterized by a childhood history of trauma (particularly physical threats). On the other hand, FM differs from the other groups in that it scored significantly higher in both the inability to identify feelings and the use of neurotic defensive strategies.

Conclusion. Psychological factors play a significant role in CP syndromes, particularly among women with FM alone and FM mixed diagnoses. To enable improvement in the quality of life of these women, all clinicians should consider the impact of psychological variables.

P-18

Central sensitivity and fibromyalgia: a discriminating construct within different chronic pain conditions

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Background. Fibromyalgia (FM) is a chronic pain (CP) syndrome; FM patients often suffer from multiple CP comorbidities, mainly: tension-type headache or migraine, irritable bowel syndrome, and low back pain. The IASP defines Central Sensitivity (CS) as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold inputs. While international literature connects CS to psychological burdens in CP conditions like FM and chronic headache (CH), there's limited exploration comparing FM patients with and without other CP comorbidities. **Objective.** To investigate whether CS discriminates between FM patients, those with different CP comorbidities, and healthy controls (HCs).

Methods. 944 women participated (n=240 CH; n=204 FM; n=376 FM with comorbidities; n=124 HCs) and completed an online self-administered protocol, including the Central Sensitivity Inventory and socio-anamnestic information. A general linear model ANCOVA, covarying for age, tested CSI score differences.

Results. Data analysis showed a good fit of the model (R2 Adjusted =0.340; df=4; F=116; p=0.001) and a significant difference between groups in CSI scores (p=0.001). Post-hoc test showed that all the clinical groups scored significantly higher than HCs (all p=0.001); FM and FM with comorbidities scored significantly higher than CH (both p=0.001). FM with comorbidities scored higher than FM alone (p=0.015), indicating the highest scores among groups.

Conclusion. CS appears to play a discriminating role among CP conditions, especially in FM with other CP comorbidities. Integrating CS assessment in the clinical evaluation of CP patients could enhance understanding of the complex connection between CP and mental health.

P-19

Traumatic experiences and defensive mechanisms: examining the influence of psychological factors in women with fibromyalgia and chronic pain syndromes in comorbidity

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Background. Fibromyalgia (FM) patients frequently experience multiple chronic pain (CP) comorbidities, recently included among chronic nociplastic syndromes. "Nociplastic pain" (NP) results from altered function of pain-related sensory pathways in the nervous system, leading to pain hypersensitivity. NP-characterized conditions share neurophysiological mechanisms; this framework allows a new understanding of the co-occurrence of different CPs and the role of related psychological factors. Among these, the literature highlights traumatic experiences and defense mechanisms (DM). However, these variables are understudied.

Objective. To investigate whether FM and FM with different CP conditions show differences regarding childhood traumatic experiences and DM.

Methods. 528 women (n=201 FM; n=327 FM with comorbidities) completed a self-administered online protocol consisting of Traumatic Experience Checklist (TEC), Defense Mechanism Rating Scales (DMRS), and socio-anamnestic information.

Results. Data analysis shows significant differences in TEC emotional abuse scale (F=3.976; df=2; p=0.006) and total score (F=2.938; df=2; p=0.019) with FM with comorbidities group reporting higher scores. About DMRS the groups differ only in the scale of immature defenses (F=6.648; df=2; p=0.039), with the FM group with comorbidities scoring higher.

Conclusion. Greater childhood emotional abuse and immature DM seem

to characterize FMs with comorbidities. It can be speculated that greater exposure to traumatic events may have hindered the development of more mature DM. This could be a risk factor for both the development and management of a complex and disabling disease such as FM, especially when associated with other CP syndromes. Physicians should consider psychological variables as they may contribute to the symptomatology of CP.

P-20

Chronic fatigue and dysautonomia following COVID-19 vaccination is distinguished from normal vaccination response by altered blood markers

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SARS-CoV-2 mRNA vaccination can entail chronic fatigue/dysautonomia tentatively termed post-acute COVID-19 vaccination syndrome (PACVS). We explored receptor autoantibodies and interleukin-6 (IL-6) as somatic correlates of PACVS. Blood markers determined before and six months after first-time SARS-CoV-2 vaccination of healthy controls (n=89; 71 females; mean/median age: 39/49 years) were compared with corresponding values of PACVS-affected persons (n=191; 159 females; mean/median age: 40/39 years) exhibiting chronic fatigue/dysautonomia (≥three symptoms for ≥five months after the last SARS-CoV-2 mRNA vaccination) not due to SARS-CoV-2 infection and/or confounding diseases/medications. Normal vaccination response encompassed decreases in 11 receptor antibodies (by 25–50%, p=0.0001), increases in two receptor antibodies (by 15–25%, p=0.0001) and normal IL-6. In PACVS, serological vaccination-response appeared significantly (p=0.0001) altered, allowing discrimination from normal post-vaccination state (sensitivity = 90%, p=0.0001) by increased Angiotensin II type 1 receptor antibodies (cut-off ≤10.7 U/mL, ROC-AUC = 0.824 ± 0.027), decreased alpha-2B adrenergic receptor antibodies (cut-off ≥25.2 U/mL, ROC-AUC = 0.828 ± 0.025) and increased IL-6 (cut-off ≤2.3 pg/mL, ROC-AUC = 0.850 ± 0.022). PACVS is thus indicated as a somatic syndrome delineated/detectable by diagnostic blood markers.

P-21

Unraveling the complex web of fibromyalgia

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Background. Fibromyalgia, a complex, chronic pain disorder, is characterized by widespread musculoskeletal pain, fatigue, and heightened sensitivity. Its recognition as a global health burden marks a significant shift in understanding and acceptance, transcending demographic boundaries.

Objective. To provide an updated overview of fibromyalgia, encompassing its clinical features, diagnosis, etiology, pathophysiology, and impact on quality of life. The study also explores current management strategies and emerging research in the field.

Methods. The study reviews the evolution of diagnostic criteria, shifting from tender point reliance to a more holistic approach. It examines the etiology and pathophysiology of fibromyalgia, highlighting genetic predisposition, neurotransmitter dysregulation, central sensitization, and immune

system involvement. The study also assesses various risk factors such as gender, age, family history, and comorbid conditions.

Results. Fibromyalgia's profound impact on quality of life, encompassing physical and social aspects and often accompanied by mood disorders, is emphasized. Management approaches include pharmacological interventions, non-pharmacological therapies, lifestyle modifications, and alternative treatments.

Conclusion. This study offers a nuanced perspective on fibromyalgia, aiming to enhance understanding and support for individuals affected by this complex condition. It underscores the need for ongoing research and innovation in management strategies to improve quality of life for patients.

Genetics, Pharmacogenetics, and Epigenetics

P-22

Understanding pathophysiological mechanisms of chronic pain resolution in the presence of widespread pain via transcriptomics-wide analysis

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Background and Objective. The resolution of chronic pain remains poorly understood. We investigated the pathophysiological mechanisms behind chronic low back pain (LBP) resolution in association with widespread pain. A transcriptome-wide analysis of 32 participants with chronic LBP in peripheral immune cells was conducted, following 14 weeks of physical exercise. **Methods.** Blood samples were collected from 32 participants with LBP undergoing a 14-week physical exercise program. 15 participants reported chronic widespread pain and 17 participants did not. The first draw occurred after two weeks of low-intensity exercise, and the second after the final session. Pain ratings were collected two weeks before the study and two weeks after its conclusion. Participants were categorized as "improved" or "persistent" based on 7-day average pain intensity and as "absent" or "present" for widespread pain at the baseline. DESeq2 and fgsea programs were used for transcriptomics analysis. **Results.** Participants without widespread pain exhibited similar trends in transcriptional activities to those who improved. These patients showed significantly higher transcriptional regulation. In "improvers" and "absent" groups we consistently observed downregulation in inflammatory pathways over the course of exercise, but not in the "persistent" and "present". Finally, "improvers" and "absent" groups demonstrated higher downregulation of blood cell activation than "persistent" and "present". **Conclusion.** Our findings suggest that active biological processes underlie pain resolution in chronic LBP patients during the course of physical exercise, with a significant contribution from active down-regulation of inflammation. These active biological processes are inhibited in patients with widespread pain.

Neuro-biological Underpinnings of Fibromyalgia and Centralized Pain

P-23

Decoding fibromyalgia by considering sleep and anxiety as part of the etiopathogenesis: a systems biology approach unveiling protein interactions and drug repurposing opportunities

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Background. Fibromyalgia (FMS) remains a complex syndrome with an elusive etiopathogenesis and a multifaceted polysymptomatology, posing a significant challenge for effective therapeutic interventions. Despite ongoing efforts, the dearth of efficacious therapies persists. Building upon our successful implementation of an algorithm demonstrating promising results in drug-receptor pair probability scoring, as evidenced in our proof-of-concept study focused on anxiety, we now aim to apply this artificial intelligence-based drug repurposing approach to proteins implicated in FMS. **Objective.** The primary objective of this study is to generate a complete network of proteins involved in FMS, according to the symptomatology referred from patients by integrating information from protein-protein interaction (PPI) networks related to sleep and anxiety symptoms. Secondly, the prioritized proteins will be considered as target candidates for the virtual screening.

Methods. Leveraging the DisGeNET database, we retrieved FMS-related proteins and expanded our analysis to include PPI networks associated with sleep and anxiety symptoms. Cytoscape was employed to generate and topologically analyze the integrated networks by adding first interactors and considering the intersection network. Principal Component Analysis (PCA) on relevant features and logistic regression were used to refine potential drug targets. Our Python-based algorithm, previously successful in assigning probability scores to drug-receptor pairs, utilized DrugCentral for drug retrieval and AlphaFold for structure prediction of FMS-associated proteins.

Results. Integrating information on FMS (8196 proteins), sleep (2145 protein), and anxiety symptom-related proteins (3090 proteins), we constructed an intersection comprehensive PPI network (844 proteins) revealing unexpected interconnectedness ($p < 1e-16$). Topological analysis identified key nodes, with CFTR, LRRK2, ESR1 exhibiting the highest betweenness centrality, suggesting their pivotal roles in FMS etiopathogenesis. By considering these 3 nodes as main targets for drug repurposing, we obtained scores of drug-receptor pairs to select possible new therapeutic strategies.

Conclusion. The increased connectivity observed in the integrated FMS PPI network implies shared biological pathways among proteins associated with FMS, sleep, and anxiety symptoms. Notably, central nodes emerged as promising druggable targets. Ongoing efforts involve refining drug-receptor pair probability scoring, as well as leveraging PCA and logistic regression analyses to advance our understanding of potential therapeutic interventions for FMS.

P-24

Immunohistochemical method for the characterization of auto-antibodies in fibromyalgia

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Autoimmune reactions are having an ever-increasing influence on the pathophysiology of many chronic diseases due to changes in environmental and living conditions. Fibromyalgia syndrome (FMS) can also be understood as a chronic disease of the myofascial system, which is why immune reactions could also be involved in various causative or resulting processes. As current scientific studies have so far failed to provide any clear information on the existence of autoimmune reactions in FMS, a novel histochemical method was used to detect the presence of specific autoantibodies in the serum of FMS patients.

For this purpose, a total of 40 patients (fibromyalgia patients, FP) were compared with a comparison group (CG) of 35 volunteers who had neither autoimmune diseases nor a diagnosis of FMS. Unknown serum antibodies of the respective FP and CG were visualized histochemically on different

tissue sections in an immunoperoxidase staining by the reaction with an enzyme-labelled secondary antibody.

70% of the FP showed autoantibodies in the histological picture and approximately 60% of them were localized in the extracellular matrix/connective tissue, which also plays a prominent role in the pathophysiology of FMS. In contrast, only about 35 % of the subjects in the CG showed autoantibodies, 50 % of which were located in the thyroid gland.

The newly developed histochemical test is therefore an interesting diagnostic tool for the rough screening of possible autoimmune diseases and can provide important information and possibilities for future diagnostic and therapeutic intervention approaches.

P-25

Correlation of fibromyalgia, attention deficit hyperactivity disorder, depression and serum cortisol: a cross-sectional study

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Background. Patients with Fibromyalgia (FM) have a disrupted hypothalamic pituitary adrenal axis (HPA) axis in which hyposecretion of cortisol may be present. FM patients have comorbid depression (hypercortisolemia) and attention deficit hyperactivity disorder (ADHD) (low serum cortisol levels). The stress axis in FM may be exacerbated by the presence of depression and ADHD but the relationship of these factors and the cortisol link is unclear.

Objective. The aim of this pilot cross-sectional study is to analyze the neuroendocrinology of patients with FM, depression and ADHD and understand the range of cortisol serum levels.

Methods. After IRB approval, FM patients with prior serum cortisol testing, available Adult ADHD Self-Report Scale score (ASRS-v1.1) and depression diagnosis were identified. After written informed consent, ASRS-v1.1 was administered to FM patients seen at Loyola Outpatient center. Patients without serum cortisol were excluded. The reference value for cortisol serum is 2.9-19.4 Ug/DL.

Results. FM with serum cortisol n= 64, Female: 59, Male: 5, Mean age: 63, average BMI: 38.8. FM with no psychiatric diagnosis n=16, Serum cortisol mean: 9.06. FM patients with positive ASRS-v1.1 leading to a probable ADHD diagnosis n=6, cortisol mean: 10.66 mg/dl. Of these 6 patients, 5 patients had a diagnosis of depression. FM with depression n=14, cortisol mean: 13.00.

Conclusion. FM patients have a wide range of inflammatory cortisol serum values based on psychiatric conditions such as depression and ADHD. This has implications for future study on treatments that may focus on the HPA axis.

P-26

Pain perception and rapid eye movement (REM) sleep changes in fibromyalgia patients with obstructive sleep apnea undergoing continuous positive airway pressure treatment: a cross-sectional study

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Background. Fibromyalgia (FM) is often comorbid with obstructive sleep apnea (OSA). Rapid Eye movement (REM) sleep loss is associated with hyperalgesia. Increased REM sleep correlates to improved health, with most individuals averaging 70 min per night, which is 25% of total sleep time (TST). **Objective.** In FM and OSA, CPAP therapy leading to REM rebound can help treat OSA and thus will decrease pain perception.

Methods. After IRB approval, patients included in our study had a diagnosis of FM and OSA. After obtaining consent, participants completed Short-Form McGill Pain Questionnaire (SF-MPQ) assessing pain symptoms. REM duration and REM total sleep time (TST) percentages were reviewed at baseline polysomnography and after CPAP titration.

Results. In this sample FM+OSA, n=17, (female n=14, male n=3). Mean age: 57.48. SF-MPQ overall scores, FM and OSA (Median: 21.00, IQR: 15.00–25.00). Frequently reported present pain intensity was distressing (52.94%), followed by discomforting (29.41%), horrible (11.76%), mild (5.88%). FM and OSA Sleep study results of patients with MPQ 16 or less

undergoing CPAP therapy (n=6) baseline REM TST=3.68%. REM TST after CPAP was 21.46%. Sleep study of patients with MPQ 16 or higher undergoing CPAP therapy (n=11), 6 patients had an available baseline sleep study pre-CPAP and the REMTST was 12%. Five post-CPAP sleep studies were available, and REM TST after CPAP was 14%.

Conclusion. These findings suggest CPAP patients with REM rebound had decreased pain. By better understanding how sleep abnormalities affect pain perception we can more effectively treat FM patients with co-morbid OSA.

Treatment of Fibromyalgia

P-27

Amigos de FIBRO (FIBRO Friends) - Effect of an interdisciplinary educational program associated with physical exercise to promote the health of people with fibromyalgia in Brazil: randomized clinical trial

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Background. Amigos de Fibro is a recently created and innovative program, through the joint action of patients and health professionals.

Objective. To evaluate the effect of an interdisciplinary health promotion educational program associated with physical exercise in improving pain intensity, symptom severity, quality of life, sleep quality and self-care agency in people with fibromyalgia in Brazil.

Methods. Randomized clinical trial, carried out with 24 participants divided into two groups: the experimental group (EG) and the control group (CG). The GE group held online meetings through the Google Meet platform with an interdisciplinary team (10 professionals), where they gave lectures and held debates and dynamics about the importance of health promotion and self-care in fibromyalgia and followed a physical exercise protocol. The CG received an education and self-care e-book for fibromyalgia that covered similar information to the EG (<http://www.amigosdefibro.com.br>). A significance level of 5% was adopted.

Results. Compared to the baseline, all GE variables showed significant improvements ($p \leq 0.05$). There were statistically significant differences between the groups in all variables, presenting the following values: generalized pain ($p=0.028$), severity of symptoms ($p=0.002$), impact of fibromyalgia on quality of life ($p \leq 0.001$), pain ($p=0.033$), sleep quality ($p=0.033$) and self-care agency ($p=0.001$).

Conclusion. Amigos de Fibro was considered with positive results and improvement of all studied variables that address the main aspects that promote the health of individuals with fibromyalgia. Therefore, it can be considered valid for use by health professionals with the target audience in primary health care in Brazil.

P-28

Comparison of the efficacy of oxygen-ozone rectal insufflation and autoemotherapy in the treatment of fibromyalgia syndrome: preliminary results

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Background. Fibromyalgia patients often struggle with diffuse musculoskeletal pain, fatigue, and catastrophism, which can significantly reduce treatment compliance. These patients often respond poorly to treatment and have a high placebo effect. As a result, approximately 60% turn to comple-

mentary or alternative therapies. Given the limited pharmaceutical options available to manage fibromyalgia symptoms, non-pharmaceutical interventions like oxygen-ozone therapy may be beneficial. Some studies have reported evidence of this therapy effectively treating pain, sleep issues, and fatigue in chronic fatigue syndrome and fibromyalgia patients.

Objective. In many patients, peripheral venous access can be difficult, or they may be reluctant. Therefore, the rectal route appears as a less invasive alternative, but there are no structured comparison studies. This study aims to compare effectiveness Two different techniques of oxygen-ozone: rectal insufflation vs. autoemotherapy as an add-on therapy in the treatment of fibromyalgia.

Methods. Thirty consecutive patients affected by FM with poor response to the traditional pharmacological treatment (duloxetine and pregabalin at different dosages) will be included in this preliminary study. The ozone concentrations used ranged between 20 and 50 µg/mL. Patients will be treated for a 3-month period with near 14 autoemotherapy and 26 rectal insufflation. The primary end points is a 30% improvement of pain and fatigue score after a 3-month treatment.

Results. So far, we have enrolled 20 patients, 12 of whom completed the 3-month treatment. Both techniques were effective and well-tolerated. There were no significant variations in response speed. Regardless of the technique used, a consistent pattern of symptom improvement was observed. This included reduced pain, improved sleep, and less fatigue. Seven patients achieved a 30% clinical improvement after the 3-month period. No statistical analysis was conducted due to the limited data available. Adverse reactions to ozone therapy were typically mild and short-lived. The most common side effect was meteorism (gas in the digestive system), which lasted 1-2 days after ozone sessions.

Conclusion. Despite limitations such as a small sample size and lack of long-term data, the preliminary results confirmed the potential of ozone therapy for fibromyalgia treatment and that rectal insufflation could be an alternative to autoemotherapy. Nearly 50% of the patients experienced at least a 30% reduction in pain and fatigue score within a 3-month period with both techniques. Oxygen-ozone therapy could help alleviate pain, fatigue, and musculoskeletal symptoms in fibromyalgia patients. Further large-scale, standardized, long-term studies are recommended.

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P-29

Psychedelic-assisted psychotherapy for fibromyalgia: the therapeutic process of a fibromyalgia patient up until 6 months after a psychedelic retreat

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The clinical applications of psychedelics have garnered increased attention due to their potential to address hard-to-treat conditions, such as treatment-resistant depression and end-of-life anxiety. This study presents a comprehensive case analysis of a 36-year-old male clinical psychologist, pseudonymized as Adam, suffering from fibromyalgia (FM) who participated in a psychedelic-assisted therapy program. Quantitative measures, including depression, anxiety, stress, mindfulness skills, cognitive fusion, and cognitive flexibility, were collected at baseline and three subsequent time points (2 weeks, 3 months, and 6 months after a psychedelic retreat). The findings revealed significant improvements in mental health, with decreased levels of depression, anxiety, stress and cognitive fusion and improved cognitive flexibility and mindfulness skills. Interpretative phenomenological analyses were conducted on the transcriptions of semi-structured interviews conducted at each time point investigated Adam's experience of the psychedelic retreat, treatment outcomes and reported effects of integration sessions. Adam reported that the PAP program resulted in a sustained sense of inner guidance, significant lifestyle changes, and increased feelings of connection to others and his spiritual side. The retreat sessions also provided relief from

FM pain, and integration sessions helped him feel more aware and present, acknowledge suppressed trauma, and address his needs more effectively. The study's findings highlight the potential therapeutic benefits of PAP in addressing FM and improving mental health outcomes. Furthermore, the analysis suggests that PAP might facilitate processes of convergent thinking, meaning-making, and value-driven actions, leading to positive transformations in patients' lives.

P-30

Psychosomatic assessment and intervention in fibromyalgia: a clinical trial protocol

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Background. Fibromyalgia (FM) is characterized by functional disability and physical manifestations which are also the expression of a psychological distress as well as specific illness attitudes and behaviors. It is considered a functional disorder in need of a clinical diagnosis and a multidisciplinary therapeutic approach.

Objective. The aims of the present project are: (a) implementing a psychosomatic assessment for FM and verifying its clinical utility; (b) testing the efficacy of a psychosomatic intervention for FM.

Methods. FM subjects (n=100) will be recruited at the Rheumatology Unit of the Academic Hospital Careggi (Florence, Italy). The study will include a first step of assessment of patients, thus a cross-sectional observation study, and a second step proposing a randomized (1:1) controlled trial, comparing a multidisciplinary psychosomatic intervention based on cognitive restructuring vs a control condition that promotes a lifestyle psychoeducation treatment; both followed by museum therapy. FM patients will be assessed via the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.*, 1998) and the Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview (DCPR-R SSI) (Fava *et al.*, 2017) to examine mental and functional disorders and via self-report instruments measuring distress at baseline, during the treatment, at 3 and 6-month follow-up.

Results. We hypothesize the multidisciplinary psychosomatic assessment has clinical utility in fibromyalgia being able to depict a more comprehensive framework for the patients. We also hypothesize the integrated psychosomatic intervention is of clinical benefit to the patients.

Conclusion. A biopsychosocial approach seems to be a necessary framework for understanding and treating FM.

P-31

Body reprogramming for fibromyalgia and central sensitivity syndrome. a preliminary evaluation

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Background. Fibromyalgia and other Central Sensitivity Syndromes provoke continued debate highlighting ongoing diagnostic and therapeutic uncertainties. The Hyland model offers a potential conceptual framework for understanding these syndromes, based on principles of adaption in network systems. A multi-modal therapeutic group-based intervention named Body Reprogramming was developed from this model using both stakeholder patient and evidence-based, healthcare expert feedback. (Ref)

Objective. This preliminary, naturalistic and single-arm service evaluation set out to evaluate outcome after attending a group-based body reprogramming course.

Methods. 198 Patients were enrolled on the eight-week BR group course, run at two clinical sites in England. Data were collected at baseline, post course and three-months post course using questionnaires assessing symptomatology (FIQR/SIQR), Depression (PHQ9), Anxiety (GAD7) and quali-

ty of life (GQoL). Repeated measures t-tests were used, and all comparisons were conducted on an intention to treat basis.

Results. Paired samples t-tests were used to compare baseline and post course questionnaire scores. There was a significant improvement in FIQR/SIQR scores from baseline to post course. Significant improvements were also observed in the PHQ9, GAD-7 and GQoL measures from baseline to post course. All improvements were sustained at 3 month follow up.

Conclusion. This preliminary study suggests that the BR group-based approach can nurture clinically relevant and sustained improvements in physical symptomatology as well as measures that reflect psychological distress and quality of life in patients with these syndromes. Further research is warranted.

P-32

Moving body reprogramming groups onto a digital platform. Does it deliver?

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Background and Objective. A community-based pilot service was set up in Cornwall, United Kingdom, in 2019 to manage patients with Fibromyalgia, using the Body reprogramming (BR) approach. This is a multi-modal therapeutic group-based intervention based on the Hyland model (1). The Covid-19 pandemic 2020 restricted the group based face-to-face programme, so it transitioned onto an online platform (Microsoft TEAMS). This has allowed comparative evaluation of online versus F2F delivery.

Methods. The group programme consisted of 8-weekly sessions with follow up group at 3 months. Data collected: at Baseline(Q1), Post-course(Q2) and 3-month Follow-up(Q3) Questionnaires assessed FMS symptomatology (FIQR/SIQR), Depression (PHQ9), Anxiety (GAD7), quality of life (GQoL) and Pain (BPI). Initially repeated measures t-tests were used to detect significant improvement within groups. Then a repeated measures ANOVA (face-to-face vs TEAMS) was used to determine if improvement in questionnaire scores observed in one BR format were significantly greater than the other.

Results. 76 patients with a mean age of 43 years were enrolled (40 F2F and 36 Digital platform). For both F2F and online delivery, questionnaire scores improved significantly ($p=0.05$) between Baseline (Q1) and Follow-up (Q3). No significant differences were noted between F2F and online delivery for the FIQR and BPI. However, for Baseline (Q1) and post course (Q2), scores improved significantly more in the online groups compared to F2F for PHQ-9, GAD-7 and QoL ($p=0.05$).

Table I. Questionnaire scores at three time points as a function of how BR was delivered to patients.

	Baseline (Q1)		Post Course (Q2)		Three Month follow-up (Q3)	
	Face to Face	TEAMS	Face to Face	TEAMS	Face to Face	TEAMS
FIQR No. of patients Stand. Dev	69.08 (40) 17.84 SD	72.62 (36) 14.65 SD	59.97 (33) 19.42 SD	62.79 (26) 16.67 SD	44.86 (22) 19.81 SD	42.91 (17) 15.75 SD
PHQ9 No. of patients	15.98 (40) 5.82	18.91 (36) 5.33	13.36 (33) 6.43	12.12 (26) 5.52	10 (22) 6.12	9.12 (17) 6.55
GAQ7 Anxiety	13.01 (40) 5.51	14.52 (36) 5.20	10.67 (33) 6.05	9.04 (26) 4.14	7.50 (22) 5.26	6.35 (17) 6.01
QoL Quality of Life	46 (40) 23.10	35.97 (36) 19.82	52.12 (33) 17.19	48.50 (26) 20.94	62.62 (21) 12.71	53.35 (17) 23.17
BPIA Brief Pain Inventory	5.87 (40) 1.53	6.36 (36) 1.55	5.38 (33) 1.92	5.85 (26) 1.78	4.17 (22) 2.20	4.57 (17) 1.53
BPIB Brief Pain Inventory	6.81 (40) 2.08	7.33 (36) 1.63	5.65 (33) 2.50	6.13 (26) 2.37	4.31 (22) 2.40	4.17 (17) 2.03

Conclusion. This early analysis suggests potential non-inferiority of a digital platform FMS group programme compared to F2F. This has important logistic ramifications particularly in more rural locations.

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P-33

Negative childhood events in women with fibromyalgia – not a lifelong sentence

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Methods. In clinical practice physical or psychological trauma is often reported by fibromyalgia patients (1). The aim of this study was investigating if the association between negative childhood events and symptoms of fibromyalgia could be alleviated with cognitive behavior therapy, assessed by a protocol addressing pain and stress.

Forty-eight women with fibromyalgia according to the ACR 1990 criteria (2) participated in the study. Questionnaires to reveal connection between self-reported negative childhood events (3) and pain (4), fatigue (vital exhaustion) (5), depression (6), and self-reported stress behavior (7) were used.

Results.

- At least one negative childhood event was reported by 36 (76.6%) women and four or more were reported by 15 (32%) women.
- More negative childhood events were related to more negative impact on well-being in adult life.
- Negative childhood events were significantly associated with vital exhaustion ($p=0.004$).
- This association was attenuated after cognitive behavior therapy ($p=0.395$).
- Although the therapy protocol did not address negative childhood experiences, it may have affected the impact of ACE.

Conclusion. Among women with fibromyalgia, negative childhood events were associated with fatigue (vital exhaustion), one of the key symptoms of fibromyalgia, in adult life. This association was attenuated after cognitive behavior therapy indicating that the impact of negative childhood events may be modified. Fibromyalgia patients who have suffered from negative childhood experiences, might be able to enhance their quality of life by cognitive behavior therapy providing tools aiming to improve resilience and cognitive skills without addressing traumatic events.

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P-34

Pregnenolone deficiency in patients with fibromyalgia syndrome with and without small fiber pathology - an interesting biomarker and potential therapeutic target, especially in fatigue

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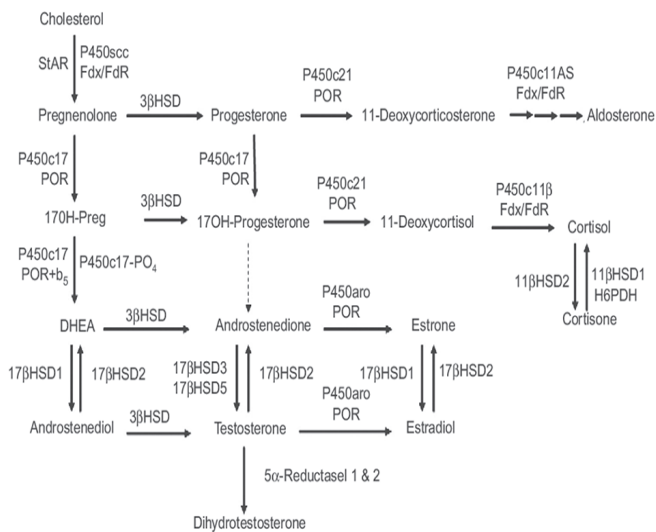
Background. Pregnenolone (PR) synthesis is the first and rate-limiting step in steroidogenesis, in which cholesterol is converted in mitochondria to pregnenolone (Figure), a precursor of all steroid hormones. SFN in FMS is estimated to be common in 49% of FMS patients in a meta-analysis (Oaklander 2019).

Objective. We tested the hypothesis that decreased pregnenolone levels are common in patients with fibromyalgia (FMS).

Methods. Serum pregnenolone sulfate (PR-S) levels were analyzed to assess PR deficiency. Levels ranged from 27 to 80 ug/L depending on age. We studied 50 patients with a clinical diagnosis of FMS (23 females/2 males) with a mean age of 55.1 years. Twenty-five (25) had a confirmed diagnosis of SFN by skin biopsy, the other half (25) had a negative SFN biopsy result. All PR-S serum levels were compared to a control group.

Results. The mean PR-S level in the study group of 50 FMS patients was 24.5 ug/l (median 24). No difference was found between the PR-S levels of SFN-positive patients and those with normal small fiber density. The mean PR-S range in FMS patients was lower compared to a control group of 35 patients with a mean age of 51.6 years (31f/4m) with migraine/MS with a PR-S range of 44.6 ug/l (median 44).

Conclusion. These results suggest a high probability of low PR-S levels/PR deficiency in FMS patients. As a limiting hormone for all biological steroid hormones, PR is a likely biomarker for mitochondrial dysfunction. This and the “forgotten” effects of PR as an active neurosteroid could lead to possible future therapeutic approaches. Further extensive studies are needed to prove the hypothesis that low PR-S levels cause a “supply chain problem” and thus explain the variety of symptoms in FMS and are particularly interesting as a therapeutic target for fatigue and post-exertional malaise.



P-35

Taking action: recovery experiences of patients with fibromyalgia

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Background. Stress is assumed to play a role in FM. Prior patients' experiences suggest that making sense of illness experiences in relation to daily life stressors is crucial for becoming better. Therefore, a stress-modifying patient education program was developed.

Objective. To examine the patients' experiences during the 1.5 years after completing the program.

Methods. At entry of the program, 10 randomly chosen patients among 40 participants were interviewed, and 1.5 years afterwards, 7 new randomly chosen and 3 prior patients were interviewed. Both times, everyone was asked to narrate their illness and recovery experiences from the time the illness started to the present. The interviews were audiotaped, transcribed, and subjected to a narrative analysis.

Results. At the entry of the program, a long, winding illness trajectory with no definite start and uncertain prospects for the future was portrayed. These stories were difficult to understand as they included limited information about concrete experiential events. It was a story of suffering and frustration. After 1.5 year, the stories included more distinct, concrete significant events, reasons and evaluation of their importance. The patients portray a process of active searching of what, why and how things matter in life for them. They tell that they experience more good days and express hopes for future progress.

Conclusion. The narrative portrays a change from an overwhelming passivizing ill-being to an active engagement in rebuilding a less stressful life situation.

P-36

Immune-inflammatory pathways of the FIBROWALK multi-component program in fibromyalgia

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Background. Fibromyalgia (FM), a syndrome with generalized pain, fatigue, anxiety and depression, was studied with the FIBROWALK (FW) program, an intervention that combines education in pain neuroscience, therapeutic exercise, cognitive therapy and mindfulness, tested in different modalities.

Objective. To evaluate the effects of FW in online (FIBRO-On) and outdoor (FIBRO-Out) formats in addition to treatment-as-usual (TAU) on immune-inflammatory biomarkers in blood and Brain-Derived Neurotrophic Factor (BDNF).

Methods. Women with FM, randomly assigned to the TAU, FIBRO-On and FIBRO-Out groups. This controlled trial, part of a larger study with 225 participants, measured core FM clinical variables and analyzed immune-inflammatory blood biomarkers such as CXCL-8, IL-4, IL-6, IL-10, IL-17A, hs-CRP along with BDNF levels. Intervention of 12 weeks, before and after and analysis with linear regressions of mixed effects.

Results. Sample of 120 women with an average age of 55 years. Significant reductions in functional impairment and kinesiophobia were observed in the FIBRO-On and FIBRO-Out groups. The FIBRO-Out program also improved pain, fatigue and depressive symptoms. The decrease in the pro-inflammatory cytokine IL-6 levels in the FIBRO-Out and FIBRO-On group was higher than in TAU, and the anti-inflammatory cytokine IL-10 was only significant in FIBRO-Out compared to TAU. No other significant differences were found for any other inflammatory biomarker.

Conclusion. The results showed that the FW program in Outdoor and Online formats are effective in reducing the clinical severity of FM and promote changes in inflammatory biomarkers indicative of a less inflamed status, particularly in the Outdoor version of the programme.

P-37

Comparative effectiveness of the FIBROWALK multicomponent therapy in online and outdoor formats for individuals with fibromyalgia: the On&Out study

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Background. Addressing fibromyalgia (FM), a prevalent, disabling condition lacking curative treatments, is a major concern in healthcare systems worldwide. Multicomponent interventions that combine pain science education, physical exercise, and psychotherapy are proposed as standard therapeutic approaches for this condition (ref. NCT05377567 at clinicaltrials.gov).

Objective. To evaluate the effectiveness of the FIBROWALK multicomponent program, offered in two versions: online (FIBRO-On) and outdoor (FIBRO-Out), added to treatment-as-usual (TAU), for managing FM.

Methods. This randomized controlled trial (RCT) was conducted at Vall d'Hebron University Hospital, Barcelona, and included 225 FM patients allocated to TAU alone, TAU plus FIBRO-On, or TAU plus FIBRO-Out. Assessments at baseline, 6 weeks, 12 weeks (post-intervention), and 6 months' follow-up focused on the primary outcome of functional impairment and secondary outcomes of pain, fatigue, mental health symptoms, stress, central sensitization, physical functioning, sleep quality, cognitive function perception, kinesiophobia, and pain catastrophism. Mixed linear models were used to evaluate the effectiveness of the interventions.

Results. Both FIBRO-On and FIBRO-Out have proven clinically effective in the short and long term compared to standard treatment alone, with moderate effect sizes on FM impact and small-to-large effect sizes for study secondary outcomes (e.g., pain, depression, kinesiophobia, perceived stress, pain catastrophism). No statistically significant differences were observed between FIBRO-On and FIBRO-Out, suggesting equal effectiveness.

Conclusion. The results of this RCT underscore the value of both online and outdoor FIBROWALK interventions in effectively managing FM in both short and long-term scenarios.

P-38

The use of mindfulness intervention as a potential 'add-on therapy' to the usual treatments for the management of fibromyalgia and its impact on Hope levels

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Background. Hope is a goal-orientated cognitive construct comprising two components: pathways (achieving goals strategy) and agency (inspiring thoughts motivating to pursue goals). In rheumatic diseases, Hope is related to compliance and correlates with depression and symptoms worsening.

Objective. The present study aims to assess Hope levels in patients with Fibromyalgia (FM) compared to healthy subjects (HS) and investigate whether a Mindfulness-based stress reduction (MBSR) intervention could increase Hope levels in FM patients and improve their physical and psychological status.

Methods. 64 FM female patients were consecutively enrolled in Campus Bio-Medico of Rome outpatient clinics and randomly assigned to either an MBSR intervention (n=31, consisting of 6 sessions once a week) or not (n=32). Moreover, 47 age- and sex-matched HS were recruited. All the groups completed the Adult Hope Scale (AHS) questionnaire at baseline. Only FM patients completed psychometric questionnaires at baseline and after three months.

Results. FM patients showed lower hope levels than HS ($p=0.0001$). FM patients undergoing MBSR intervention showed improvement from baseline of AHS ($p=0.046$), specifically of the agency ($p=0.0059$) and not the pathways ($p=0.28$) component, WPI ($p=0.0300$), SSS ($p=0.0141$), FSS ($p=0.0104$), FIQ-R ($p=0.0001$), HADS ($p=0.0005$), pain catastrophizing scale ($p=0.0004$), and VAS pain. FM patients not undergoing MBSR intervention did not improve compared to baseline in any questionnaire.

Conclusion. Hope levels in FM are significantly reduced compared to the healthy population. In FM, MBSR intervention induces improvement in several domains, including Hope and, more specifically, its Agency component.

Table 1 – Demographic characteristics of study population

Demographic characteristics	Group 1 FM patients	Group 2 Healthy subjects
Total population	64	47
Age, median (25 th -75 th percentiles)	51 (45-56.5)	48 (36-57)
Female, N (%)	100%	100%

N, number.

Table 2 – Evaluation of Hope at baseline

	Group 1 FM patients N= 64	Group 2 Healthy subjects N= 47	p-VALUE
AHS Agency, median (25 th -75 th percentiles)	10 (9-12)	13 (12-14)	<0.0001
AHS Pathways, median (25 th -75 th percentiles)	12 (10-13)	13 (12-14)	<0.0001
AHS, median (25 th -75 th percentiles)	22 (19-24)	26 (24-27)	<0.0001

AHS, Adult Hope Scale.

TABLE 3 - Evaluation of clinical and psychological parameters pre and post MBSR intervention

Parameters	Baseline	Post MBSR intervention	p-VALUE
WPI, median (25 th -75 th percentiles)	11.5 (8-14)	10 (6-12)	0.0300
SSS, median (25 th -75 th percentiles)	9 (8-10)	8 (6-9)	0.0141
FSS, median (25 th -75 th percentiles)	20 (17-23)	17 (14-23)	0.0104
FIQ-R, median (25 th -75 th percentiles)	66 (49-76)	51 (38-63)	<0.0001
AHS Agency, median (25 th -75 th percentiles)	9.5 (9-10)	10.5 (9-11)	0.0059
AHS Pathways, median (25 th -75 th percentiles)	11.5 (9-13)	12 (10-13)	0.2801
AHS, median (25 th -75 th percentiles)	21 (18-23)	21 (19-24)	0.0462
HADS Anxiety, median (25 th -75 th percentiles)	11.5 (10-16)	9 (7-10)	0.0005
HADS Depression, median (25 th -75 th percentiles)	10 (8-13)	8 (5-11)	0.0063
HADS, median (25 th -75 th percentiles)	23 (19-26)	17 (14-20)	0.0006
SCS, median (25 th -75 th percentiles)	2.83 (2.55-3.1)	2.91 (2.58-3.16)	0.0888
RS-14, median (25 th -75 th percentiles)	63.5 (59-71)	68 (61-80)	0.0885
PCS Helplessness, median (25 th -75 th percentiles)	17 (9-20)	12 (9-15)	0.0005
PCS Rumination, median (25 th -75 th percentiles)	12 (5-14)	8 (5-11)	0.0054
PCS Magnification, median (25 th -75 th percentiles)	7.5 (5-9)	6 (4-7)	0.0125
PCS, median (25 th -75 th percentiles)	36 (27-42)	27.5 (19-33)	0.0004
VAS-pain, median (25 th -75 th percentiles)	8 (7-9)	7 (5-8)	0.0006

WPI, Widespread Pain Index; SSS, Symptom Severity Scale; FSS, Fibromyalgia Severity Scale; FIQ-R, Revised Fibromyalgia Impact Questionnaire; AHS, Adult Hope Scale; HADS, Hospital Anxiety and Depression Scale; SCS, Self-Compassion Scale; RS-14, 14-item Resilience Scale; PCS, Pain Catastrophizing Scale; VAS-pain, Visual Analogue Scale.

P-39

Association between step count measured with a smartphone app (Pain-Note) and pain level in patients with chronic pain: observational studyChie Usui¹, Ogawa Takahisa², Hatta Kotaro¹¹Department of Psychiatry, Juntendo University School of Medicine, Japan;²Department of Orthopedic Surgery, Tokyo Medical and Dental University, Japan

Background. Chronic pain is the leading cause of disability, affecting between 20% and 50% of the global population. The key recommended treatment is physical activity, which can be measured in daily life using a pedometer. However, poor adherence to pedometer use can result in incorrect measurements. Furthermore, only a few studies have investigated a possible curvilinear association between physical activity and chronic pain.

Objective. In this study, we developed the Pain-Note smartphone app to collect real-world data on step count, using the smartphone's built-in pedometer. The aims of our research are (1) to evaluate the association between daily step count and pain level among patients with chronic pain and (2) determine if the association between daily step count and pain level was curvilinear.

Methods. We conducted a cross-sectional study based on step count data collected with the app and on the results of questionnaires, which measured the duration and intensity of pain, the widespread pain index, the symptom severity score, and the insomnia severity scale, including 7 questions for symptoms of depression. We analyzed the association between step count and pain level as a nonlinear relationship using a restricted cubic spline model. A prespecified subgroup analysis was also conducted based on fibromyalgia criteria.

Results. Between June 1, 2018, and June 11, 2020, a total of 6138 records were identified, of which 1273 were analyzed. The mean age of the participants was 38.7 years, 81.9% (1043/1273) were female, and chronic pain was present for more than 5 years in 43.2% (550/1273) of participants. Participants in the third and fourth quartiles for step count (more than 3045 and 5668 steps a day, respectively) showed a significant positive association between higher step count and lower numerical pain rating scale (mean difference -0.43, 95% CI -0.78 to -0.08, $p=0.02$; -0.45; 95% CI -0.8 to -0.1, $p=0.01$, respectively) than those in the first quartile (less than or equal to 1199 steps a day). The restricted cubic spline model for the association between step count and pain scale displayed a steep decline followed by a moderate decrease as the step count increased; the inflection point was 5000 steps. However, this association was not observed among participants who met the fibromyalgia criteria (491/1273), who showed a steep positive increase below 2000 steps. Data were collected between June 1, 2018, and June 11, 2020, and were analyzed on November 18, 2021.

Conclusion. Step count measured with the Pain-Note app showed a nonlinear association with pain level. Although participants with and without fibromyalgia showed a negative correlation between step count and pain level, participants who meet the criteria for fibromyalgia may present a different relationship between walking and pain perception compared to those in the general chronic pain population.

P-40

A treatment method for fibromyalgia

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Fibromyalgia has both physical and psychological symptoms. The Swedish Psychiatrist Palle Villemoes developed a treatment method, called "Ego-structuring" developed specifically for the treatment of schizophrenic patients but also applicable for patients suffering from Fibromyalgia. Both illnesses have a psychological component. Villemoes addresses the psychological underdevelopment in those patients. Villemoes starts with the observation that the psychological underdevelopment of these patients makes those patients unable to be real dialogue partners. Hence, Villemoes does not place these patients in front of the therapist. Rather he invites those patients to sit next to the therapist. Next, Villemoes states that such patients have an underdeveloped relationship with language. This is confirmed by a patient of mine who said the following: "If I look at the world with my senses it is infinitely rich. If I describe it with language, I lose the richness of

the sensual world. What am I supposed to do?" Villemoes' method then consists in improving the realistic use of language. He invites the therapist to describe the objects in the room. In a next step Villemoes invites the patient to describe his first memories of objects. Then memories of objects later in the life of the patient. Soon the patient reports interactions with people. The patient thereby discovers who (s)he has become. The therapy ends when the patients has reported her(his) whole life story.

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Correlation of oxidative stress with pain severity in fibromyalgia

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Background. Oxidative stress is reportedly associated with fibromyalgia. However, there is no clarity about the potential cause for such an association.

Objective. To correlate the indices of oxidative stress with the severity of musculoskeletal pain reported in fibromyalgia (FM).

Methods. A total number of 80 patients with FM were examined. The examination included assessment of the 18 tender points, depending on the reaction of the patient, the points were rated with: 0 – no pain, 1 – tenderness reported with no emotional or physical reaction, 2 – tenderness reported with an objective physical reaction, 3 – tenderness reported with intense emotional and physical reaction, 4 – intangible area, the patient anticipating and avoiding touch. The levels of Superoxide dismutase (u/l), Serum catalase (mkmol/l), Late lipid peroxides (u/l), Serum malondialdehyde (mkmol/l), serum nitric oxide (mkmol/l), Total pro- and anti-oxidant activity (mmol/l), Early lipid peroxides (u/l) and Intermediate lipid peroxides (u/l) were assessed.

Results. All the indices showed correlation with the severity of pain assessed in decreasing order: Superoxide dismutase (u/l) ($r=1.00$, $p<0.05$) Serum catalase (mkmol/l) ($r=0.79$, $p<0.05$) Late lipid peroxides (u/l) ($r=0.76$, $p<0.05$), Serum malondialdehyde (mkmol/l) ($r=0.71$, $p<0.05$), Serum nitric oxide (mkmol/l) ($r=0.65$, $p<0.05$), Total anti-oxidant activity (mmol/l) ($r=0.63$, $p<0.05$), Total pro-oxidant activity (mkmol/l) ($r=0.62$, $p<0.05$), and Early lipid peroxides (u/l) ($r=0.50$, $p<0.05$). The weakest correlation was observed with Intermediate lipid peroxides (u/l) ($r=0.43$, $p<0.05$).

Conclusion. In our study, oxidative stress was associated with severity of musculoskeletal pain, suggesting potential benefit from anti-oxidant remedies in the comprehensive treatment of fibromyalgia.

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Sexual life quality in female patients affected by fibromyalgia syndromeMartina Favretti¹, Giulio Dolcini¹, Chiara Gioia¹, Roberta Priori^{1,2}, Cristina Iannucelli¹, Manuela Di Franco¹¹Rheumatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Italy; ²Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Background. Fibromyalgia (FM) is a common cause of chronic widespread pain. Although pain is its most distinctive feature, FM is characterized by a complex polysymptomatology that, among others, can reduce sexual functioning. The administration of a questionnaire for sexuality evaluation might be an acceptable method of communication for this sensitive issue.

Objective. To identify features associated with sexual dysfunction evaluated through Qualisex questionnaire, recently validated to Italian language for FM female patients.

Methods. 489 FM women (2016 ACR criteria), median age 50, referring to our out-patients *Fibromyalgia Clinic* answered an anonymous survey, including demographic characteristics, medical and pharmacological history, Hospital Anxiety and Depression Scale (HADS), and Qualisex questionnaire.

Results. Univariate analysis showed worse sexual functioning in women with lower educational level, housekeepers, women with a concomitant diagnosis of chronic pelvic pathology (CPP) or psychiatric disorder, and women who used drugs which can reduce sexual desire. Among women in an active relationship, sexual understanding with the partner was inversely

associated with sexual functioning (Table I). Multivariate linear model showed a significant influence of the presence of a partner, a very good sexual understanding with the partner, a diagnosis of CPP, and the use of drugs which can reduce sexual desire on sexual life quality (Table II).

Conclusion. Sexuality should be evaluated in FM patients and it should be taken into account in the multidisciplinary therapeutic intervention. A concomitant CPP should be investigated and treated. When drugs known to be associated with a reduced sexual desire are prescribed, the possible onset or worsening of this symptom should be considered. The improvement of the sexual life quality can contribute to the overall quality of life in FM patients.

Table I. Univariate analysis.

	Qualisex Score median (IQR)	HADS anxiety Median (IQR)	HADS Depression median (IQR)
Educational status, n=486			
Primary/Secondary	6.1 (4.2)**	12 (6)	10 (6)**
Higher	5.2 (3.8)	11 (5)	9 (5)
Occupational status, n=477			
Employed	6 (4.4)	12 (6)	9 (5)
Unemployed	4.9 (3.9)	13 (8)	9 (5)
Housekeeper	5.8 (3.5)*	11 (5)	13 (6)
Retired	3.4 (3.9)*	11 (8)	11 (4.5)
Menopause, n=486	5.6 (4.8)	12 (6)	9 (6)*
Marital status, n=484			
In a relationship	5.9 (6.6)*	12 (6)	10 (7.7)*
Non in a relationship	4.8 (3.7)	12 (5)	9 (5)
Sexual understanding, n=439			
Bad	7.7 (4.4)***	13 (5.7)*	13 (7)***
Poor	7.2 (2.9)***	13 (15.5)*	11 (6)***
Good	5.5 (2.8)***	11 (6)	9 (4)***
Very good	4.0 (4.2)***	10.5 (6)*	7.5 (5)***
Comorbidity, n=489			
Chronic pelvic pathology	6.9 (2.7)*	13 (4.5)	10 (4)
Psychiatric disorder	7.7 (2)**	14.5 (4)*	12 (4.2)**
Taking drug reducing sexual desire	6.7 (3.6)***	12 (6)	7 (6)*

* p-value <0.05, ** p-value <0.005, *** p-value <0.0001

Table II. Linear regression analysis.

	Multivariate model*		
	Coefficient	IC 95%	p-value
Educational status	-0.16	-0.63;0.29	ns
Occupational status			
Unemployed	0.02	-0.49;0.54	ns
Housekeeper	-1.27	-2.29;-0.25	0.01
Retired	-0.43	-0.98;0.11	ns
Marital status	0.93	0.36;1.50	0.001
Sexual understanding			
Poor	-0.06	-0.78;0.65	ns
Good	-0.65	-1.39;0.09	ns
Very good	-1.40	-2.22;-0.57	<0.001
Comorbidity			
Chronic pelvic pathology	1.08	-0.16;1.87	0.02
Psychiatric disorder	0.70	-0.15;2.66	ns
Taking drug reducing sexual desire	0.88	0.61;1.52	<0.001

*Adjusted for age and HADS score.

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