線維筋痛症における争点に関する国際会議

Tuesday, 05 March

08:00-08:30	Registration
08:30-10:00	**Session 5** Etiology of Fibromyalgia: "Known Knowns, Known Unknowns and Unknown Unknowns..." Chairperson: Daniel Clauw, *USA*

08:30-09:00

IS IT ALL IN YOUR GENES?

(GENETICS OF FIBROMYALGIA)

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

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

terms of familial aggregation among FM patients were also reported in two studies by Buskila et al. (6-8)
Psychological factors such as depression and personality traits also demonstrate familial aggregation among FM patients.
Glazer et al. (9) searching for shared personality traits in FM patients and first-degree relatives, reached the conclusion that hereditary factor determining personality traits may play a role in FM development as well.

Genome-wide association studies (GWAS)

Genome-wide association studies (GWAS) investigated genes potentially involved in fibromyalgia pathogenesis (3). Feng et al. (10) performed whole-exome sequencing and subsequent directed mutation analysis to discover possible candidate genes for FM. Two nonsense mutations associated with high levels of specific cytokines were identified. The W32X mutation in C11orf40 and the Q100X mutation in in ZNF77 (zinc finger protein 77) correlated with high plasma MCP-1 (monocyte chemoattractant protein 1) and IP-10 (interferon γ-induced protein 10) levels, and with high plasma IL-12 (interleukin 12) levels, respectively (11).
Other potential candidate genes found associated to fibromyalgia are SLC64A4, TRPV2, MYT1L, and NRXN3. Furthermore, a gene-environmental interaction has been proposed as triggering mechanism, through epigenetic alterations: In particular, fibromyalgia appears to be characterized by a hypomethylated DNA pattern, in genes implicated in stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities (12,13).

Genetic polymorphism

Associations between FM and certain genetic polymorphisms affecting the serotonergic, dopaminergic, and catecholaminergic pathways have been found via candidate gene analyses (4).
A variety of studies found that FM was associated with disturbances in serum and cerebrospinal fluid (CSF) serotonin metabolism and neurotransmission; the levels of 5-HT and metabolites thereof were significantly lower in the serum and CSF of FM patients (14-16).
Catechol-O-methyl transferase is one of the major enzymes responsible for metabolizing and inactivating catecholamine neurotransmitters including dopamine, norepinephrine and epinephrine, as well as catechol-containing

drugs. COMT in the CNS affects catecholamine neurotransmission in the prefrontal cortex (17). SNPs of the COMT gene may contribute to FM susceptibility and symptom severity.

Disruption of dopaminergic response to painful stimulation has been demonstrated among FM patients and there is some clinical indication of a role played by Dopamine in FM pathophysiology (3). Smith et al. (18) performed a large-scale candidate gene analysis using a dedicated gene-array chip which assays variants of over 350 genes known to be involved in biological pathways.. After replication analysis using an independent cohort, the authors suggested that the trace amine-associated receptor 1 (TAAR1), regulator of G protein signaling 4 (RGS4), cannabinoid receptor 1 (CNR1), and glutamate ionotropic receptor AMPA type subunit 4 provided (GRIA4) genes were potentially associated with the development of FM.

In FM, Vargas-Alarcon et al. (19) found that patients with polymorphisms in the sodium channel SCN9A gene, expressed in the dorsal root ganglia, had higher FIQ scores. Furthermore, Vargas-Alarcon et al.(20) found an association between adrenergic receptor (AR) gene polymorphisms and FM.

MicroRNA analysis

Bjersing et al. (21) conducted the first microRNA study, identifying nine microRNAs that were significantly lower in the CSF of FM patients than controls. In another study, Bjersing et al. (22) identified eight serum-circulating microRNAs that were differentially expressed between FM patients and healthy female controls.

In view of this it appears likely that novel genetic approaches are poised to expand our understanding of the genetic underpinnings of FM in the future.

Conclusions

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

The genetic studies conducted over the past two decades have not completely explained the molecular mechanisms of FM. Moreover, the effects of genetic factors on FM disease progression, therapeutic response, and outcomes have not yet been defined (5). Additionally, pharmacogenetic research is likely to have an impact on the pharmacological management of FM in the future.

Hence, the genetics of FM remains a project under construction.

References

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09:00-09:30

THE TIMES THEY ARE A'CHANGIN: EPIGENETICS OF CHRONIC PAIN

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

09:30-10:00

"FEAR AND AWE": HOW IMPORTANT IS STRESS AFTER ALL?

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

The interaction of pain and fear as an etiological factor has been observed in

patients with chronic pain, in psychosocial [1-5], psychophysiological [6, 7], psychophysical [8], endocrine [9, 10], genetic [11, 12] and central responses [13, 14], however inconsistent results suggest a heterogeneity in stress responses of chronic pain. Biopsychological mechanisms such as classical [15] and operant learning [16, 17] of different stress responses will be discussed.

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

Our study with 120 female fibromyalgia patients examined the relationship of psychophysiological response patterns with psychological characteristics and comorbid mental disorders [7]. Surface electromyographic data, systolic and diastolic blood pressure (BP), heart rate (HR), and skin conductance levels were recorded continuously during baseline, stress, and relaxation tasks. Cluster analysis revealed 4 subgroups of patients who differed on pain intensity, cognitive, affective, and behavioural responses to pain and stress (Table 1):

Table 1. Relationship of stress response pattern and psychological responses

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

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

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

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

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

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

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Figure 1: NTS reflex arcs

Figure 1: NTS reflex arcs

Memo

Psychobiological mechanisms:

The behavior of the cell is completely changing･･･
By the stimuli of the action potential

Repeated stimulation changes the memory pathways

Insula:
Crossover of the sensory -discrimiatib¥ve cognitive-affective
Sensory memory VS Affective memory
Increased Pain processing
Central mechanisms[the subjective pain perception is real
Fear and Pain; Stress and pain
When classical conditioning of increase of pain
FM related stress, Stress+catastrophic
Heterogeneiety in psychophysiological Stress Response Pattern in FM

Hypertensive baseline VS Hypotensive baseline
Different stress response

Baroreflex Sensitivity

Reduced Baroreflex Sensitivity(BRS) in chronic pain patients
Increased RBS- activation of both descending spinal and subspinal pain inhibition

Nociceptive effect of stress in chronic disease
Nucleus Tractus

Attenuation of skeletal reflexes and pain perception

Somato

Pain and social forces[birth of operant conditioning

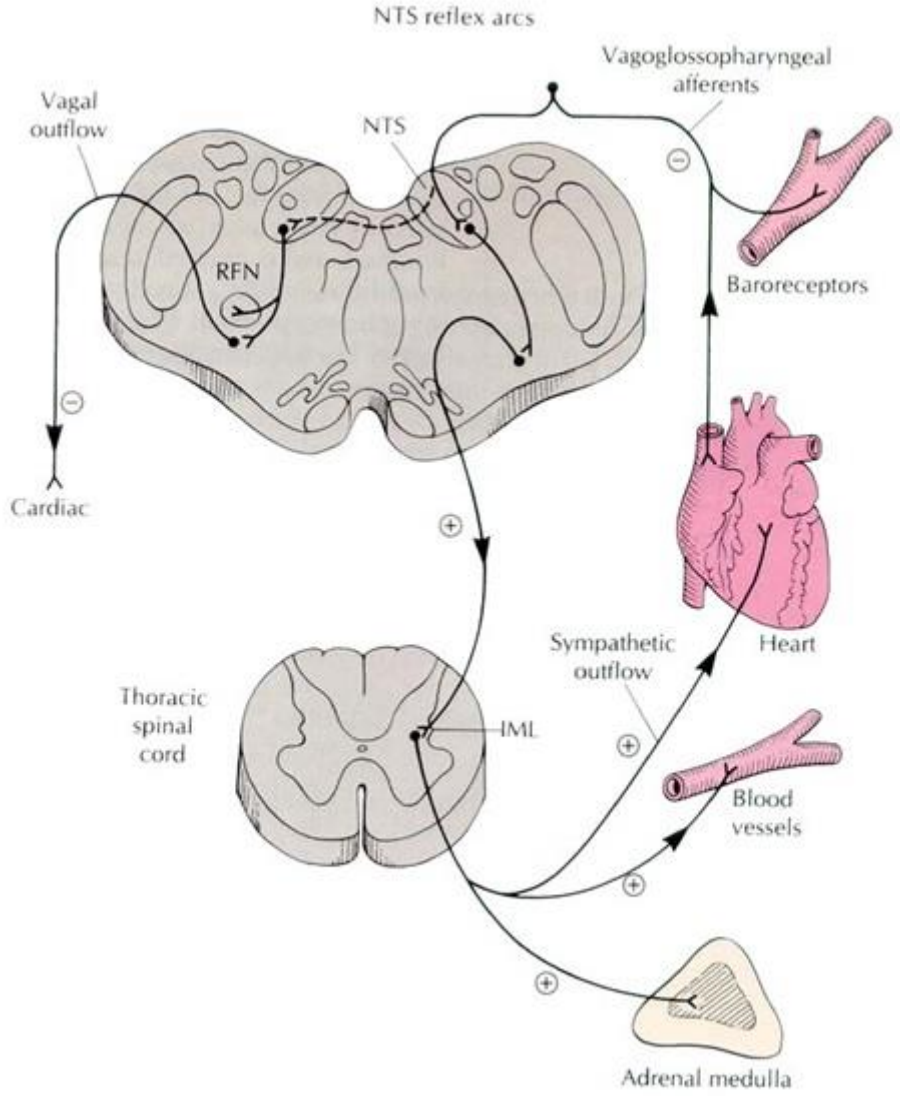
Pain behaviors: dysfunctional maladaptation
Pain perception,empathy,

Psychosocial subgroups

1) Dysfunction higher level of pain
2) Interpersonally distressed lower level of pain
3) Group of adaptive copers low pain intensity

Biological learning

Broreflex Training may re-program
Baroreceptor Training and Extinction Training
SET and OT(Operant therapy)-TENs
Improvement



10:00-10:30	*Networking, Coffee Break, Poster Viewing and Visit the Exhibition*

10:30-12:00	**Session 6** Is it All in your Head? The Neuroscience of Fibromyalgia Chairperson: Riccardo Torta, *Italy*

10:30-11:00

NOVEL PARADIGMS OF CENTRALIZED PAIN IN FIBROMYALGIA (PAIN SIGNATURES)

Daniel Clauw
University of Michigan, USA

The term centralized pain is used to refer to chronic pain states that are caused or maintained by the central nervous system. This new mechanism of pain has been much better understood over the past few decades and is now officially recognized by the IASP as nocicplastic pain.

The centralized pain phenotype is now understood to include widespread or multifocal pain accompanied by other CNS symptoms such as fatigue, sleep, memory and mood problems, as well as by hypersensitivity to multiple types of sensory stimuli.

Objective evidence of this centralized pain phenotype can be identified on quantitative sensory testing and functional, chemical and structural neuroimaging.

Changes in functional connectivity patterns are emerging which seem to be biomarkers for this type of pain.

There is also emerging evidence that these centralized pain states are accompanied by a primed inflammatory response that might contribute to symptomatology.

MEMO:

Classic peripheral pain syndromr

Poor relationship between structural abnormalities

Nociceptitive/Neuropathic/centralized(neuroplastic):Mixed Pain States

Pain Amplifyer:CNS

Top down: Functional Somatic Syndromes
Bottom up: Central sensitization

Pathological process of centralization
CNS transmitters influencing pain
Increased the weight o
Low grade inflammation

Summary:
1) small fiver damage
2) VD deficiency
3) Low level neuroinflammation
4) Epigenetics/DNA modification

Question:
Low dose opioids and corticosteroids are Ok,but high dose are not OKC
Acupuncture works
Universal pain

11:00-11:30

RE-TUNING THE BRAIN: NEUROMODULATION FOR FIBROMYALGIA

Roberto Casale
Opusmedica, PC&R Patient, Care & Research Network, Piacenza, Italy

The concept of neuromodulation is commonly referred to the chronic therapeutic electrical stimulation of the central nervous system or special nerves with an implanted stimulating device.

In a more broad way INS (International Neuromodulation Society) defines neuromodulation as “the process of inhibition, stimulation, modification,

regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral or autonomic nervous systems. It is the science of how electrical, chemical, and mechanical interventions can modulate the nervous system function" (Krames, ES., et al. 2009).

The use of electrical currents is the most common form of neuromodulation to interact with the brain, spinal cord, peripheral nerves, plexuses of nerves, the autonomic system, and muscles, while chemical neuromodulation uses direct placement of chemical agents to neural tissues through utilization of technology of implantation such as epidural or intrathecal delivery systems.

In this presentation we will not put attention on neuromodulation as described above rather than to a more basic science paradigm such as plasticity.

Indeed any form of "modulation" is based on the specific property of the nervous system to be modified in both ways for bad and for good (Costigan, M., Scholz, J., & Woolf, C. J. 2009).

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

If we consider any therapy as the attempt to restore the homeostasis, pushing or pulling, blocking or activating, inhibiting or exciting any given "altered" function or activity within the body we have to enlarge the concept of neuromodulation to any form of physical, pharmacological as well as psychological intervention as a attempt to re-modulate a given function or neural activity.

This attempt is done in rehabilitation when the maladaptive motor and sensory responses are the effect of a lesion and therefore our ability to act on plasticity is limited by the lesion itself but also in more subtle and apparently inexistent malfunctioning of motor and sensory systems as we see in fibromyalgia.

Now we realised that fibromyalgia is the terminal of a sequence of inadequate responses to physical, psychological and social stressful events (May, A. 2011) without signs of lesion, leading to a more and more generalised maladaptive responses involving any aspect of the bio-psycho-social paradigm.

Indeed there are no signs of anatomical lesion in nervous system of persons affected by fibromyalgia, however a consistent bulk of evidences are pinpointing

the existence of functional dysregulation not only in the sensory system but also in motor cortical areas (Saavedra, L. C., Mendonca, M., & Fregni, F. 2014).

This leads to the maintenance of a vicious circle involving sensory afferences, cortical sensory-motor coupling and non-adequate motor responses. Being fibromyalgia a severe form of maladaptive plasticity, any interventions should be tailored as also any form of therapy can be "interpret" in a maladaptive context.

Although therapies such as the hyperbaric oxygen therapy (Casale et al 2019), transcranial magnetic stimulation (Macfarlane, G. J., et al. 2017) or other therapies are showing promising results "re-tuning" the metabolism -i.e the activity of different cortical areas- however factors such as **resilience and the inner ability to overcome stressor events** can be considered in the light of a still not acceptable percentage of persons affected by fibromyalgia non responding to any effort to re-tuning our brain.

MEMO:

INS definition of Neuromodulation
A form of therapy in which neurophysiological signals are initiated or influenced

Environmental factors:microglial plasticity and neuronal plasticity
Brain plasticity
Expansion of receptor fields during central sensitization
Actively-dependent central sensitization
Cutaneous receptive field properties of flexeor

Adaptive VS maladaptive sensoru restoration VS

Free Radical Oxidative Stress

HBOT promotes tissue repair
Rectify abnormal brain function
Induce neuroplastic
Stem cell proliferation
Angiogenesis
Muscle fatigue
Normal sensory

FM cacophonic orchestra
Re-turning
Sensory-motor integration processes

No brain, no chronic pain
phenotype muscles are potential predictor of fibromyalgia
EEG-mapping

FBOT
1) glia
2) standard protocol
3) identify subgroups
4) stability of results

Question:
Glia should be targeted
Apply electric shock(small current electric stimulation)

11:30-12:00

TOWARDS NOVEL CLASSIFICATION OF COMPLEX BRAIN - RELATED SYNDROMES: LESSONS FROM BRAIN IMAGING

Dr Neil Basu, Senior Clinical Lecturer of Rheumatology, University of Glasgow

Disorders such as fibromyalgia and chronic fatigue syndrome represent some of the most clinically challenging conditions in Medicine. Their excess biological and phenotypic heterogeneity is a primary driver of this. A situation which is further conflated by their prevalent co-existence with other,

mechanistically distinct, disorders.

Numerous initiatives have sought to characterise and ultimately classify these syndromes with varying degrees of success and controversy. These have almost entirely been 'top-down' in approach i.e. derived from either expert consensus or phenotypic data. With historically limited knowledge of pathogenesis, it has been challenging to adopt a biologically based 'bottom-up' approach to classification.

However, advances in brain imaging, which at long last have begun to deliver mechanistic insights into these syndromes, offer a significant opportunity. The possibility to classify patients into homogenous subgroups will greatly support aetiological research - until now true signals have likely been masked by methodological artefacts generated from studying centralised syndromes as single entities rather than focusing on potentially mechanistically distinct subtypes. Clinically, the ability to firstly **parse out** co-existing centralised features in peripherally dominated chronic diseases will support the judicious use of existing therapeutics.

In the future, mechanism based sub-classification will help triage patients towards optimal interventions, in keeping with the ideals of personalised medicine.

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

MEMO

Classifying Fibromyalgia Sub-types
Fatigue in RA

Could centarlised mechanisms
FMness appears to be important in RA
Abnormalities in functional brain activity exist in FM
Functiona Connectivity(fc)MRI
Default model

DMN-Insula connectivity is longitudinally correlates with FMness among RA patients

Hypothesis:

RA

Clinical assessments-infalammation(ESR,CRP)

Questionnaur

How does peripheral inflammation influence CNS?

Multiple brain network

Medial prefrontal-cortex and inf parietal lobe are the hub of brain inflammation

Increased connection

Insula-L IPL functional connectivity is significantly associated with

Peripheral inflammation in RA-FM

Do FM neurological markers respond to biologic?RA Patitent priority

pへの、めたぼ、pろてお、tらんscりpと、epi-geno

Normal mental

Machine learning approaches to classification

Supervised Machine Leaning

Neuroimaging sub-classifification

12:00-13:00	*Lunch Break, Poster Viewing and Visit the Exhibition*

13:00-14:30	**Session 7** Treating Fibromyalgia in 2019: Meds, Non-Meds and Cannabis Chairperson: Dan Buskila, *Israel*

13:00-13:30

NON-PHARMACOLOGICAL TREATMENT FOR FIBROMYALGIA : COMPLEMENTARY/ALTERNATIVE TREATMENT MAY BE YOUR FIRST CHOICE…

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Fibromyalgia (FM) is a complex syndrome characterized by chronic widespread pain, sleep disturbances, fatigue and cognitive impairment, associated in some cases with anxiety and depression.

FM affects quality of life in many aspects (personal, familial, social and professional) and remains a therapeutic challenge. Comprehensive treatment of this condition aims not only to alleviate pain but rather needs a holistic approach to address both physical and psychological symptoms; to treat pain and functional consequences of pain. In this regard, non-pharmacological interventions have been shown to be effective, most of them with low cost and high tolerability.

Education is the first required step to ensure adherence and compliance to treatment program. Understanding fibromyalgia, its causes, natural history, and treatment options leads to better coping and improved outcomes. Validation of the diagnosis of FM also helps reducing health-related anxiety.

Low-intensity aerobic exercise training, starting gradually, has been shown to improve health-related quality of life (HRQOL), decrease pain intensity and improve physical function. **Aquatic training** is beneficial for improving wellness, symptoms, and fitness in adults with fibromyalgia.

Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials

Winfried Häuser[1]Petra Klose[3], Jost Langhorst[3], Babak Moradi[4], Mario Steinbach[4],

Marcus Schiltenwolf[4] and Angela Busch[5]*Arthritis Research & Therapy*2010**12**:R79

Exercise training (exercise performed against a progressive resistance) may improve function, pain, tenderness and muscle strength in women with FM.

Meditative movement therapies (MMT) - involving core elements of specific movements, meditative instruction and breath regulation- are considered as a complex intervention integrating concepts of mind and body, with physical, emotional and spiritual aspects. In recent years, there is abundant literature reporting benefits of MMT in various chronic pain conditions, including fibromyalgia.

Qi Gong and Tai Chi have shown significant improvement regarding pain, sleep disturbances, fatigue, depression and HRQOL. Better outcomes are obtained when MMT is practiced daily, which may be challenging for FM patients. One recent study has shown that Tai Chi improves cardiac autonomic function, sympatho-vagal balance, pain, fatigue, strength and flexibility in women with fibromyalgia. Another study shows that Yoga may modulate abnormal pain processing in fibromyalgia, demonstrated by improvements in heat pain tolerance and pressure pain threshold.

Balneotherapy (BT) (treatment based on thermal mineral water from natural springs) and hydrotherapy (HT) (normal water) are additional alternative interventions usually recommended in the management of FM. Studies of BT and HT in FM patients have shown improvement on pain and HRQOL, with no significant effects on depressive symptoms. How these therapies may improve FM symptoms is not fully understood, but effects on pain alleviation may be explained by hydrostatic pressure and effects of temperature on the nerve endings, as well as by muscle relaxation.

Cognitive Behavioral Therapy (CBT) aims to reinforce self-efficacy in managing symptoms of FM and plays a central role in the non-pharmacological

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

MEMO:

Multifactorial model
Multimodal treatment is potential
Strategy to manage pain and disabilities
Patient's perspective
Cost-effectiveness
Patient education:intervention and benefits
Exercise:difficult to start and maintain low impact aerobic exercises
Improved HRQOL
Exercise-induced analgesia:antinociception
Hydrotherapy /Balneotherapy
Buoyance,immersion,resistance,temperature
Mind-Body Approach
Meditative movement therapies / TaiChi,Qigong,Yoga
Neuro-imaging studies in MMT
Nociceptive memory
Allostatis
Tai Chi &Autinomic function
Cognitive Behabioral Therapy
Modify
Brain changes in Cognitive/Meditative Therapies[

Attenuate pain-related symptoms
Acupuncture:
Pain modulation continue 3 months after treatment
Nutrition:remove oxidative stress
Excitotoxicity:Glutamate role in chronic pain/central pain
Artificial sweeteners:Glutamate ,Aspertate
VitC,E
Omega
Obesity
EULAR recommendations
Individualized

Question:
All of them acts on the brain

13:30-14:00

MEDICATING FIBROMYALGIA IN 2019: ANY NEWS IN THE PIPELINE?

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Fibromyalgia syndrome (FM) continues to pose an unmet need regarding pharmacological treatment and many patients fail to achieve sufficient relief from existing treatments (1).

Recently published guidelines recommend the adoption of a symptom-based approach to guide pharmacologic treatment. Emerging treatment options for FM may be best differentiated on the basis of their effect on comorbid symptoms that are often associated with pain (e.g. sleep disturbance, mood, fatigue)

(2). None of the currently available drugs are fully effective against the whole spectrum of FM symptoms, which seem to benefit from multidisciplinary management (3).

Various drugs have been recommended in the different guidelines, but none have been approved by the European Medicines Agency, and only three by the Food and Drug Administration (FDA): the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine and milnacipran, and pregabalin, which acts via the α2δ subunit of voltage-gated calcium channels. However, a significant number of patients do not respond adequately to these drugs or experience intolerable side effects (3).

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

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

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

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

Mirogabalin is a gabapentinoid with significantly higher potency than pregabalin. In the three, 13-week, double-blind, global, phase 3 ALDAY clinical

trials evaluating mirogabalin for the treatment of pain associated with FM, mirogabalin did not meet the primary efficacy endpoint to demonstrate a statistically significant reduction in the weekly average of worst daily pain score from baseline to Week 13. In Japan, the company submitted a marketing application only for treatment of peripheral neuropathic pain.

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

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

Even though current evidence is too scarce and weak to support the use of cannabinoids in FM, it would be interesting to investigate their potential role. The existing data are limited to the synthetic cannabinoids, nabilone, and dronabinol, but future studies should also investigate the role of the efficacy and long-term safety of other synthetic or natural cannabinoids (12).

Evidence-based interdisciplinary guidelines give a strong recommendation for aerobic exercise and cognitive behavioral therapies. Drug therapy is not mandatory. Only a minority of patients experience substantial symptom relief with duloxetine, milnacipran, and pregabalin or with a combination of different drugs (13).

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MEMO:

Recommentions for the pharmacological treatment
Identifying
Initial management should focus on non-pharmacological therapies
Patient education and information sheet
For severe pain, for severe sleep problems
recommendation
Miglogabalin (Daiichi)failed

14:00-14:30

CANNABIS FOR FIBROMYALGIA: THE GREAT GREEN ELEPHANT IN THE ROOM

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In recent years, cannabis had been approved for medical use in more than 30 countries: from United States to Europe and Israel. Worldwide, cannabis is the third most commonly used substance after alcohol and tobacco.

The use Medicinal cannabis is highly controversial amongst doctors.
There are only a few studies in the literature on the use of cannabis by fibromyalgia patients. In these studies, the patients used unlicensed/illegal cannabis from different suppliers, and the studies contained no information on either the type or amount of cannabis used.

The medical community needs to adheres to the principle that substances intended for therapeutic purposes be fully characterized chemically,

pharmacologically and toxicologically. The use of medications, including medicinal cannabis, should not be the core component of therapy.
Although herbal cannabinoids may offer some therapeutic effect, caution regarding any recommendation should be exercised pending clarification of general health and psychosocial problems and a clear follow-up program should be used.
At the present time, the scientific evidence for the efficacy of cannabinoids in the management of people with fibromyalgia patients is insufficient to justify endorsement of clinical guidelines.
Specific concerns should address also risk of doctor shopping, risk of harms, media and public pressure and the emergence of a new industry, rather than on the foundation of robust evidence.

MEMO:
An endocannabinoids deficiency:anadomide 2-arachidonoglycerol(2-AG)
Immmnnosuppressive
Immunologic cells:modulation cell migration,microglia(possible role in Alzheimer's)
DA*
Glu
Good efficacy but side effects
Risks Associated with chronic Marijuana Use
Motion of the treatment prospect

14:30-15:00	*Networking, Coffee Break, Poster Viewing and Visit the Exhibition*

15:00-16:00	Oral Abstract Presentations Chair: Jacob Ablin, Israel

16:00-17:00	**Session 8** Final Session: The Road Ahead...

	Chairpersons: Daniel Clauw, *USA* Lars Arendt-Nielsen, *Denmark*

16:00-16:30

FITNESS FOR WORK-PRACTICAL ASPECT

AYALA KRAKOV ISRAEL

FFA(FIT FOR

BLUEPRINT FOR "FUTURE FIBROMYALGIA"

CONFERENCE

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

Fibromyalgia remains a project under construction. While decades of research as well as clinical experience have added greatly to our current understanding and appreciation of fibromyalgia, the true nature of the disorder and the scope of the problem remain elusive.

Diagnostic criteria continue to evolve, reshaping both the clinical spectrum as well as the epidemiology and cultural understanding of fibromyalgia as a nosological entity.

At the same time, cutting-edge research technologies continue to be developed, constantly opening new windows and new perspectives into the pathogenesis of fibromyalgia and chronic pain in general. Functional neuroimaging, next generation sequencing and epigenetics, as well as novel tools for inducing neuroplasticity, all may reshape fibromyalgia as we know it over the coming years.

Fibromyalgia continues to hold an unusual place among rheumatological disorders. While the major clinical symptoms of fibromyalgia, i.e. widespread musculoskeletal pain, fall squarely into the field of rheumatology, probably

encompassing many of the very patients who would have been described in past generations as suffering from “rheumatism” of one kind or another, it has become ever more obvious that the underlying pathogenic mechanisms involved in initiating and perpetuating the fibromyalgia syndrome are connected more closely to dysfunctional processing within the central nervous system then to “rheumatological” tissues such as synovium and cartilage. Thus, fibromyalgia should better currently be addressed in similar strategies as are being applied to other complex CNS disorders, including depression.

In this aspect it is noteworthy to pay attention to the inspirational “**Research Domain Criteria**” (acronym RDoC) which is being developed and implemented by the National Institute of Mental Health [1].This ambitious project is striving to integrate emerging findings from hitherto diverse fields of research such as genetics, physiology, network analysis and psychology in order to create a new matrix for classifying and diagnosing patients suffering from mental disorders. This approach, which conceptually may eventually replace the criteria – based taxonomies such as the DSM, aims at eventually reaching true individualized precision medicine. It is appealing to vision, that other complex conditions involving the CNS such as fibromyalgia, will eventually similarly be addressed. In such a system an individual patient would actually not necessarily need to be given an ICD – based label such as fibromyalgia, but would rather undergo extensive genetic (and epigenetic) profiling, including pharmacogenetic evaluation, as well as functional neuroimaging aimed at identifying abnormal patterns of connectivity; physiologic pain processing could also be incorporated such as assessment of **conditioned pain modulation** (CPM) and other patterns of pain processing. Psychological and cognitive assessment would also be incorporated as well as psycho-social evaluation. Ultimately, this process would culminate in a very personalized plan of treatment, combining optimal pharmacological agents together with non-pharmacological tools all aimed at alleviating pain, minimizing disability and restoring function.

This description may yet sound somewhat utopian at the current point in time. Currently, fibromyalgia patients are diagnosed based on criteria which change at a rather alarmingly rapid pace and often the diagnosis appears to be made by physicians not very well acquainted with the diagnostic criteria to begin with. Both over – diagnosis and under diagnosis are abundant and many misconceptions remain among both laymen as well as in the medical community, regarding what fibromyalgia is and what it is not.

Patients are all to often frustrated to encounter lack of knowledge as well as disrespect and disbelief, all of which naturally impede clinical rapport and reduce any prospect for significant improvement. These predicaments can only gradually be overcome through better education and increased awareness.

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

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

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MEMO:

16:30-17:00

IS THERE A ROLE FOR PREVENTION OR EARLY DIAGNOSIS IN FIBROMYALGIA?

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

Acute pain is of sudden onset and expected to last less than 3 months. Chronic pain is defined as ongoing or recurrent pain, lasting beyond the usual course of injury healing or more than 3 to 6 months. The development of chronic pain results from complex interactions between biological, psychological, and social factors. There is increasing evidence that the transition from acute to chronic pain (particularly FM) is associated with permanent neurophysiological transformations (i.e., central sensitization, gliopathy, and an emotional shift in the brain circuitry involved in nociception) and genetic and epigenetic factors (4,5). A variety of different conditions can play a role in the transition from acute to chronic pain: demographic aspects (e.g., female gender and low socio- economic status), injury-related (e.g., lower limb injury and compensable injury), autoimmune or neoplastic diseases, small fiber neuropathies, surgery (e.g., mastectomy, thoracotomy, and amputation), psychological risk factors such as anxiety, depression, pain catastrophizing and pain-related fear.

Because of the link between FM and exposure to stress, and because both the neuroendocrine and autonomic nervous systems could cause many of the

symptoms of FM, these factors have been fairly extensively studied; however, these factors are now generally thought to play a role in some individuals, but not to be central pathogenic factors in all individuals with these conditions (6,7).

The prevalence of FM varies from 2 to 5%, depending on the population sampled and the method of evaluation (8). The incidence of FM was determined in a population-based sample of Norwegian women between the ages of 20 and 49 years who were followed for 5.5 years. The incidence of FM among women who began the observation period without any complaints of musculoskeletal pain was 3.2%, corresponding to an average annual incidence of 583 cases/100,000 women between 20 and 49 years of age.

For those with any self-reported pain at the beginning of the study, the incidence was 25% and risk factors for the development of FM included pain for 6 years or more, self-assessed depression, lack of professional education, and the presence of 4 or more associated symptoms, such as disturbed bowel function, unrefreshing sleep, paresthesia, and subjective swelling (9).

In another cohort of 1,198 early arthritis patients followed by rheumatologists, the incidence of FM was 6.77/100 person-years in the first year after diagnosis of arthritis, and declined to 3.58/100 person-years in the second year. Pain severity and poor mental health predicted FM risk (10).

Why prevention is so difficult in potential FM patients? This is a list of some potential topics: 1) there is no biomarker; 2) we should treat any type of acute pain to prevent cronicity; 3) we do not know why central sensatization occurs in some patients and not in others; 4) can we improve resilience or is it only genetically and/or enviromentally determined? 5) what is the role of psycoaffective and/or personality problems in these patients?

We do not have an answer to these questions and we can only treat patients early both with non pharmacological or /and pharmacological armamentarium. We can teach the patient how to handle fibromyalgia (perceived self-efficacy in pain management and pain acceptance) but not how to get rid of it or even better how not to develop the syndrome in presence of risk factors.

Long-term outcome data for FM are limited. Although available studies indicate that symptoms of FM often persist, many patients are able to identify

strategies over time that can moderate symptoms (7).

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MEMO: