
MATERA
CASA CAVA
18-20
MAGGIO
2023
Atlas
Annual Thinking LAb on
Fibromyalgia Syndrome
2nd edition

Workshop

VENERDI’ 19 MAGGIO

14.30-17.30 workshop LA CURA 1 *Piercarlo Sarzi Puttini, Gianni Forte*

14.30-17.30 workshop LA CURA 2 *Claudia Finocchiaro, Giusy Fabio*

Circa 3 ore

SABATO 20 MAGGIO

9.00-12.00 workshop LA CURA 1 *Piercarlo Sarzi Puttini, Gianni Forte*

9.00-12.00 workshop LA CURA 2 *Claudia Finocchiaro, Giusy Fabio*

11.00-11.15 coffee break

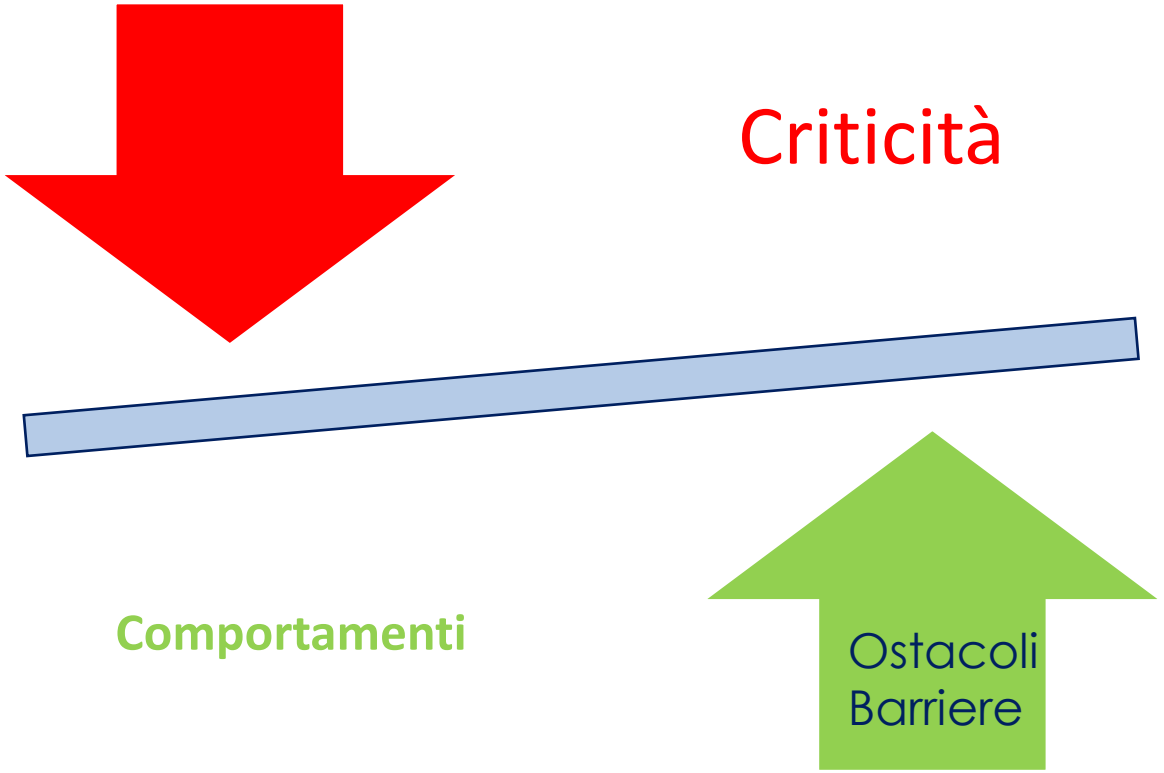
Circa 3 ore

Argomenti

- **Esperienze di real life** nel trattamento farmacologico del paziente con fibromialgia

- **Come organizzare un ambulatorio multidisciplinare**

Obbiettivo



., nervo scoperto!

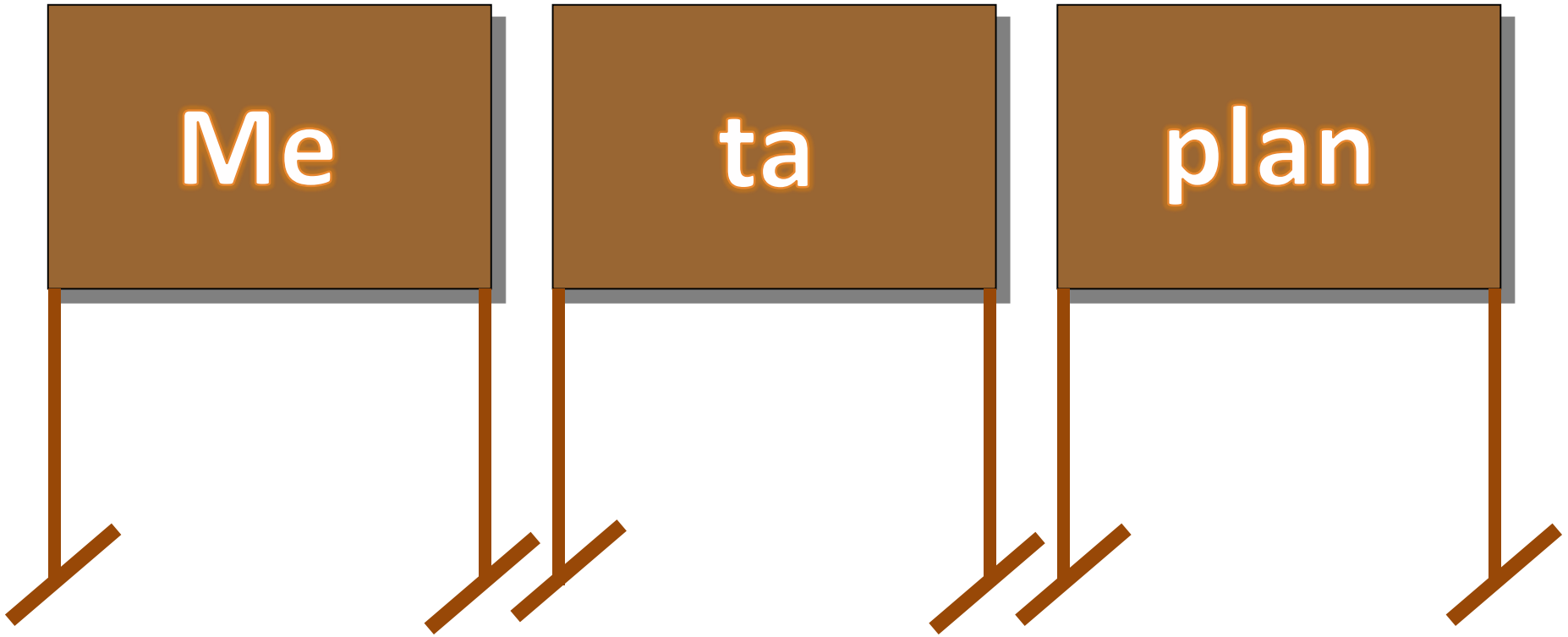
Nella giornata di sabato,

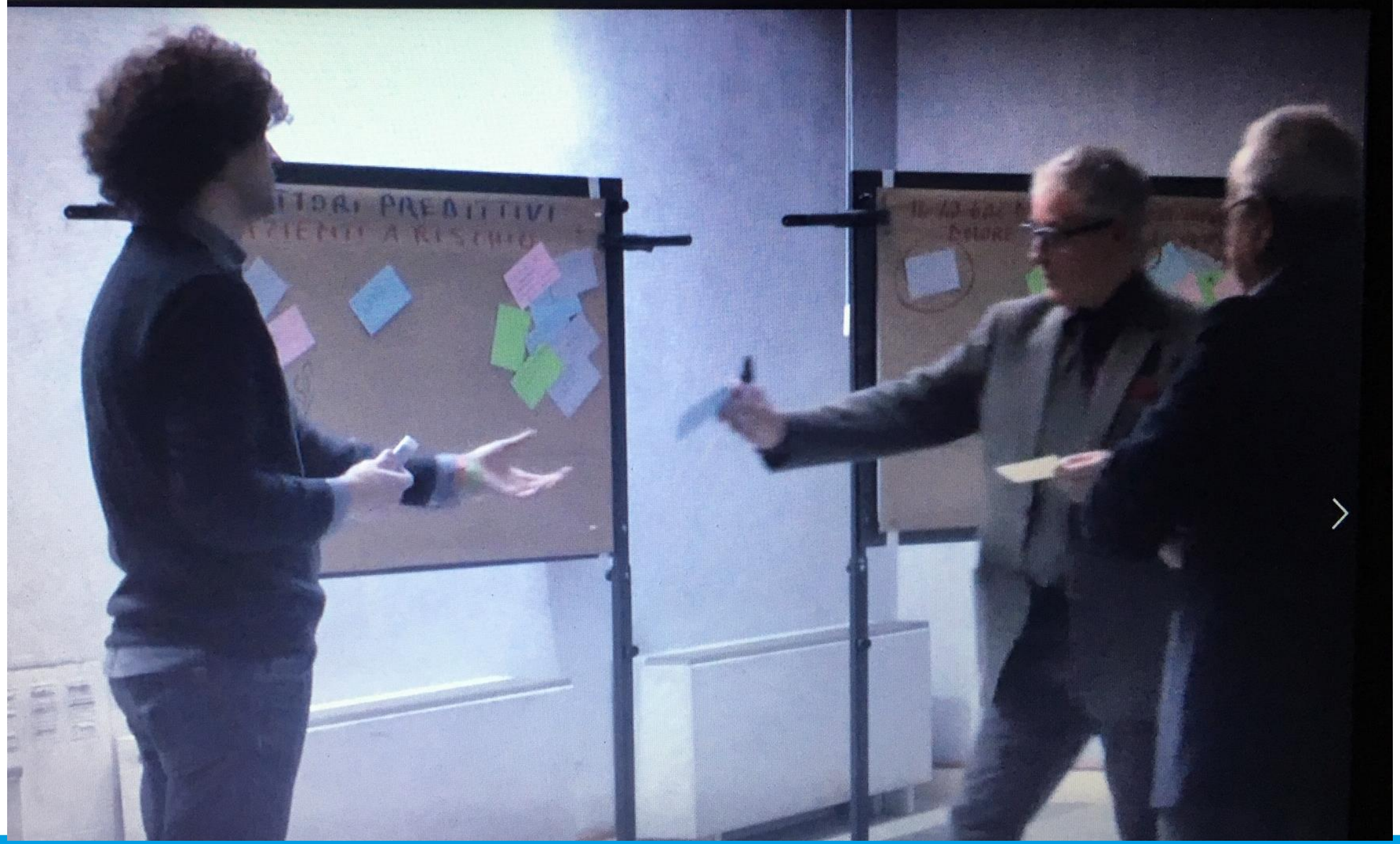
un rappresentante per ciascun gruppo

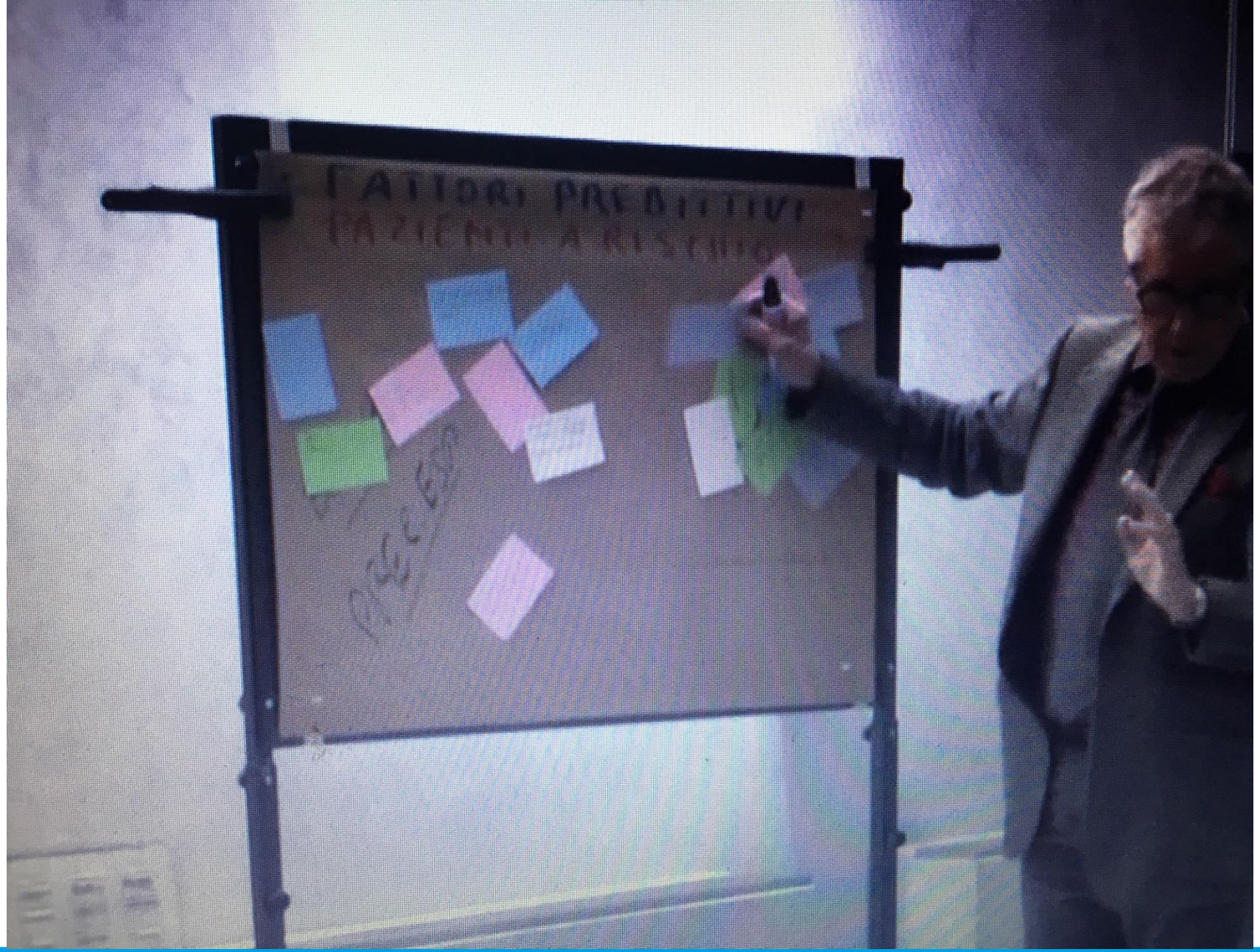
relazionerà alla platea sulle attività svolte

e sulle considerazioni emerse 5’

Tecnica di facilitazione basata sulla visualizzazione








20. Secondo la vostra esperienza, quali sono gli obiettivi
trattamento del paziente con disturbo depressivo?

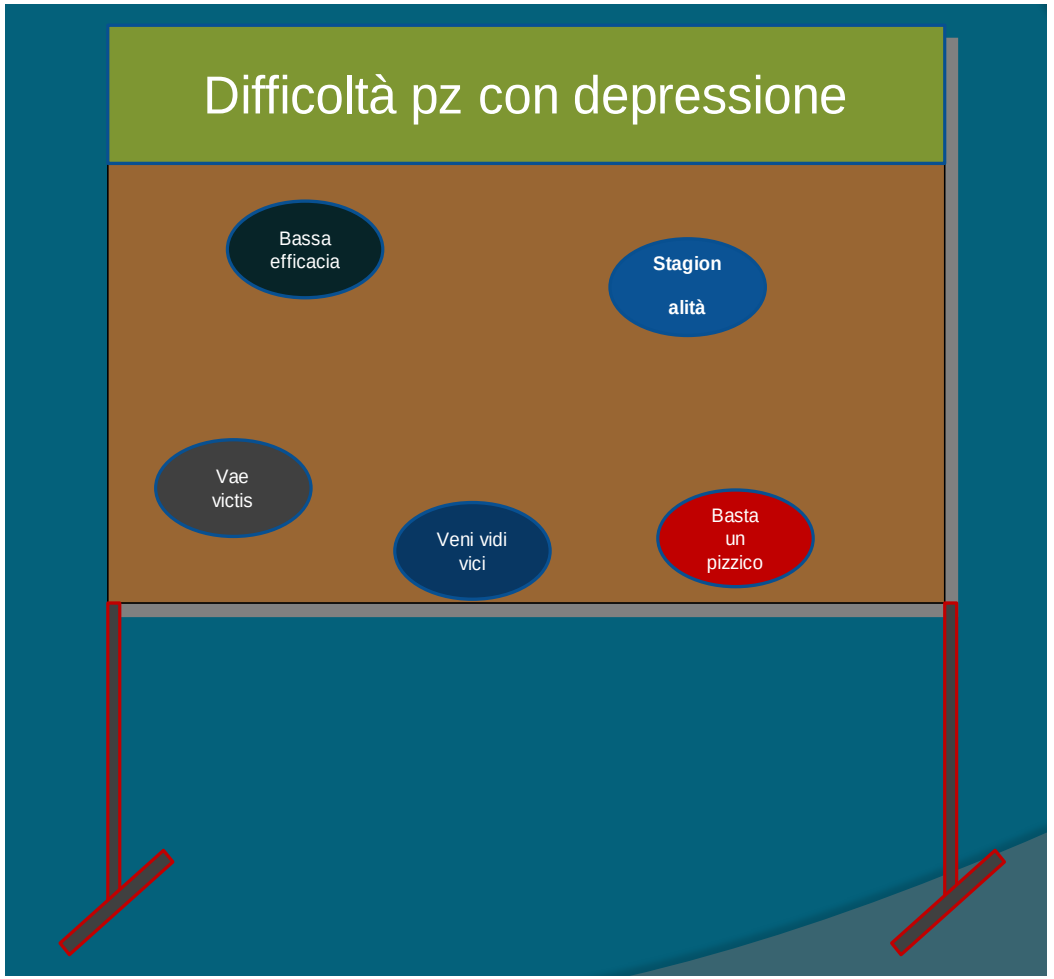

1. I° SS Secondo la vostra esperienza, quali aggettivi caratterizzano maggiormente i pazienti con fibromialgia?
2. I° SS Quali criteri utilizzi nel porre la diagnosi di FM?
3. I° SS Quali sono le principali patologie rispetto alle quali effettuare la diagnosi differenziale e le indagini diagnostiche (di laboratorio e strumentali) raccomandate?

1. Quali sono le maggiori aree di difficoltà nella gestione del paziente con depressione?

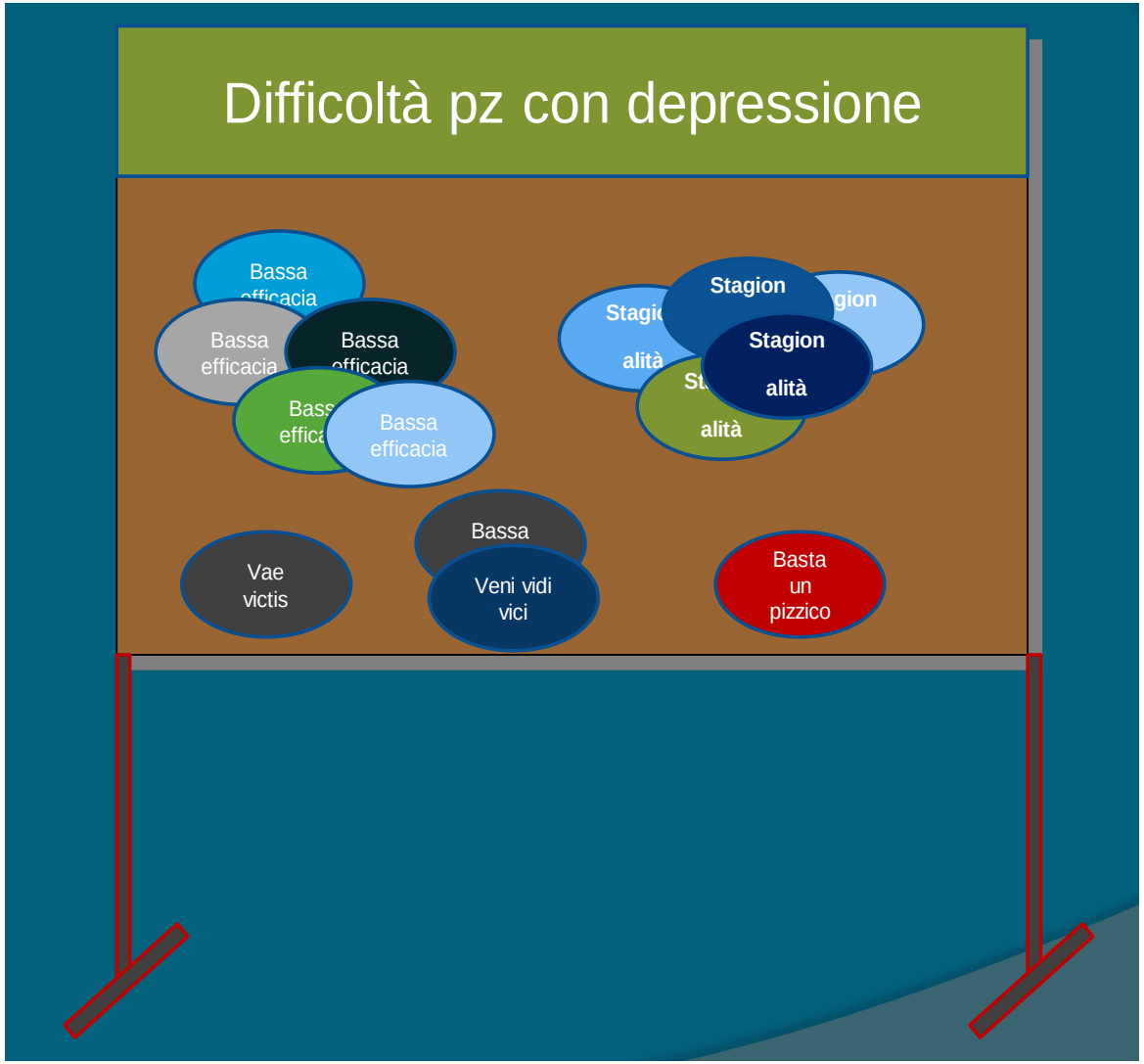
MP


Punta fine
Punta grossa
Pennarello alimentare
Pennarello alimentare

1. GF raccoglie i cartoncini
2. Li legge
3. Chiede dove inserirli sul pannello
4. Fino alla costruzione di differenti cluster

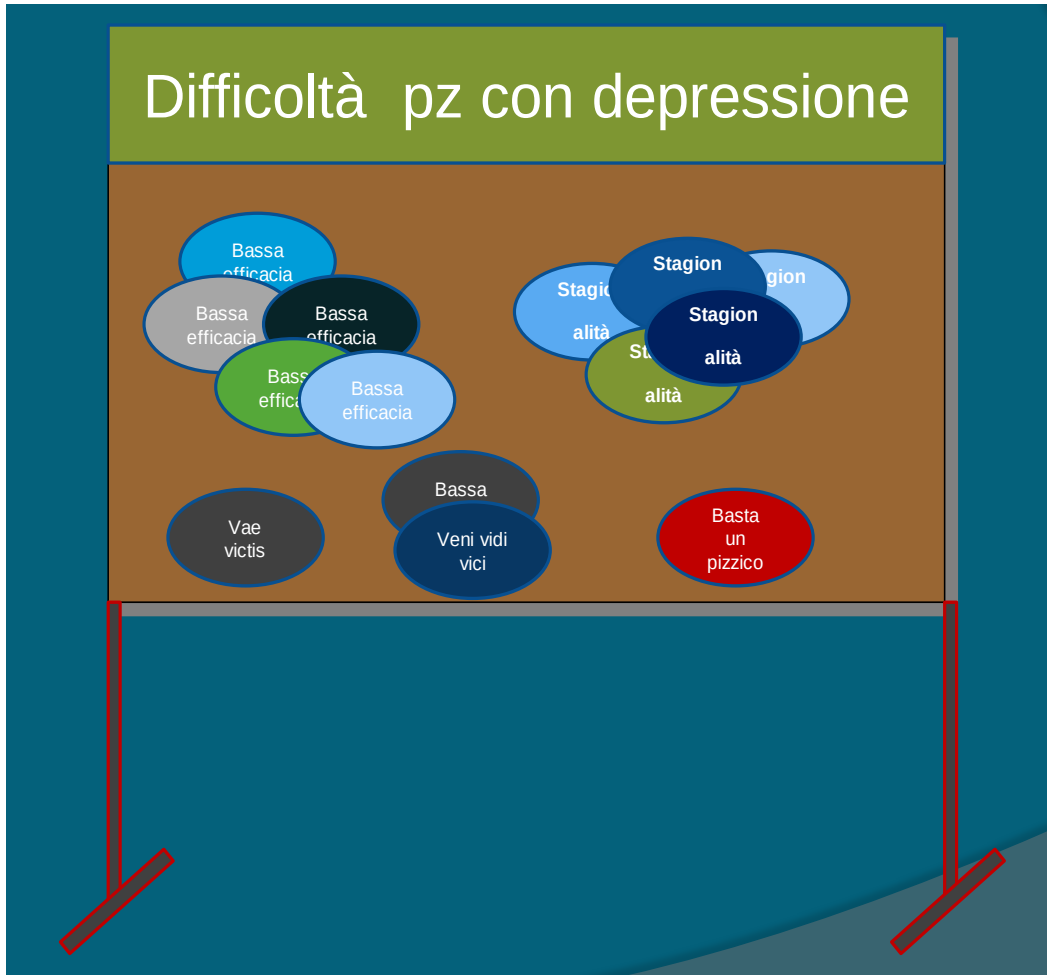


Costruzione di differenti cluster



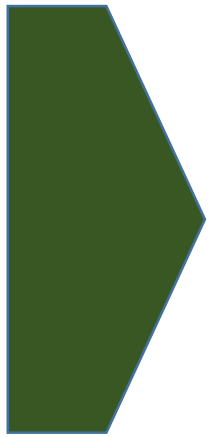
Costruzione di differenti cluster

Commento relatori



1. Quali sono le maggiori aree di difficoltà nella gestione del paziente con ….

1. Criteri diagnostici
2. Dosaggio iniziale
3. D/V varie formulazioni
4. Gestione del dolore di base
5. Aderenza
6. Altro
7. Nessuna

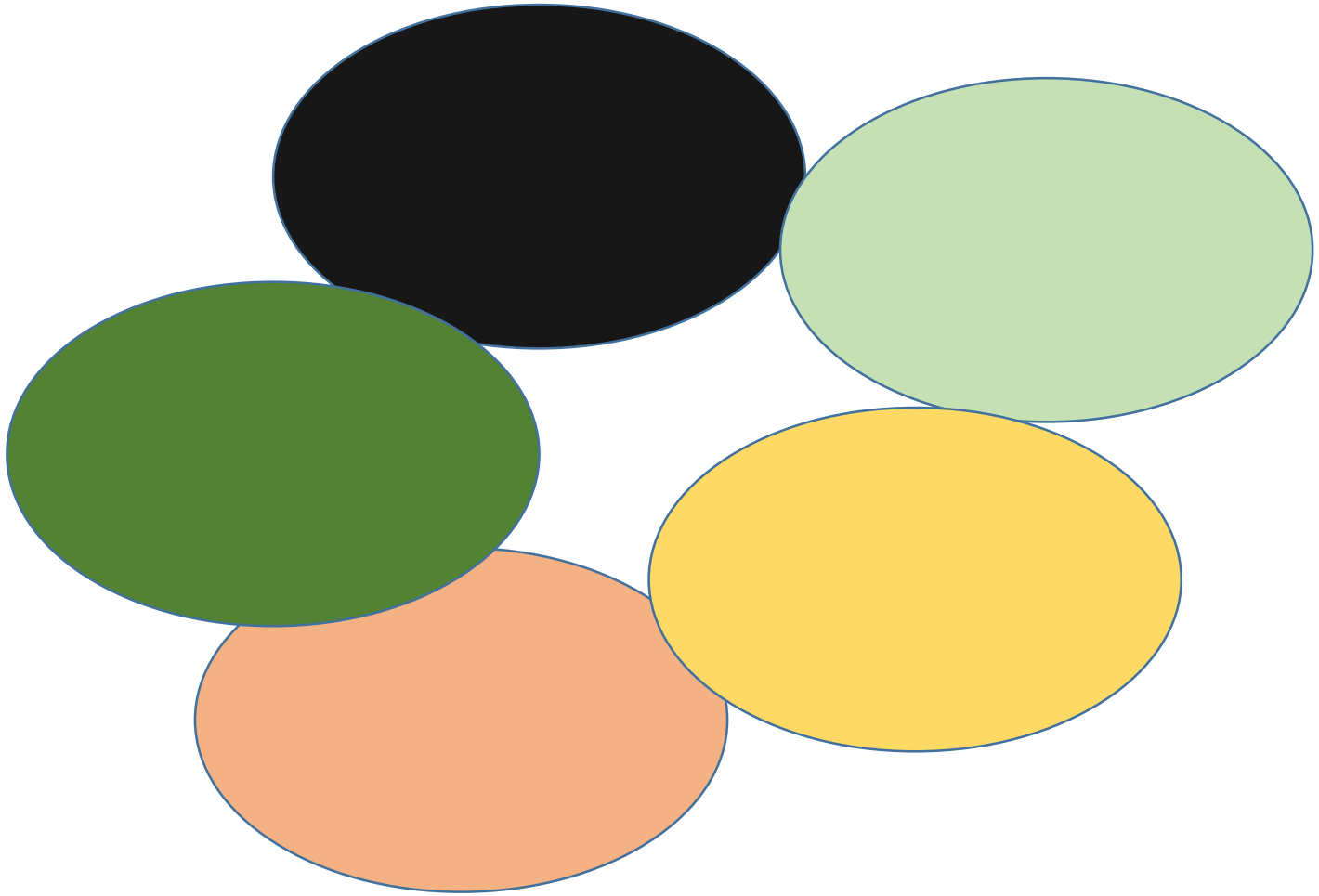


SPIEGAZIONE CON DIAPO E DISCUSSIONE

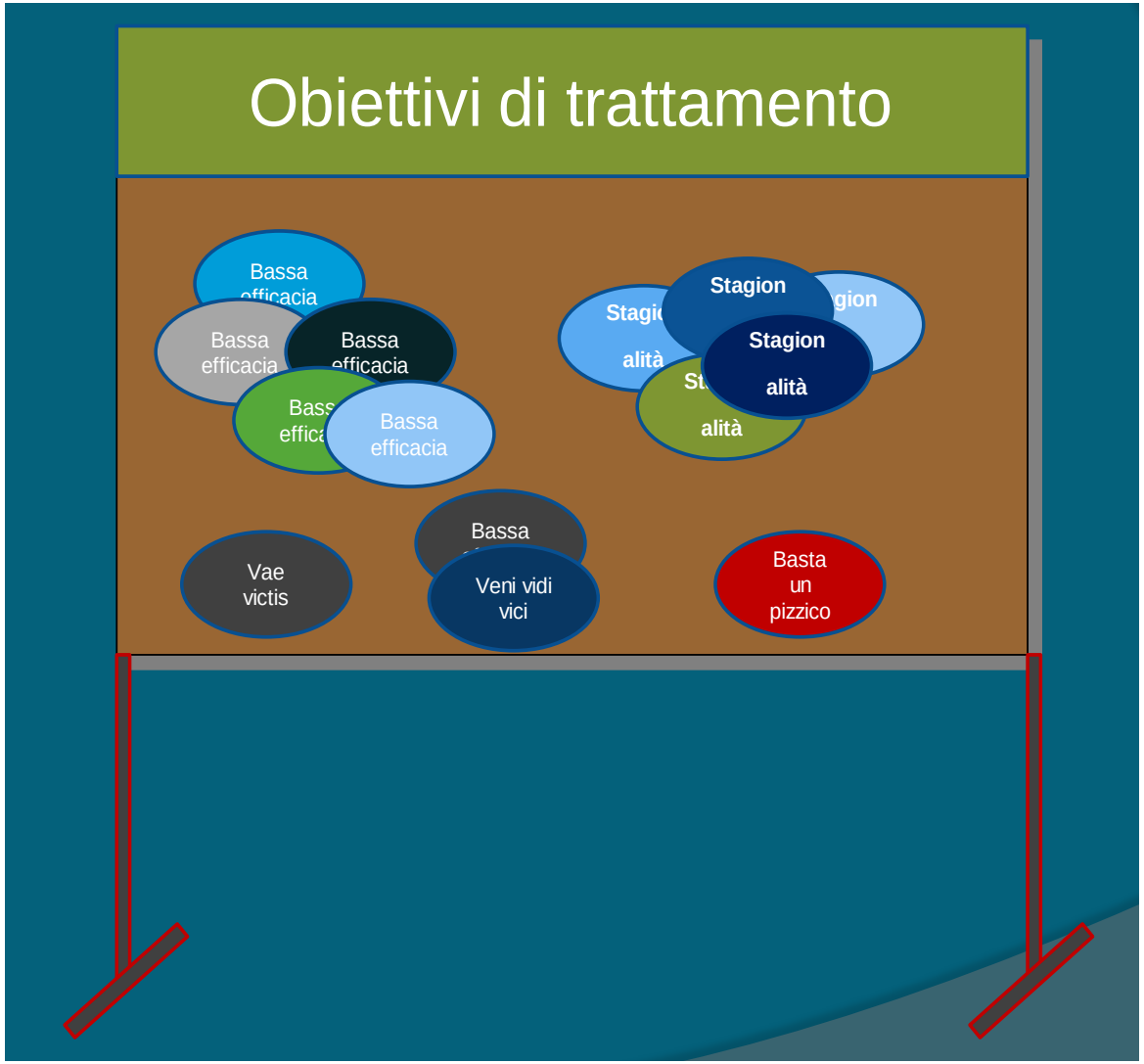
Il metodo consente di arrivare progressivamente alla identificazione
delle problematiche emergenti ed alla condivisione della soluzione

2. Quali sono gli obiettivi di trattamento nella gestione del paziente con dolore?

MP



Costruzione di differenti cluster



Costruzione di differenti cluster


Me
ian
E così via


Buon lavoro

Workshop

- **Esperienze di real life** nel trattamento farmacologico del paziente con fibromialgia

- **Come organizzare un ambulatorio multidisciplinare**

- **TERAPIA**: Conoscenza dei meccanismi patogenetici-impiego di farmaci per controllare i sintomi

- **CURA**: percoso di consapevolezza del paziente che partecipa attivamente alla gestione della malattia

  - APPRENDERE CHE TUTTI I SINTOMI SONO ESPRESSIONE DI UN'UNICA MALATTIA
  - TENDERE A VALORIZZARE LA QUALITA' DI VITA
  - MOTIVAZIONE A SVOLGERE ATTIVITA' DI RESILIENZA

SINDROME

. **syn**- insieme

. **drome** – pista per corsa

. Determinare il tracciato del percorso

. Osservare il percorso dei componenti della sindrome di un paziente

Importanza di una Definizione Clinica

Le definizioni correnti della FM

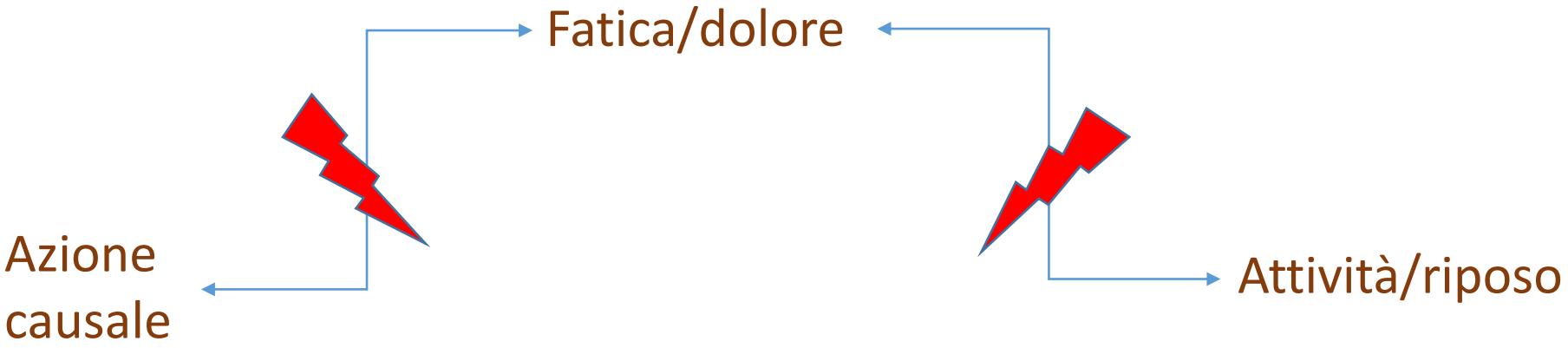
. Insieme statico dei sintomi

. Aspetti dinamici sottovalutati

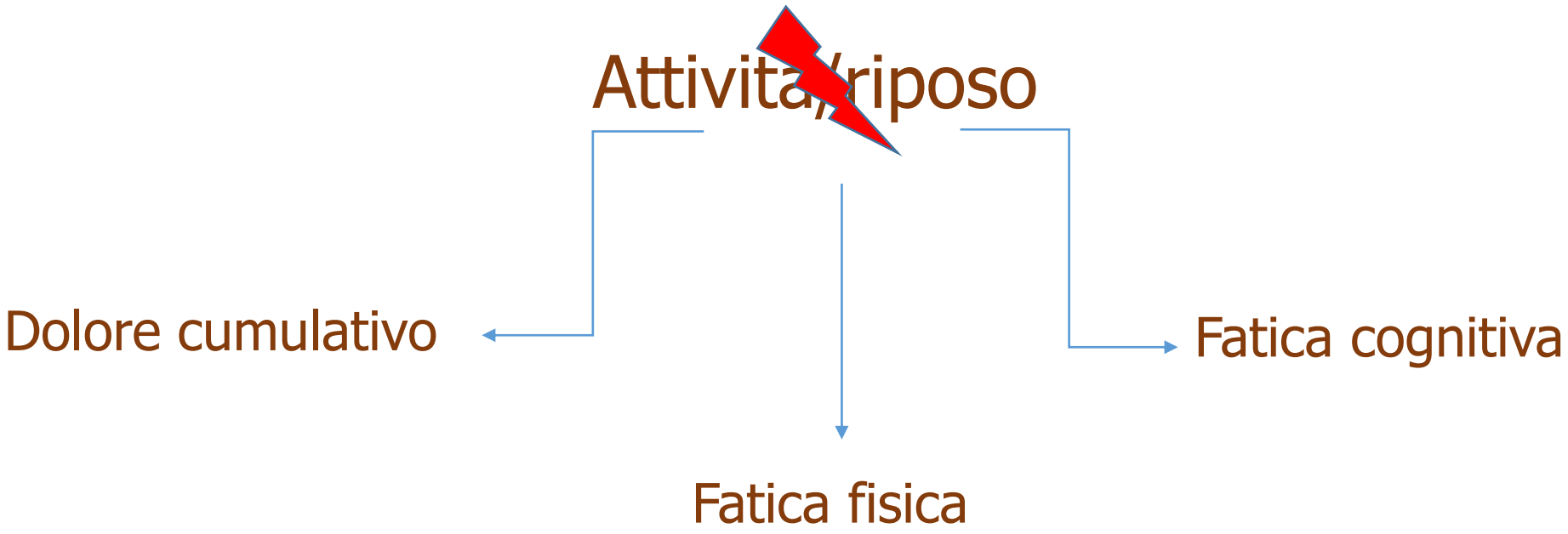
, ignorando gli aspetti critici di questa sindrome, così come vissuta dai pazienti

Importanza di una Definizione Clinica

La confusione dei modelli



Importanza di una Definizione Clinica



Importanza di una Definizione Clinica

- Insieme dei sintomi
- Loro interazione
- Effetti additivi

, interferenza nella vita del paziente nel tempo

Storia naturale della FM

Costante peggioramento
della disabilità funzionale

La prognosi individuale deve basarsi sulla valutazione clinica del singolo paziente poiché essa non può essere predetta con certezza

Obiettivi e principi terapeutici / Linee Guida

Il medico curante conosce
il paziente meglio degli altri

Tutto il personale riabilitativo deve essere ben informato sulla FM

La fisiopatologia della FM deve essere ben conosciuta e si deve riflettere in tutti i trattamenti

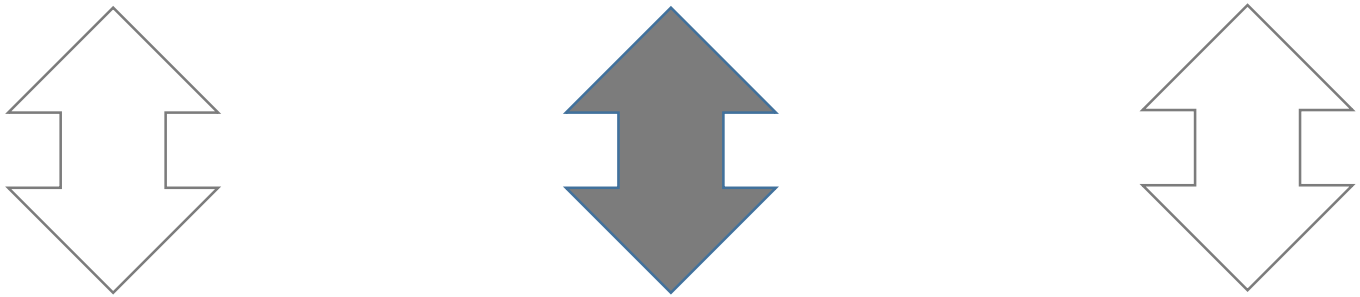
. **L'impatto complessivo della malattia**
. **L'interazione tra i sintomi**
. **La fluttuazione dei limiti di attività**
. **La scarsa resistenza**
. **I fenomeni di sovraccarico**

Concentratevi sulla riduzione della sintomatologia e sul mantenimento della funzionalità

1. Secondo la vostra esperienza, quale deve essere l'obiettivo terapeutico nel paziente affetto da FM?

Obiettivi e principi terapeutici / Linee Guida

Il rafforzamento del paziente

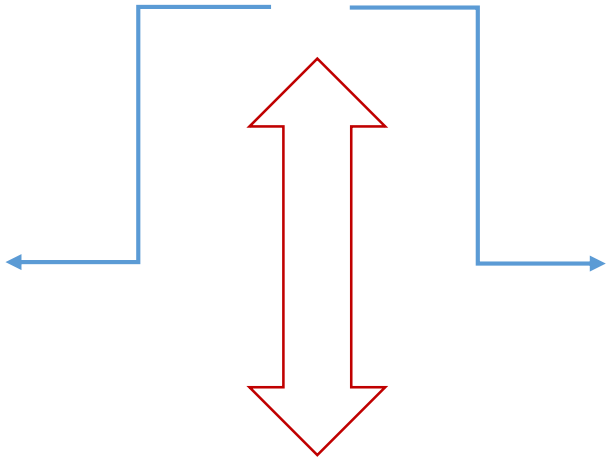


Incoraggiare i pazienti a fidarsi della loro conoscenza del loro corpo e delle loro esperienze

Obiettivi e principi terapeutici / Linee Guida

Educazione dei pazienti

mantenere
l'autonomia



regolare
i ritmi

Attività complessive

Obiettivi e principi terapeutici / Linee Guida

Il trattamento della fibromialgia è finalizzato principalmente

a ridurre o attenuare la gravità dei sintomi caratteristici
(dolore cronico diffuso, affaticamento, disturbi del sonno, sintomi cognitivi, etc)

Ad oggi

. No unico trattamento efficace

. Approccio multidisciplinare

Programma di cura individualizzato
Interventi farmacologici
Interventi non farmacologici

Coinvolgere i pazienti

. Obiettivi realistici

. Programmi individualizzati

, massimizzare la guarigione e minimizzare lo stress

Incoraggiare i pazienti

- riconoscere fattori aggravanti
- riposare quando necessario
- non travalicare i personali limiti di attività
- pianificare strategie alternative per riacutizzazione

, esplorare vie per estendere i limiti di attività, se e quando ne siano in grado

European League Against Rheumatism (2017)

1. Educazione del paziente

2. Integrazione con trattamenti non farmacologici

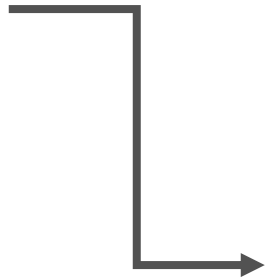
3. Integrazione con il trattamento farmacologico.

Fattori limitanti

- Scarsa aderenza
- Comorbidità

‘Cyberchondria’

. Abuso di Internet
. Informazione globale



. Pregiudizi
. Autodiagnosi
. Confronto

Dolore cronico generalizzato

, una vera sfida

- Accettare la versione del paziente
- Evitare valutazioni personali

Dolore cronico generalizzato

, una vera sfida

- Overmedicalizzazione
- Eccesso di indagini
- Eccesso di trattamento
- Sottovalutazione psicologica

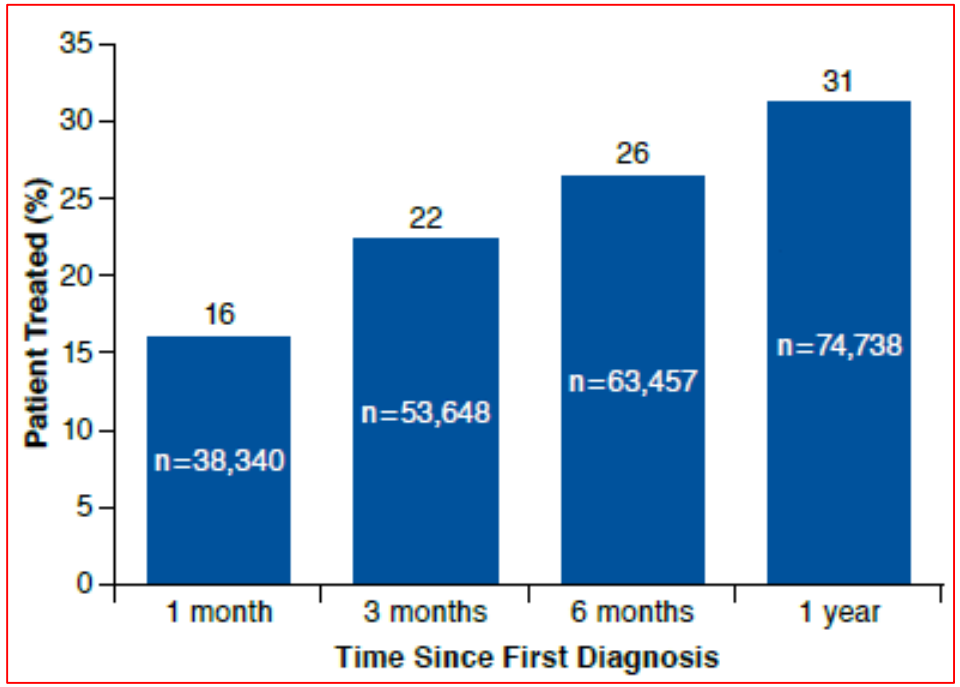
- Classificare i sintomi come ‘psicologici’
- Trascurare malattie organiche trattabili

La terapia della sindrome fibromialgica: un problema insormontabile?

- Non esiste un solo farmaco nato specificatamente per la sindrome fibromialgica
- Lo stesso vale per le terapie non farmacologiche
- Il paziente pertanto deve essere educato ed educarsi alla malattia
- Il paziente deve comprendere ed adattarsi al concetto di self-management

Treatment Patterns Associated with ACR-Recommended Medications in the Management of Fibromyalgia in the United States

Yifei Liu, PhD; Chunlin Qian, PhD; and Mei Yang, PhD



Percentage of Patients Receiving 1 of the 8 Medications of Interest at Each Time Point Since First Diagnosis of Fibromyalgia (N = 240,144)

J Manag Care Spec Pharm, 2016 Mar;22(3):263-271

2. Quale classe di farmaci prescrivi d’abitudine?

Commonly prescribed drugs for fibromyalgia treatment and their adverse effects

Drug	Class of drug	FDA-approved drugs for fibromyalgia	Adverse effects[169,174,184,187,203,239–242]
Antidepressants			
Duloxetine	SNRI	Yes[243]	Nausea, palpitations, headache, fatigue, tachycardia, insomnia, xerostomia, constipation and serotonin syndrome[a] (REFS[244,245])
Milnacipran	SNRI	Yes[246]	
Amitriptyline	Tricyclic antidepressant	No	Xerostomia, constipation, weight gain, urinary retention, sedation and serotonin syndrome[a]
Anticonvulsants			
Pregabalin	GABAergic drug	Yes[247]	Sedation, dizziness, vertigo, asthenia, nausea and weight gain
Gabapentin	GABAergic drug	No	
Muscle relaxants			
Cyclobenzaprine	Serotoninergic muscle relaxant	No	Nausea, palpitations, headache, fatigue, xerostomia, constipation and serotonin syndrome[a]
Tizanidine	α2 receptor agonist	No	Dizziness, asthenia, xerostomia, vomiting, constipation, liver test abnormalities, bradycardia, hypotension and blurred vision
Analgesic drugs			
Tramadol	Weak opioid and SNRI	No	Constipation, nausea, vomiting, dizziness, fatigue, headache, itching and xerostomia
Paracetamol	Analgesic and antipyretic drug	No	Nausea, vomit, constipation and liver disease
Hypnotic drugs			
Zolpidem	GABAergic and non-benzodiazepine hypnotic drug	No	Dizziness, headache, somnolence, confusion, agitation, abdominal pain, constipation and xerostomia
Antipsychotic drugs			
Quetiapine	Atypical antipsychotic drug	No	Somnolence, headache, dizziness, extrapyramidal symptoms, weight gain, dyslipidaemia, hyperglycaemia, xerostomia, vomiting and nausea, and constipation
Cannabis or cannabinoids			
Nabilone	Pure cannabinoid (tetrahydrocannabinol)	No	Drowsiness, dizziness, nausea, xerostomia, confusion, anxiety and tachycardia
Cannabis	Phytopharmaceutical (different concentrations of tetrahydrocannabinol and cannabidiol)	No	Drowsiness, dizziness, nausea, xerostomia, blurred vision, increased/decreased appetite, vertigo, tachycardia and hypotension

Sarzi-Puttini P. Giorgi V, Marotto D, Atzeni F.
Nat Rev Rheumatol 2020 Nov;16(11):645-660

Interventions used by the survey responders *[in descending order of frequency]*

Intervention	Frequency	Effectiveness [0–10 scale]
Resting	86%	6.3 ± 2.5
Distraction [reading, watching TV etc.]	80%	4.7 ± 2.5
Heat modalities [warm water, hot packs]	74%	6.3 ± 2.3
Nutritional supplements	68%	3.8 ± 2.8
OTC pain medications	67%	3.8 ± 2.3
Prescription pain medications	66%	6.3 ± 2.4
Gentle walking	64%	4.6 ± 2.6
Prescription antidepressants	63%	6.2 ± 2.8
Stretching	62%	5.4 ± 2.6
Prayer	57%	6.0 ± 2.9
Prescription sleep medications	52%	6.5 ± 2.7
Relaxation/meditation	47%	5.1 ± 5.5
Massage/reflexology	43%	6.1 ± 2.8
Aerobic exercise	32%	5.0 ± 3.0
Cold therapy [ice packs etc.]	30%	4.8 ± 2.8
Chiropractic manipulation	30%	5.1 ± 3.0
Counseling [psychologist, MSW, pastor]	29%	4.8 ± 3.0
Pool therapy	26%	6.0 ± 3.0
Non-aerobic exercise [stretching, yoga, Tai Chi]	24%	5.1 ± 2.9
Physical therapy	24%	4.7 ± 3.1
OTC sleep medications	22%	4.0 ± 2.9
TENS unit	21%	4.3 ± 2.9
Trigger point injections	21%	5.0 ± 3.3
Support groups	19%	4.6 ± 3.0
Strength training	18%	4.3 ± 2.9
Pain clinic	17%	4.8 ± 3.1
Acupuncture	15%	4.5 ± 3.5
Pilates	8%	4.6 ± 3.3
Cognitive behavioral therapy	8%	4.3 ± 3.2
Energy healing [e.g. Reiki]	7%	4.0 ± 3.2
Biofeedback	6%	2.9 ± 2.9
Spinal surgery	4%	3.4 ± 3.4
Hypnosis	3%	2.5 ± 2.9

Bennett, R. M., Jones, J., Turk, D. C., Russell, I. J. & Matallana, L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet. Disord. 8, 27(2007)

Inoltre…

Farmaci utilizzati in relazione ai differenti sintomi

	Dolore	Sonno	Astenia	Rigidità	Umore
Triciclici	+	+	+	±	-
SSRIs	±	±	±	±	+
SNRIs	+	-	+	±	+
I-MAO	±	±	±	±	±
FANS	-	-	-	-	-
Antiepilettici	+	+	+	+	-
Sedativi/Ipnotici	-	+	-	+	-
Oppioidi	+	+	-	-	-
Miorilassanti	+	-	±	+	±
Cortisonici	-	-	-	-	-

SSRIs = inibitori selettivi della ricaptazione della serotonina; SNRIs = inibitori della ricaptazione della serotonina e della noradrenalina; I-MAO = inibitori delle monamino-ossidasi; FANS = antinfiammatori non steroidei

Manuale pratico per il paziente affetto da sindrome fibromialgica

Scegliere il farmaco giusto o la combinazione di farmaci giusta per il Singolo paziente…

30% pain reduction rates in randomized controlled trials with antidepressants and pregabalin in patients with fibromyalgia syndrome

Drug reference	Number of RCT/participants	30% reduction true drug versus placbo	RR pain reduction 30% (95% CI)	Dropouts rate due to adverse events, percentage	RR dropout rate due to adverse events (95% CI)
Duloxetine	5/1884	46.8 vs 34.0	1.33 (1.18-1.51)	18.7 vs 10.4	1.65 (1.30-2.09)
Milnacipran	4/4110	36.6 vs 28.1	1.38 (1.25-1.51)	21.5 vs 11.0	2.00 (1.47-2.73)
SSRI	7/414	36.4 vs 20.6	1.59 (1.01-2.52)	9.5 vs 7.0	1.60 (0.84-3.04)
TCA	9/542	48.3 vs 27.8	1.60(1.15-2.34)	5.22 vs 6.5	0.84 (0.46-1.52)
Pregabalin	5/3259	40.0 vs 29.1	1.37(1.22-1.53)	19.4 vs 11.0	1.68 (1.36-2.07)

Häuser et al. Arthritis Research & Therapy 2014, 16:201

NYX-2925 – disappointing results

- **NYX is a new NMDA receptor modulator** which was shown by Khan et al. to affect NMDA receptor synaptic plasticity.
- Results from a Phase 2b clinical study evaluating **the effects of NYX-2925** in patients with fibromyalgia. NYX-2925 did not achieve statistically significant separation from placebo on the study's primary endpoint, which assessed the change from baseline in average daily pain on the numeric rating scale (NRS) during week 12.

M. A. Khan, D. R. Houck, A. L. Gross et al., "NYX-2925 is a novel NMDA receptor-specific spirocyclic-*β*-lactam that modulates synaptic plasticity processes associated with learning and memory," *International Journal of Neuro- psychopharmacology*, vol. 21, no. 3, pp. 242–254, 2018.

Treatment Patterns Associated with ACR-Recommended Medications in the Management of Fibromyalgia in the United States

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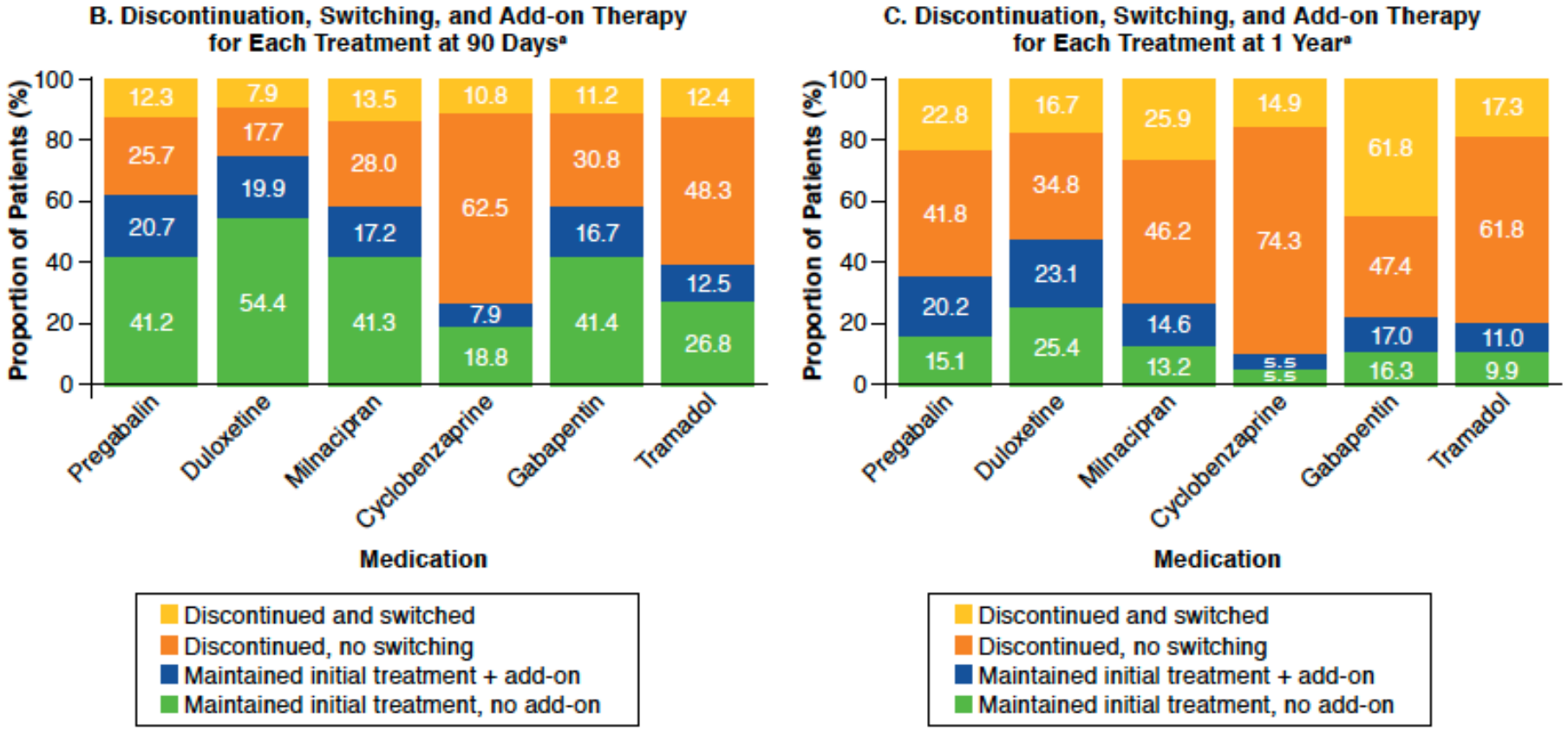


[a]*Switches and add-on therapies were tracked within the 6 medications of interest only.*

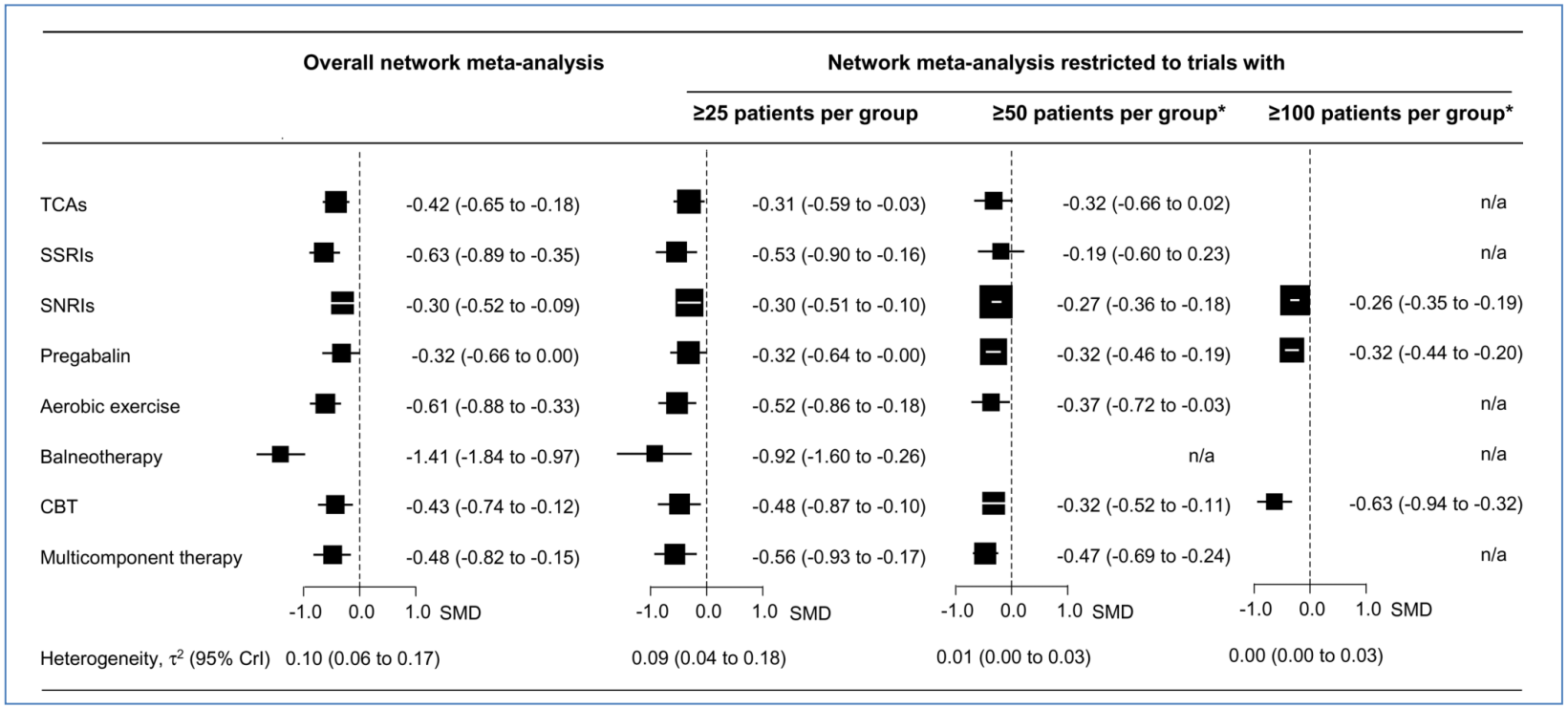
Alterations in Use of the Medications of Interest over the First Year of Therapy

J Manag Care Spec Pharm, 2016 Mar;22(3):263–271

Pain

Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis

Eveline Nüesch,[1,2] Winfried Häuser,[3,4] Kathrin Bernardy,[5,6] Jürgen Barth,[1] Peter Jüni[1]



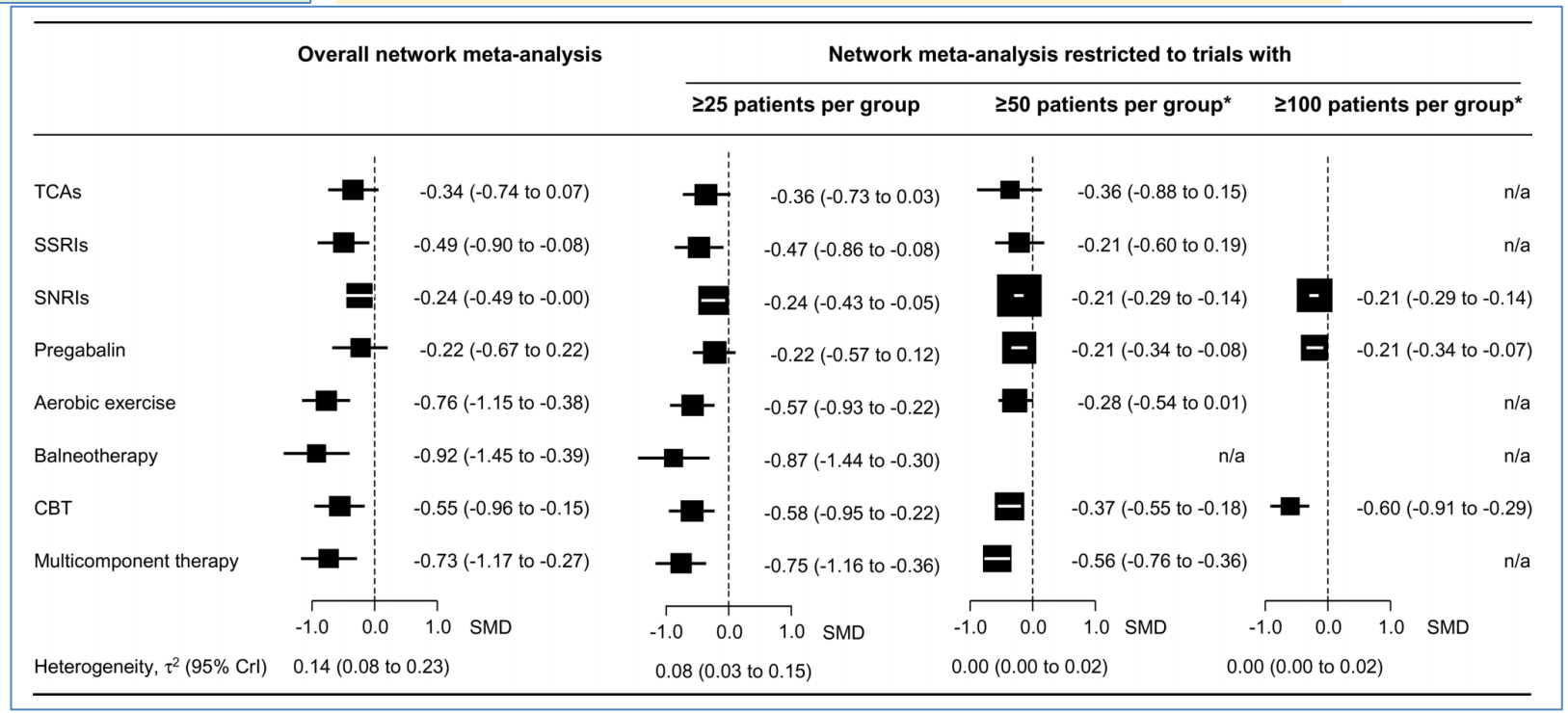
Estimates of standardised mean differences (SMDs) with 95% credibility intervals (95% CrI) in pain for therapeutic interventions compared with placebo from overall network meta-analyses and network meta-analyses restricted to trials with ≥25, ≥50 and ≥100 patients per group and corresponding between-trial heterogeneity variance estimates τ2 (95% CrI)

Ann Rheum Dis 2013;72:955–962

Quality of life

Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis

Eveline Nüesch,[1,2] Winfried Häuser,[3,4] Kathrin Bernardy,[5,6] Jürgen Barth,[1] Peter Jüni[1]



Estimates of standardised mean differences (SMDs) with 95% credibility intervals (95% CrI) in quality of life for therapeutic interventions compared with placebo from overall network meta-analyses and network meta-analyses restricted to trials with ≥25, ≥50 and ≥100 patients per group and corresponding between-trial heterogeneity variance estimates τ2 (95% CrI).

Ann Rheum Dis 2013;72:955–962

Combination pharmacotherapy for the treatment of fibromyalgia in adults

- The most frequent combinations of drugs included the association of NSAIDs with benzodiazepine, amitriptyline with fluoxetine, tramadol with paracetamol, and monoamine oxidase inhibitor with 5-hydroxytryptophan

Thorpe J, ShumB, Moore RA, Wiffen PJ, Gilron I: Combination pharmacotherapy for the treatment of fibromyalgia in adults. Cochrane Database Syst Rev 2018; 2: CD010585

Combination pharmacotherapy for the treatment of fibromyalgia in adults

- The most frequent combinations of drugs included the association of NSAIDs with benzodiazepine, amitriptyline with fluoxetine, tramadol with paracetamol, and monoamine oxidase inhibitor with 5-hydroxytryptophan.
- **The combination of drugs seemed to give a greater advantage on pain than a single treatment alone, with only mild side effects reported**.
- However, **the results were biased by the heterogeneity of the study designs and variability in sample sizes**.

Thorpe J, ShumB, Moore RA, Wiffen PJ, Gilron I: Combination pharmacotherapy for the treatment of fibromyalgia in adults. Cochrane Database Syst Rev 2018; 2: CD010585

The rule of 30% pain reduction

30% of pain reduction in randomized controlled clinical trials with atidepressants and pregabalin in patients affected by FM

Drug (reference)	Number of RCTs/participants	30% pain reduction true drug vs. placebo (%)	RR 30% pain reduction (95% CI)	Dropout rate due to adverse events, percentage	RR dropout rate due to adverse events (95% CI)
Duloxetine[a] [17]	5/1,884	46.8 vs. 34.0	1.33 (1.18-1.51)	18.7 vs.10.4	1.65 (1.30-2.09)
Milnacipran[b] [17]	5/4,110	36.4 vs. 28.1	1.38 (1.25-1.51)	21.5 vs.11.0	2.00 (1.47-2.73)
SSRIs[c] [20]	7/414	36.4 vs. 20.6	1.59 (1.01-2.52)	9.5 vs. 7.0	1.60 (0.84-3.04)
TCAs[d] [20]	9/542	48.3 vs. 27.8	1.60 (1.15-2.34)	5.2 vs. 6.5	0.84 (0.46-1.52)
Pregabalin[e] [22]	5/3,259	40.0 vs. 29.1	1.37 (1.22-1.53)	19.4 vs. 11.0	1.68 (1.36-2.07)

[a]Dosages 60 mg/day, 120 mg/day, and 60 to 120 mg/day flexible pooled together. [b]Dosages 100 mg/day, 200 mg/day, and 100 to 200 mg/day flexible pooled together. [c]Citalopram 20–40 mg/day, Fluoxetine 12–80 mg/day, Paroxetine 20–60 mg/day. [d]Amitriptyline 10–50 mg/day. [e]Dosages 150 mg/day, 300 mg/day, 450 mg/day, 600 mg/d, and 300–450 mg/day flexible pooled together. One study with 556 participants and an enriched enrolment withdrawal design could not be included in meta-analysis. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Can we improve ?

A Systematic Review of Atypical Antipsychotics in Chronic Pain Management

Olanzapine Demonstrates Potential in Central Sensitization, Fibromyalgia, and Headache/Migraine

Xavier F. Jimenez, MD, MA, Tharani Sundararajan, MD, and Edward C. Covington, MD

Clin J Pain 2018;34:585–591

Antipsychotics for Fibromyalgia in Adults

Antipsychotics for Fibromyalgia in Adults

Benefits	Harms
1 in 8 had at least 30% reduction in pain	1 in 12 gained 11 lb (5 kg) or more
1 in 4 had a reduction in sleep problems	
1 in 6 had a reduction in depressed mood	
1 in 5 had a clinically significant improvement in the quality of life	

The NNT Group rating system:

Green:	Benefits greater than harms
Yellow:	Unclear benefits
Red:	No benefits
Black:	Harms greater than benefits

Journal of Pain Research

Dovepress
open access to scientific and medical research

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REVIEW

The Safety and Efficacy of Low-Dose Naltrexone in Patients with Fibromyalgia: A Systematic Review

Juan Yang[1], Kyung-Min Shin[2], Alex Do[1], Dennis M Bierle[1], Abd Moain Abu Dabrh[3], Ziying Yin[4], Brent A Bauer[1], Arya B Mohabbat[1]

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Correspondence: Arya B Mohabbat, Division of General Internal Medicine, Mayo Clinic, 200 First Street SW, RO_GO_17_102GIM, Rochester, MN, 55905, USA, Tel +1-507-284-2511, Email Mohabbat.Arya@mayo.edu

Abstract: Fibromyalgia (FM) is a chronic pain sensitivity syndrome characterized by diffuse musculoskeletal pain and many other systemic manifestations. Low-dose naltrexone (LDN) has been increasingly used as an off-label treatment option in FM. However, current evidence on the safety and efficacy of LDN in patients with FM is not well known. To systematically assess the current evidence on the safety and efficacy of LDN use in the treatment of FM. A comprehensive bibliographic search was conducted on EBM Reviews – Cochrane Central Register of Controlled Trials, EBM Reviews – Cochrane Database of Systematic, Embase, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions and Scopus databases in September 2022. Inclusion criteria were articles that were published in English, focusing on clinical trials involving LDN for the treatment of FM. Two reviewers independently screened and extracted the data. A qualitative analysis was used due to the high methodological heterogeneity between studies. The electronic search produced 805 articles. After applying the inclusion criteria, 9 articles (one RCT, two case reports, two case series, and four pilot trials) were selected for evaluation. LDN intervention protocols, study designs, and follow-up periods were different among the included studies. Overall, LDN was found to be effective in the symptomatic management of FM, and of the 78% of included studies that evaluated for safety, no severe adverse events were reported. Proving the efficacy and safety of low-dose naltrexone is a future possibility based on current study data, but the level of scientific evidence is limited. Future well-designed trials with large sample sizes are required.

Keywords: fibromyalgia, naltrexone, low-dose naltrexone, chronic pain, review

Introduction

Fibromyalgia (FM) is a chronic, centralized, pain sensitivity syndrome, mainly characterized by widespread musculoskeletal pain, fatigue, nonrestorative sleep, mood issues, deconditioning, and cognitive impairments.[1] The prevalence of FM is approximately 2–8% worldwide with a higher prevalence for women.[2] Age, sex, family history, and certain conditions/factors (rheumatoid arthritis, systematic lupus erythematous, repetitive injuries, stressful or traumatic events, and preceding infections) are associated risk factors for the development of FM.[3] Individuals with FM report a wide range of somatic and psychological symptoms, which contribute to significant symptom burden and functional impairment. The annual associated direct costs, per patient, range from $ 1750 to $ 35,920 in the USA.[4]

The underlying mechanisms for FM continue to be investigated, with a greater focus on the pathophysiological process known as central sensitization.[5] Central sensitization involves the amplification of both central and peripheral pain and sensory processing in the ascending and descending sensory pathways, due to a variety of antecedent triggers (including pain, infection, inflammation, or prolonged stressors).[6,7] Recent research has focused on the underlying trigger of neuroinflammation as a potential contributor to the development of central sensitization in the setting of FM. Increased blood–brain barrier permeability is an important feature of neuroinflammation, which results in increased leukocyte relocation into the central nervous system. Recent immunological evidence indicates that inflammation-

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Published: 21 March 2023

The Safety and Efficacy of Low-Dose Naltrexone in Patients with Fibromyalgia: A Systematic Review. Journal of Pain Research 2023:16 1017–1023. Yang J et al.

Mechanisms of action and clinical use in regard to different doses of naltrexone used

Dose Range	Dose Specific Mechanism of Action	Clinical Use
Standard (50–100 mg)	Opioid receptor antagonism	Alcohol and opiate abuse
Low-dose (1–5 mg)	Toll-like receptor 4 antagonism, opioid growth factor antagonism	Fibromyalgia, multiple sclerosis, Crohn's disease, cancer, Hailey-Hailey disease, complex-regional pain syndrome
Very low-dose (0.001–1 mg)	Possibly same as low-dose	Add-on to methadone detoxification taper
Ultra low-dose (<0.001 mg)	Binding to high affinity filamin-A (FLNA) site and reducingμ-opioid receptor associated Gs-coupling	Potentiating opioid analgesia

Toljan K, Vrooman B. Low-Dose Naltrexone (LDN)-Review of Therapeutic Utilization. Med Sci (Basel). 2018 Sep 21;6(4). pii: E82. doi: 10.3390/medsci6040082

Low-Dose Naltrexone for the Treatment of Fibromyalgia

Findings of a Small, Randomized, Double-Blind, Placebo-Controlled, Counterbalanced, Crossover Trial Assessing Daily Pain Levels

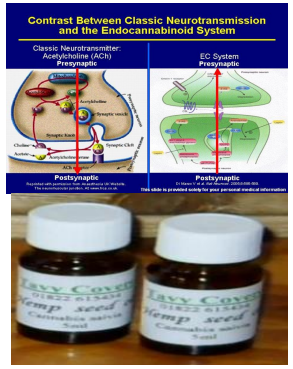
Jarred Younger, Noorulain Noor, Rebecca McCue, and Sean Mackey

- **Significantly greater reduction of baseline pain**

- **Low-dose naltrexone was also associated with improved general satisfaction with life (P = 0.045) and with improved mood (P = 0.039), but not improved fatigue or sleep**

Arthritis Rheum. 2013 Feb;65(2):529-38.

Cannabinoids



- PhytoCanabinoids → Herbal Cannabis → More than 120 active ingredients

- EndoCanabinoids → Anadomide; 2-arachidonoylglycerol (2-AG) → **endogenous cannabinoid**
- SyntheticCanabinoids → NABINOL, DRONABINOL, MARINOL → Cripy, Mamba, Spice

Cannabis contains many substances, including at least 120 active ingredients with a synergistic activity.

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
2019, VOL. 15, NO. 10, 1019–1032
https://doi.org/10.1080/1744666X.2019.1665997

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REVIEW

Medical cannabis and cannabinoids in rheumatology: where are we now?

Piercarlo Sarzi-Puttini[a], Alberto Batticciotto[b], Fabiola Atzeni[c], Laura Bazzichi[d], Manuela Di Franco[e], Fausto Salaffi[f], Daniela Marotto[g], Angela Ceribelli[a], Jacob N Ablin[h] and Winfred Hauser[i]

[a]Rheumatology Unit, ASST Fatebenefratelli-Sacco, University of Milan, Milan, Italy; [b]Rheumatology Unit, Internal Medicine Department, ASST Settelaghi, Ospedale Di Circolo - Fondazione Macchi, Varese, Italy; [c]Rheumatology Unit, University of Messina, Messina, Italy; [d]Rheumatology Unit, AOU Pisana, Pisa, Italy; [e]Department of Internal Medicine and Medical Specialities, Rheumatology Unit, Sapienza University of Rome, Rome, Italy; [f]Rheumatological Clinic, Università Politecnica delle Marche, Jesi, Ancona, Italy; [g]Rheumatology Unit, P-Dettori Hospital Tempio Pausania, Tempio Pausania, Italy; [h]Internal Medicine H, Tel Aviv Sourasky Medical Center, Tel Aviv Israel; [i]Department of Internal Medicine 1, Klinikum Saarbrücken, D-66119 Saarbrücken, Germany

ABSTRACT

Introduction: Clinicians involved in pain management can finally include cannabis or cannabis-related products in their therapeutic armamentarium as a growing number of countries have approved them for pain relief. Despite the several benefits attributed to analgesic, anti-inflammatory and immunomodulatory properties of cannabinoids, there are still significant areas of uncertainty concerning their use in many fields of medicine.

The biosynthesis and inactivation of cannabinoids are regulated by a complex signaling system of cannabinoid receptors, endocannabinoids (the endogenous ligands of cannabinoid receptors) and enzymes, with a variety of interactions with neuroendocrinological and immunological systems.

Areas covered: A review of studies carried out during clinical development of cannabis and cannabis medical products in systemic rheumatic diseases was performed, highlighting the aspects that we believe to be relevant to clinical practice.

Expert opinion: The growing public opinion, pushing toward the legalization of the use of cannabis in chronic pain and various rheumatological conditions, makes it necessary to have educational programs that modify the concerns and widespread preconceptions related to this topic in the medical community by increasing confidence. More extensive basic and clinical research on the mechanisms and clinical utility of cannabis and derivatives in various diseases and their long-term side effects is necessary.

ARTICLE HISTORY
Received 31 March 2019
Accepted 6 September 2019

KEYWORDS
Cannabis; endocannabinoid system; fibromyalgia; SLE; rheumatoid arthritis; cannabidiol; tetrahydrocannabinol (THC)

1. Introduction

Clinicians involved in pain management can now include cannabis or cannabis-related products in their therapeutic armamentarium, as an increasing number of countries have approved its use. However, despite the known analgesic, anti-inflammatory and immunomodulatory effects, the uncertainty and controversy surrounding the scientific data make it difficult to establish the role and appropriate use of cannabis in the management of various diseases, particularly in the field of rheumatology [1,2].

Pharmaceutical products usually go through a defined process before being approved for therapeutic purposes, but standard scientific scrutiny has been by-passed in the case of cannabis, which has been approved with a variety of indications [1–4]. It is therefore important to collect further objective data concerning the benefits and risks of using medical cannabis in order to be able to counsel patients and provide appropriate clinical care.

This review will concentrate on the use of medical cannabis and cannabis-based medicines in managing rheumatic conditions, and highlight the aspects that we believe to be relevant to clinical practice.

2. Legality of cannabis

The possession of Cannabis is considered a non-criminal offense in many Western countries, while it is punished or may be punished by prison in countries in the Middle East and Asia. On the other hand, the recreational use of cannabis has been legalized throughout Uruguay, Luxembourg and Canada, in the District of Columbia and in ten states in the USA, and it is sold under license in Spain and The Netherlands.

The medical use of cannabis has been legalized in Australia, Canada, Chile, Colombia, Finland, Germany, Greece, Israel, Italy, The Netherlands, Norway, Peru, Poland, and Thailand [5], as well as in the District of Columbia and 33 states in the USA. In other countries only certain cannabis-derived pharmaceutical drugs such as Sativex, Marinol or Epidiolex to be used.

3. The endocannabinoid system

Endocannabinoids (eCBs), their receptors, and the associated mediating enzymes for synthesis and degradation comprise the endocannabinoid system (ECS) (Figures 1 and 2).

Autoimmunity Reviews xxx (xxxx) xxxx

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journal homepage: www.elsevier.com/locate/autrev

Cannabinoids in the treatment of rheumatic diseases: Pros and cons

Piercarlo Sarzi-Puttini[a,*], Jacob Ablin[b], Adva Trabelsi[b], Mary-Ann Fitzcharles[c,d], Daniela Marotto[e], Winfried Häuser[f,g]

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[b] Department of Internal Medicine H, Tel Aviv Sourasky Medical Center & Sackler School of Medicine, Tel Aviv University, Israel
[c] Alan Edwards Pain Management Unit, McGill University Health Centre, Quebec, Canada
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[e] Rheumatology Unit, P.Dettori Hospital, Tempio Pausania, Italy
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ARTICLE INFO

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Medical cannabis
Cannabinoids
Rheumatoid arthritis
Systemic lupus erythematousus
Systemic sclerosis
Fibromyalgia syndrome

ABSTRACT

Medical cannabis is being increasingly used in the treatment of rheumatic diseases because, despite the paucity of evidence regarding its safety and efficacy, a growing number of countries are legalising its use for medical purposes in response to social pressure. Cannabinoids may be useful in the management of rheumatic disorders for two broad reasons: their anti-inflammatory and immunomodulatory activity, and their effects on pain and associated symptoms. It is interesting to note that, although a wide range of medications are available for the treatment of inflammation, including an ever-lengthening list of biological medications, the same is not true of the treatment of chronic pain, a cardinal symptom of many rheumatological disorders. The publication of systematic reviews (SR) concerning the use of cannabis-based medicines for chronic pain (with and without meta-analyses) is outpacing that of randomised controlled trials. Furthermore, narrative reviews of public institution are largely based on these SRs, which often reach different conclusions regarding the efficacy and safety of cannabis-based medicines because of the lack of high-quality evidence of efficacy and the presence of indications that they may be harmful for patients. Societal safety concerns about medical cannabis (e.g. driving risks, workplace safety and pediatric intoxication) must always be borne in mind, and will probably not be addressed by clinical studies. Medical cannabis and cannabis-based medicines have often been legalised as therapeutic products by legislative bodies without going through the usual process of regulatory approval founded on the results of traditional evidence-based studies. This review discusses the advantages and limitations of using cannabis to treat rheumatic conditions.

1. Introduction

The history of cannabis is as old as it is colourful and controversial [1,2]. Cultivated in Central Asia for over 5000 years, it has been used for a variety of recreational, medical, ceremonial and even religious purposes, and so it is not surprising that one of the first documents attesting its medicinal use for indications such as rheumatic pain, constipation, female genital disorders and malaria dates back to 2737 BCE. Different parts of the plant have been used over time and in different populations: for example, the Chinese mainly used the seeds, which consist of essential fatty acids and proteins, but are deficient in D9-tetrahydrocannabinol (D9-THC). In India, cannabis is considered one of the five sacred plants and it has always been widely used for both medical and recreational purposes [3–5]: the different parts of the plant are used to obtain preparations with different concentrations of active cannabinoids (bhang, ganja, charas…), and consequently different psychotropic effects.

It quickly spread to the West, and its use in Europe was documented as long ago as in pre-Christian times [3]. The use of cannabis has always been strongly influenced by socio-economic factors. In the West, its prescription peaked in the XIX-XX centuries with the marketing of cannabis extracts by a number of pharmaceutical companies, but then the American Controlled Substances Act prohibited the possession of any quantity regardless of purpose.

However, the XXI century has witnessed a significant socio-political change, and cannabis has become increasingly socially accepted, and public demand for its legalisation has led to its possession being allowed in different amounts in different countries, and it has been

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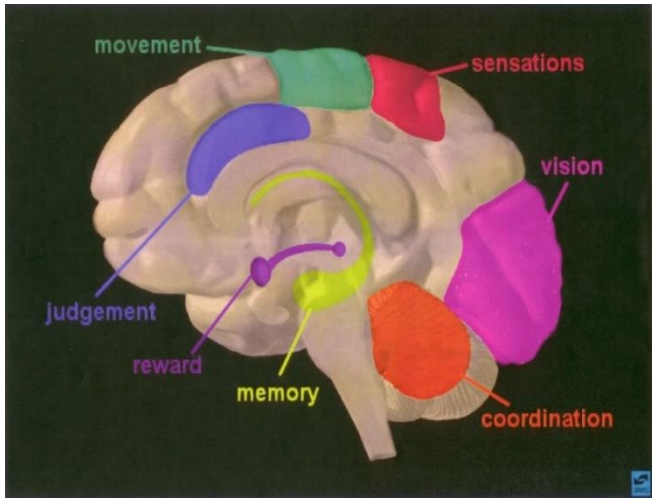
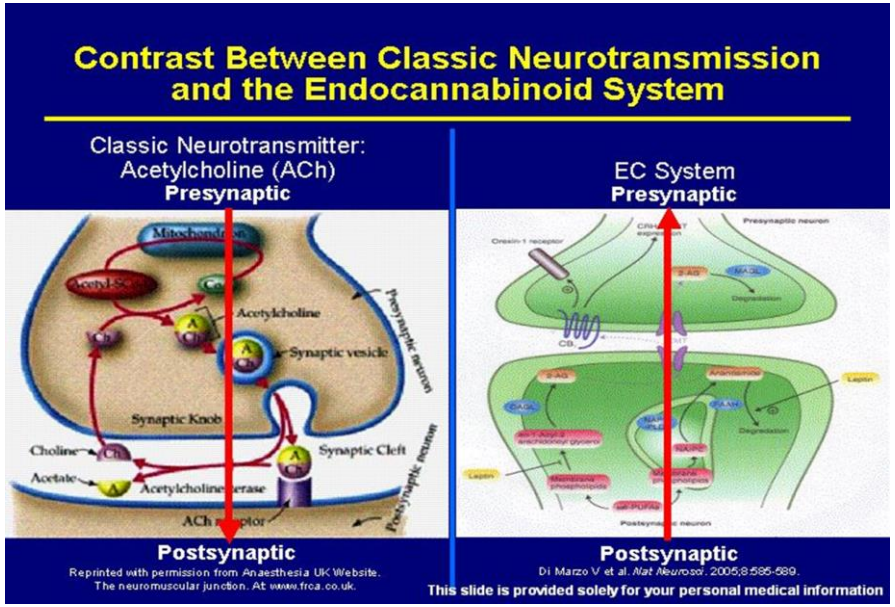
Pharmacological actions of THC

- **Psychotropic**
  - Initial euphoria and relaxation
  - Followed by a depressant period
  - Alterations memory and cognitive perceptual abilities
- **Immuno-suppressive**/ immuno-modulation
- **Cardiovascular** (tachycardia, orthostatic hypotension, peripheral vasodilation)
- **Analgesic**
- **Anti-emetic**
- **Appetite stimulant**



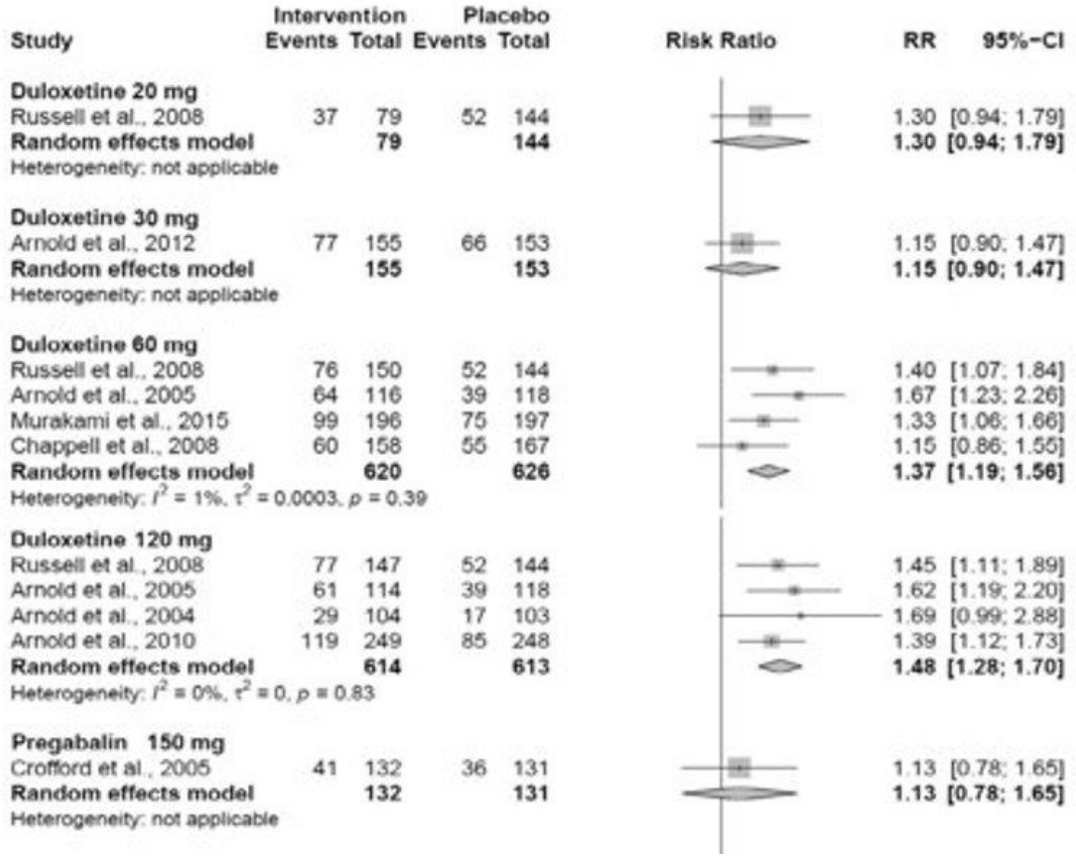
Pharmacological Effects of CBD

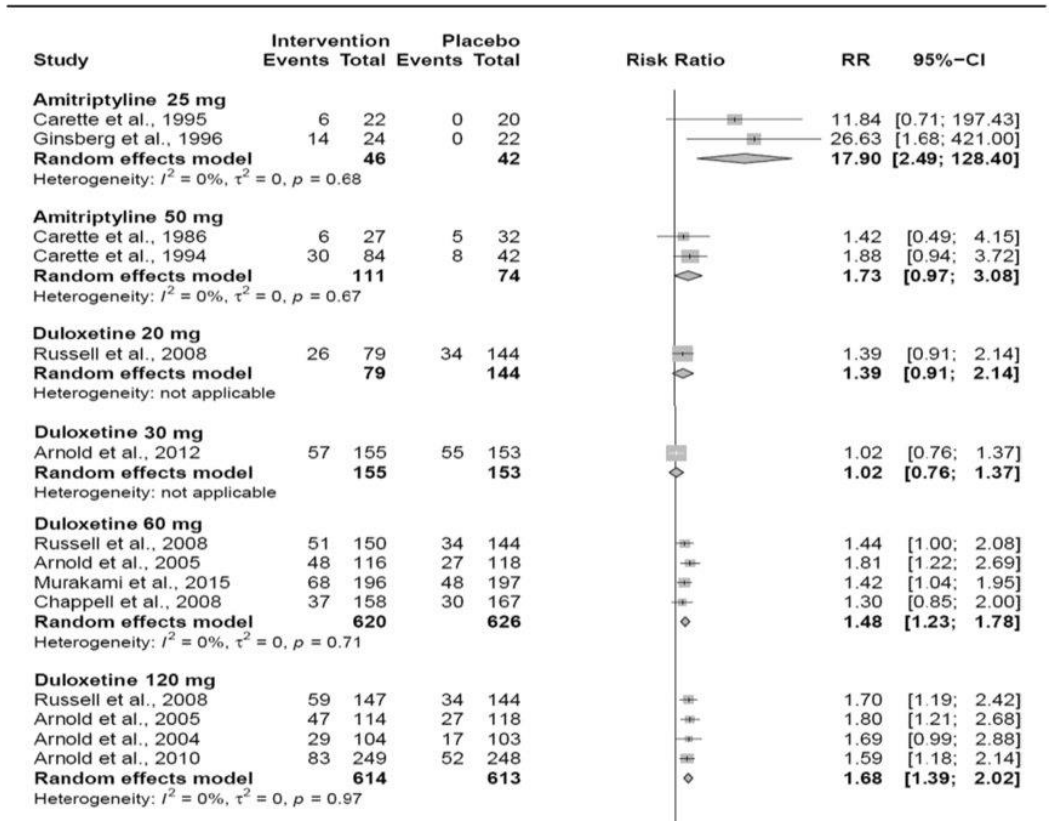
- Anticonvulsant
- Analgesic
- Anti-anxiety
- Anti-psychotic
- Anti-inflammatory
- Anti-arthritic
- Immunosuppresive



C'è una terapia migliore? Monoterapia

15 clinical trials comparing AMT (n = 273), DLX (n = 2,595), and PGB (n = 3,506) against placebo were selected





Alberti, F. F. *et al.* (2022) *Clinical Rheumatology*.

C'è una terapia migliore? Monoterapia

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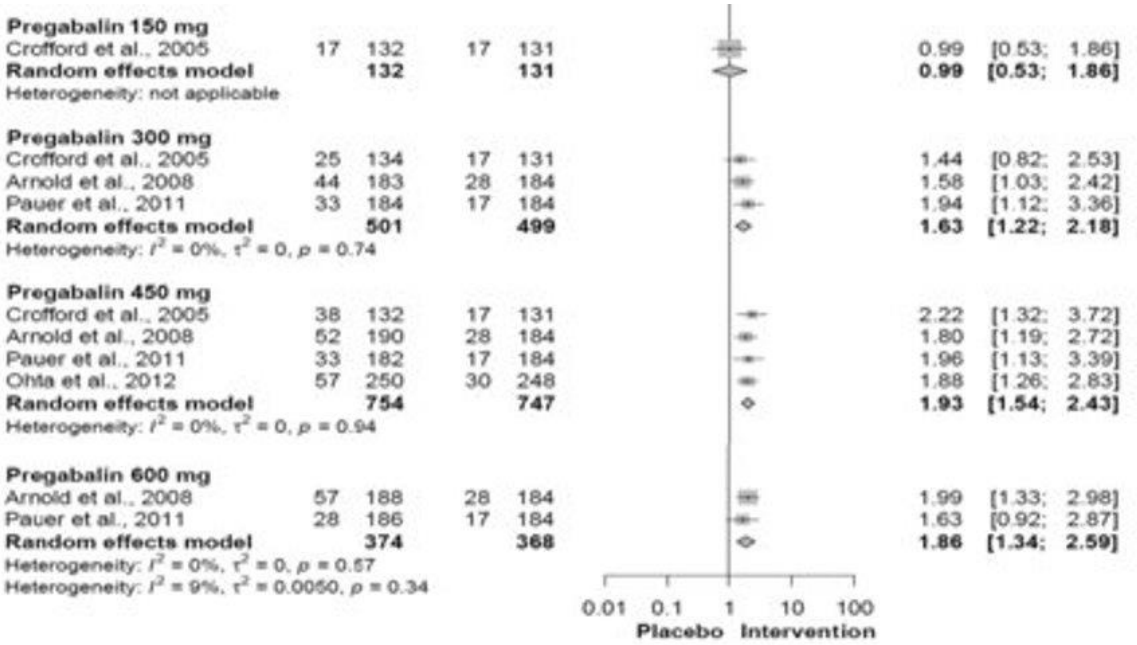
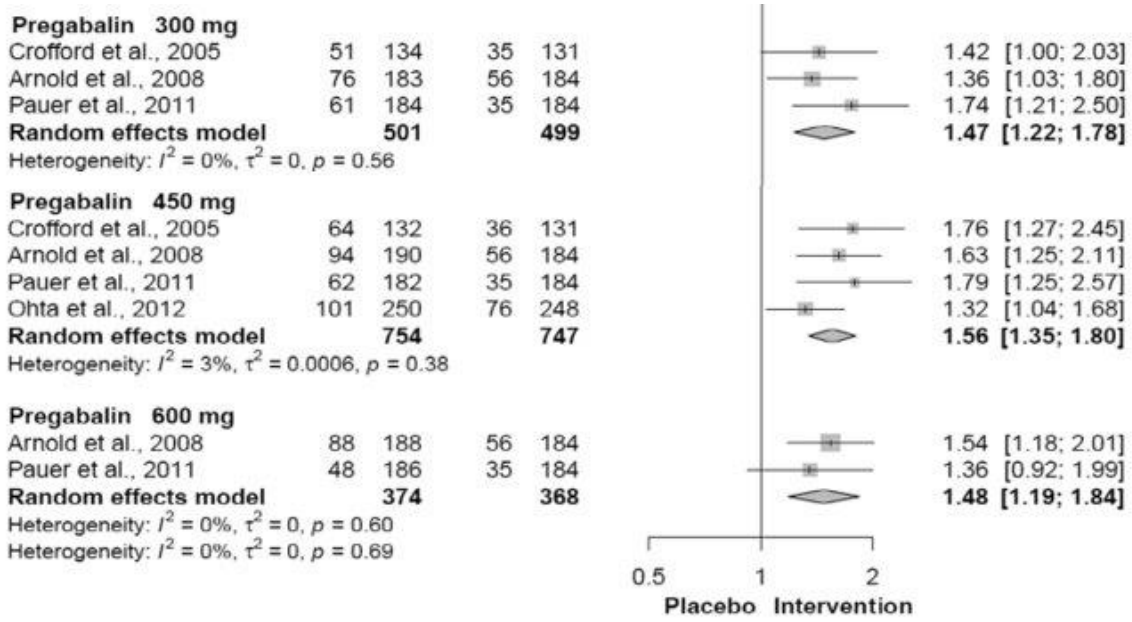




Alberti, F. F. *et al.* (2022) *Clinical Rheumatology*.

C'è una terapia migliore? Monoterapia

R30%

- PGB 450 mg > DLX 30 mg and PGB 150 mg
- DLX 20 mg and 30 mg were not superior to placebo

R50%

- AMT 25 mg > all other alternatives evaluated

Alberti, F. F. *et al.* (2022) *Clinical Rheumatology*.

C'è una terapia migliore? Politerapia

- **Pregabalin + duloxetine vs. monotherapy for each drug and placebo: (piccolo effetto)**

Very low quality evidence that combination therapy of pregabalin and duloxetine is better than pregabalin alone (68% versus 42%) or duloxetine alone (68% versus 39%) or placebo (68% versus 18%) for improving patient-reported pain relief of 30% or greater.

There was very low quality evidence that combination therapy im proved Short-form McGill Pain Questionnaire (SF-MPQ), FIQ, and SF-36 scores as compared to both monotherapy

Tramadol + paracetamol vs. placebo

Very low quality evidence that patient-reported pain relief of 30% or greater and patient-reported pain relief of 50% or greater was better in the combination group as compared to the placebo.

Tramadol combined with analgesic showed improved quality of life over placebo as measured by the Fibromyalgia Impact Questionnaire at 91 days. However, this **difference did not hold for tramadol as a single agent against placebo**.

Rathore, F. A. and Afridi, A. (2020) *Journal of Musculoskeletal and Neuronal Interactions*, 20(3), pp. 297–300; *Int J Clin Pract.* 2020; 74:e13455

3. Quale ritieni la terapia non farmacologica più utile?

FIBROMIALGIA

scarsa efficacia dei singoli
interventi curativi globali

analgesici
antidepressivi
tranquillanti
etc.

elevata efficacia dell'
intervento sui sintomi

Teoria della
gestione dei sintomi
(Coping Skill Training)
CST

esperienza del sintomo
gestione del sintomo
verifica degli esiti

riduzione della gravità del dolore
riduzione stress emozionale
aumento del senso di controllo

SELF-MANAGEMENT

auto - gestione

capacità di un individuo
di modificare il proprio comportamento

Principali approcci non farmacologici per la sindrome fibromialgica

Attività fisica	Esercizi aerobici
	Stretching
	Tecniche mente-corpo
	Postura
Nutrizione e nutraceutica	Nutraceutici ed integratori
Psicoterapia e tecniche di rilassamento	Terapia cognitivo-comportamentale (CBT)
	Interventi basati sulla mindfulness
	Ipnosi e Guided Imagery
	EMDR
Terapie fisiche	SPA-terapia, balneoterapia e idroterapia
	Energia termica
	Elettroterapia
	Magnetoterapia
	Stimolazione transcranica
	Massoterapia e terapie manuali
	Fototerapia
Miscellanea	Camera Iperbarica
	Ossigeno-Ozonoterapia
	Agopuntura
	Terapie energetiche e di movimento
	Terapia infiltrativa
	Biofeedback
	Trapianto fecale
	Omeopatia
	Religiosità e spiritualità

Interventions used by the survey responders *[in descending **order of frequency**]*

Intervention	Frequency	Effectiveness [0–10 scale]
Resting	86%	6.3 ± 2.5
Distraction [reading, watching TV etc.]	80%	4.7 ± 2.5
Heat modalities [warm water, hot packs]	74%	6.3 ± 2.3
Nutritional supplements	68%	3.8 ± 2.8
OTC pain medications	67%	3.8 ± 2.3
Prescription pain medications	66%	6.3 ± 2.4
Gentle walking	64%	4.6 ± 2.6
Prescription antidepressants	63%	6.2 ± 2.8
Stretching	62%	5.4 ± 2.6
Prayer	57%	6.0 ± 2.9
Prescription sleep medications	52%	6.5 ± 2.7
Relaxation/meditation	47%	5.1 ± 5.5
Massage/reflexology	43%	6.1 ± 2.8
Aerobic exercise	32%	5.0 ± 3.0
Cold therapy [ice packs etc.]	30%	4.8 ± 2.8
Chiropractic manipulation	30%	5.1 ± 3.0
Counseling [psychologist, MSW, pastor]	29%	4.8 ± 3.0
Pool therapy	26%	6.0 ± 3.0
Non-aerobic exercise [stretching, yoga, Tai Chi]	24%	5.1 ± 2.9
Physical therapy	24%	4.7 ± 3.1
OTC sleep medications	22%	4.0 ± 2.9
TENS unit	21%	4.3 ± 2.9
Trigger point injections	21%	5.0 ± 3.3
Support groups	19%	4.6 ± 3.0
Strength training	18%	4.3 ± 2.9
Pain clinic	17%	4.8 ± 3.1
Acupuncture	15%	4.5 ± 3.5
Pilates	8%	4.6 ± 3.3
Cognitive behavioral therapy	8%	4.3 ± 3.2
Energy healing [e.g. Reiki]	7%	4.0 ± 3.2
Biofeedback	6%	2.9 ± 2.9
Spinal surgery	4%	3.4 ± 3.4
Hypnosis	3%	2.5 ± 2.9

Bennett, R. M., Jones, J., Turk, D. C., Russell, I. J. & Matallana, L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet. Disord. 8, 27(2007)

Esercizio e fibromialgia

Le persone affette da FM dovrebbero fare esercizio fisico

Classe di evidenza 1A

Società Italiana Reumatologia

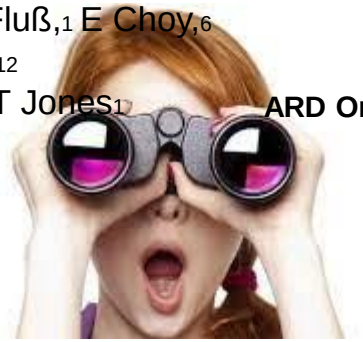
eular

The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of fibromyalgia EULAR revised recommendations for the management of fibromyalgia. doi:10.1136/annrheumdis-2016-209724

EULAR revised recommendations for the management of fibromyalgia

G J Macfarlane,[1] C Kronisch,[1,2] L E Dean,[1] F Atzeni,[3] W Häuser,[4,5] E Fluß,[1] E Choy,[6]
E Kosek,[7] K Amris,[8] J Branco,[9] F Dincer,[10] P Leino-Arjas,[11] K Longley,[12]
G M McCarthy,[13] S Makri,[14] S Perrot,[15] P Sarzi-Puttini,[16] A Taylor,[17] G T Jones[17]

LAURA



ARD Online First, published on July 4, 2016 as 10.1136/annrheumdis-2016-209724

	Level of evidence	Grade	Strength of recommendation	Agreement (%)*
Specific recommendations				
Non-pharmacological management				
Aerobic and strengthening exercise	Ia	A	Strong for	100
Cognitive behavioural therapies	Ia	A	Weak for	100
Multicomponent therapies	Ia	A	Weak for	93
Defined physical therapies: acupuncture or hydrotherapy	Ia	A	Weak for	93
Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction	Ia	A	Weak for	71–73
Pharmacological management				
Amitriptyline (at low dose)	Ia	A	Weak for	100
Duloxetine or milnacipran	Ia	A	Weak for	100
Tramadol	Ib	A	Weak for	100
Pregabalin	Ia	A	Weak for	94
Cyclobenzaprine	Ia	A	Weak for	75

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

Esercizio e fibromialgia

Le evidenze più forti sono

- la riduzione del **dolore**
- il miglioramento della qualità della vita

L'allenamento si è mostrato utile anche nel migliorare aspetti associati alla FM come:

- Depressione
- Qualità del sonno
- Stress
- Astenia

Exercise is Medicine®

Exercise

- <u>Exercise is an individual prescription</u>
  - It is likely that different form of exercises will suit different patients, hence program should be tailored to the individual

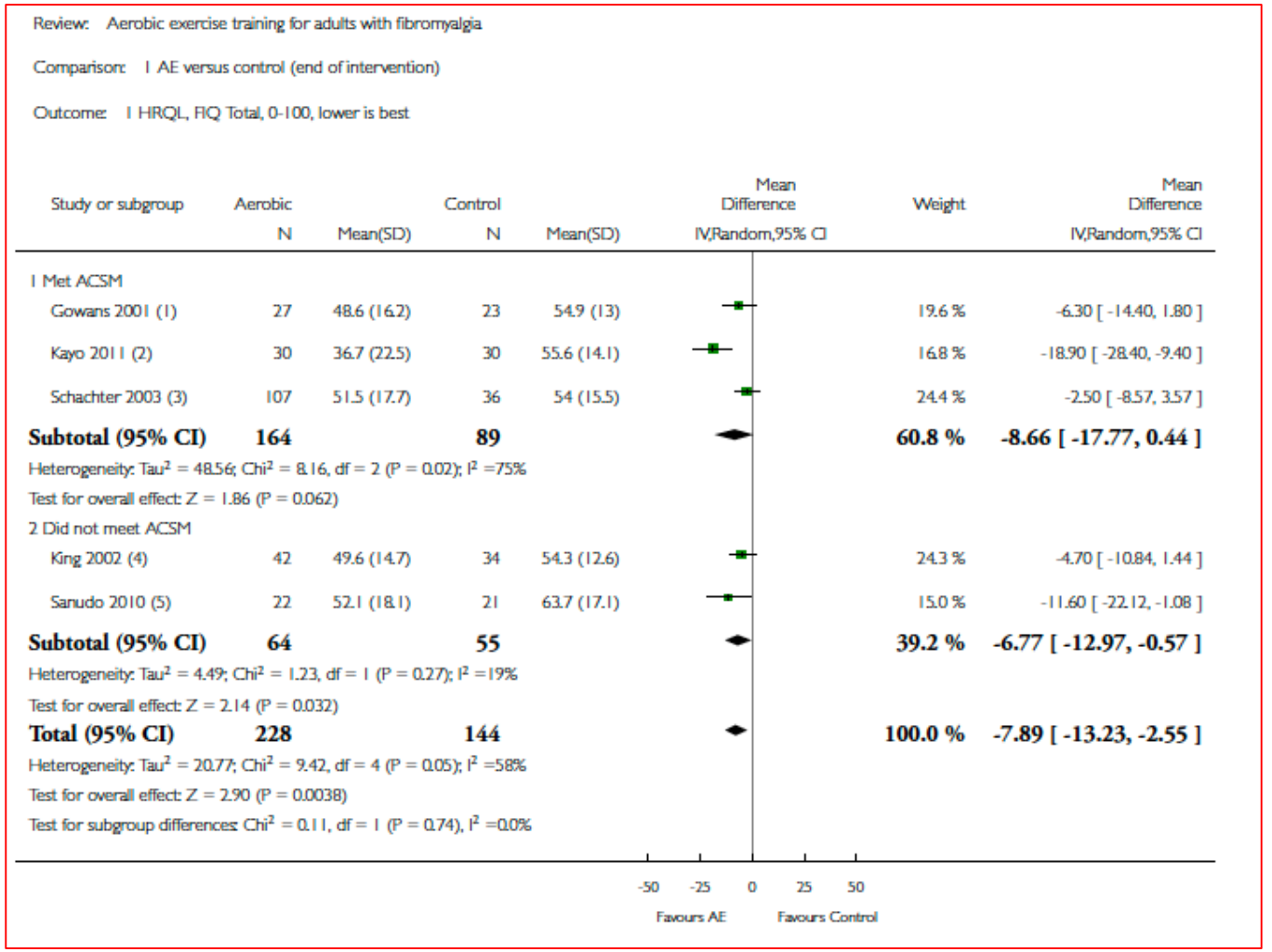
- <u>Aerobic exercise</u>
  - Demonstrated short-term improvements in cardiovascular fitness and decreased tenderness
  - Did not significantly decrease pain

Busch AJ et al. *Cochrane Database Syst Rev.* 2006. .

Harris et al. *J Altern Complement Med.* 2005;11: 663–71; .

Assefi et al. *Ann Intern Med.* 2005;143:10–19.

Aerobic exercise training in Fibromyalgia



Bidonde J, Busch AJ, Schachter CL, Overend TJ, KimSY, Góes SM, Boden C, Foulds HJA. Aerobic exercise training for adults with fibromyalgia. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD012700

Esercizio fisico e FM

Una Revisione Sistematica Di Vari Studi Sull'esercizio Fisico,

su 2494 Pazienti Indica Che L'esercizio Complessivo

Mostra Effetti Significativi Nella Riduzione Del Dolore E Dei Sintomi FM Correlati.

- Ma alcuni Pazienti sono anche intolleranti all'esercizio fisico
- Presentano una riacutizzazione grave in risposta all'esercizio fisico
- Iniziare a un livello basso in cui i pazienti possano impegnarsi senza disagio significativo, poi aumento graduale del livello di intensità, incorporare diversi tipi di esercizio e riduzione dell'intensità / durata dell'esercizio se non tollerati ma mantenere la frequenza dell'esercizio
- Il tipo di esercizio misto che include aerobico, di resistenza e flessibilità pare essere benefico

Busch AJ, et All. Review Exercise therapy for fibromyalgia. *Curr Pain Headache Rep. 2011 Oct; 15(5):358-67.*
Jones KD, et All. A six-month randomized controlled trial of exercise and pyridostigmine in the treatment of fibromyalgia. *Arthritis Rheum.* 2008;58(2):612–622.

Come influisce sulla modulazione del dolore?

- l'esercizio fisico può regolamentare le risposte immunitarie e correlate allo stress.
- Dopo 8 mesi di esercizio in acqua di 60 minuti due volte alla settimana, i pazienti con FM sedentaria hanno mostrato una riduzione significativa dei livelli di citochine pro-infiammatorie e noradrenalina
- Anche una singola sessione di modesto esercizio sembra ridurre i marker proinfiammatori
- Inoltre, un recente studio di imaging funzionale ha dimostrato la normalizzazione della connettività funzionale nelle regioni del cervello implicata nella percezione del dolore per i pazienti FM che hanno subito un programma di esercizi di 15 settimane.
- Questi risultati suggeriscono che l'esercizio fisico può aiutare a migliorare il sistema di adattamento dei sistemi sia immunitario che di reazione allo stress nella FM.

Bote Me et all. *Brain Behav. Immun.* 2014;39:107–112.
Ortega E et. *Scand. J. Med. Sci. Sports*. 2012;22(1):104–112.
Bote ME, *PLoS ONE*. 2013;8(9):e74524.
Flodin P, et al. therapy. *Neuroimage Clin.* 2015;9:134–139.

Esercizi di bassa intensità verso esercizi di elevata intensità

. Aumento livelli BDNF
. Aumento complessità dendritica
. Aumento della ramificazione

. Nessun aumento dei livelli di BDNF
. Nessun effetto su ramificazione dendritica
. Significativi livelli di Cortisolo

Esercizio intenso = Stressore

(Shihet al., 2016)

Cinque motivi per cui lo sport fa bene alle persone affette da malattie reumatiche

1. Quando si fa sport, il corpo rilascia più endorfine (gli ormoni del buonumore) e ciò ha ripercussioni positive sulla psiche.
2. Lo sport rinforza i muscoli e mantiene la mobilità.
3. Lo sport contribuisce a ridurre i fattori di rischio cardiovascolare come ad es. la pressione arteriosa elevata.
4. Lo sport riduce la stanchezza e la spossatezza tipica di chi soffre di malattie reumatiche.
5. Sport e movimento consentono di evitare o ridurre il sovrappeso, alleggerendo il carico sulle articolazioni.

Movement-Based Therapies in Fibromyalgia. Why use it?

- **Decrease fear avoidance and empower individuals to take a proactive role in their ow health and wellness**
- **Are safe, cost-effective, and potent adjunct treatments** used to supplement (not replace) standard care
- **Deliver patient-centered, integrative care** that accounts for the physical, psychological, social, and spiritual aspects of health and illness
- **Have diverse, evidence-based benefits**, including reduction in pain, stress, and disability, and improvements in range of motion, strength, balance, coordination, cardiovascular health, physical fitness, mood, and cognition

Phuphanich ME et al. Phys Med Rehabil Clin N Am 31 (2020) 577–591

Movement-Based Therapies in Fibromyalgia

- YOGA: Yoga is a practice of physical postures, breathing techniques, and sometimes meditation derived from ancient India to promote physiologic and psychological well-being
- PILATES: Pilates is low-impact exercise based on holistic movement principles including concentration centering, control, breathing, precision, and flow
- TAI CHI: Tai chi is a Chinese, meditative, martial arts practice designed to gently strengthen and relax the body and mind. It is a system featuring coordinated movements, meditation and purposeful breathing that is believed to help unlock the body's Qi
- QIGONG: Qigong is another "moving" mindfulness practice that originated from traditional Chinese medicine Similar to tai chi, qigong uses the "mind" (or concentration) to coordinat breathing and smooth movements that promote the circulation of Qi

Phuphanich ME et al. Phys Med Rehabil Clin N Am 31 (2020) 577–591

Movement based therapy (Body Awareness Programs) in fibromyalgia

- FELDENKRAIS: the Feldenkrais method (FM), founded by a physicist and engineer, is a system tha uses movement exploration for somatic learning through 2 major techniques (awareness throug movement and functional integration). Series of movements force the practitioner to use body sensation an perceptual feedback to choose between favorable (easy, comfortable) and unfavorable (painful, straining) position

- BODY AWARENESS THERAPY (BAT): Body awareness is used as an overall concept for the use of the body. It includes body consciousness, body management and deepened body experience. If the individual i helped to increase sensory awareness in the practic of movements, a sufficient degree of sensory activatio can be achieved and emotional reactions ca take place

- MENSENDIECK SYSTEM: The system is based on learning and treatment in phases: 1) the cognitive phase—understanding wha is to be done, 2) the associative phase—understandin how to do things, and 3) the automatize phase—changing and adopting a more muscularly efficient behavior without conscious thought.

Phuphanich ME et al. Phys Med Rehabil Clin N Am 31 (2020) 577–591

Cognitive behavioural therapies (CBTs)

- Cognitive behavioural therapies (CBTs) are **the dominant contemporary psychological treatments** for chronic pain
- CBTs are the '**gold-standard' psychological treatment** for FMpatients according to the Division 12 of the AmericanPsychological Association (Society of Clinical Psychology, 2017)
- However, there is no universally accepted definition of which techniques constitute CBT
- Within the label 'CBTs', 'classical', operant therapies, psychoeducation, different types of cognitive behavioural therapies and acceptance-based therapies are included

Eur J Pain 22 (2018) 242--260

Cognitive behavioural therapies (CBTs)

Table 1 Session content for CBT-I

Session number	Content
1. Sleep education	Participants will be provided with education on sleep stages; sleep and fibromyalgia and circadian rhythms and sleep. This information is given to provide a heuristic background for the specific sleep techniques used.
2. Sleep hygiene (SH)	SH will be discussed and participants are instructed to adhere to the following rules: (1) avoid caffeine after noon, (2) within 2 hours of bed, avoid exercise, nicotine, alcohol and heavy meals, (3) within 1 hour of bedtime, avoid screen time. The goal of SH is to eliminate sleep-interfering behaviours.
3. Stimulus control (SC) and brief relaxation	SC will be discussed and participants will be asked to adhere to the following recommendations: (1) do not use bed/bedroom for anything but sleep (or sex), (2) if not asleep in 15–20 min, leave bed, do something non-arousing in another room. Return to bed when sleepy. If not asleep in 20 min, repeat., (3) if awake and not back asleep in 20 min, repeat #2, (4) avoid napping. The goal of SC is to break incompatible/build compatible sleep associations. In addition, a 10 min relaxation exercise will be recorded and given to participants for practice at bedtime and once during the day. The goal of this is to induce relaxation/reduce arousal.
4. Sleep restriction	A time in bed prescription (Rx) will be set at baseline average diary reported total sleep time plus 30 min. If this value is <5 hours, Rx will be set at 5 hours. The therapist and participant will work together to set regular bed/wake times consistent with Rx. The goal of sleep restriction is to regulate sleep-wake cycle and reduce awake time in bed.
5. Monitoring automatic thoughts	Thoughts, thought patterns and emotional reactions that interfere with getting good sleep (ie, "I will never sleep well again".) will be identified and monitored.
6. Challenging/Replacing dysfunctional thoughts	The validity of sleep-interfering thoughts will be challenged and replaced with sleep conducive ones (ie, "There are things I can do to improve my sleep".)
7. Practical recommendations	Established cognitive restructuring techniques (ie, reappraisal, reattribution and decatastrophising) will be taught.
8. Review and maintenance	Learnt skills and importance of a regular sleep schedule and good sleep habits will be reviewed. Continued use of the techniques learnt will be discussed.
Booster sessions	In this brief (~20 min) telephone session, techniques from sessions 1 to 8 will be reviewed. The therapist will encourage continued practice of techniques. Problems will be trouble-shooted.

CBT-I, cognitive behavioural treatment for insomnia.

Table 2 Session content for sleep hygiene education

Session number	Content
1. Sleep education	Content is the same as CBT-I.
2. Sleep hygiene (SH)	Content is the same as CBT-I.
3. Insomnia and pain	Participants are provided education on chronic/acute insomnia (Spielman's 3 P's model)[53] and the Gate Control Theory[54] of pain.
4. Environment	Participants are provided with education on SH rules related to environmental factors (eg, noise, light).
5. Lifestyle	Participants are provided with education on lifestyle factors that influence sleep (eg, use of stimulants and other substances).
6. Diet	Participants are provided with education about diet and nutrition and their influence on sleep.
7. Exercise	Participants are provided with education about exercise and its influence on sleep.
8. Review and maintenance	In the final session, SH training reviewed and continued practice is encouraged. Problems are trouble-shooted. All education provided in previous sessions will be reviewed. Finally, continued engagement in education will be discussed.
Booster sessions	As in CBT-I, all training and education covered in SH training will be reviewed in a brief (~20 min) telephone call. Continued SH practice and education engagement are encouraged. Problems are trouble-shooted.

CBT-I, cognitive behavioural treatment for insomnia.

Participants will be assessed at baseline, post-treatment, 6 and 12 months follow-ups. The following assessments will be completed: 2 weeks of daily diaries measuring sleep and pain, daily actigraphy, insomnia severity index, pain-related disability, single night of polysomnography recording, arousal (heart rate variability, cognitive affective arousal), structural and functional MRI to examine pain-related neural activity and plasticity and mood (depression, anxiety)

McCrae CS, et al. BMJ Open 2020;10:e033760. doi:10.1136/bmjopen-2019-033760 1

EJP
European Journal of Pain

REVIEW ARTICLE

Efficacy, acceptability and safety of cognitive behavioural therapies in fibromyalgia syndrome – A systematic review and meta-analysis of randomized controlled trials

K. Bernardy[1], P. Klose[2], P. Welsch[3], W. Häuser[3,4,5]

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2 Department Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Germany
3 Health Care Center for Pain Medicine and Mental Health, Saarbrücken, Germany
4 Department Internal Medicine I, Klinikum Saarbrücken, Germany
5 Department Psychosomatic Medicine and Psychotherapy, Technische Universität München, Germany

29 RCTs with 2509 subjectswere included

CBTs were superior to controls (waiting list, attention, control, treatment as usual, other active non-pharmacological therapies)

- in pain relief of 50% or greater (RD 0.05 [95% CI 0.02–0.07] (highquality evidence),
- improvement of HRQoL of 20% or greater (RD 0.13 [95% CI 0.00–0.26], (moderate quality evidence),
- in reducing negative mood (SMD 0.43 [95% CI 0.62 to 0.24]) (high-quality evidence)
- disability (SMD 0.30 [95% CI 0.52 to 0.08]) (highquality evidence)
- fatigue (SMD – 0–27 [95% CI 0.50 to 0.03]) (high-quality evidence)

Eur J Pain 22 (2018) 242--260

Combining CBT with Exercise

Multicomponent Treatment

Growing consensus supports **a multicomponent treatment approach** for CWP that combines CBT and exercise

Hauser W, Bernardy K, Arnold B, Offenbacher M, Schiltenwolf M. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. Arthritis Rheum. 2009**;61**:216-224

Combining CBT with Exercise

Multicomponent Treatment

Growing consensus supports **a multicomponent treatment approach** for CWP that combines CBT and exercise

A recent meta-analysis found **strong evidence that such treatment significantly reduced pain, fatigue and depression**, as well as increased health-related quality of life (functioning), physical fitness and self-efficacy

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Combining CBT with Exercise

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A recent meta-analysis found **strong evidence that such treatment significantly reduced pain, fatigue and depression**, as well as increased health-related quality of life (functioning), physical fitness and self-efficacy

The effects were evident **immediately post-treatment**; however, they did **not appear to persist over time** suggesting that, like in any chronic health condition, ongoing intervention (e.g., maintenance of exercise) is required.

Hauser W, Bernardy K, Arnold B, Offenbacher M, Schiltenwolf M. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. Arthritis Rheum. 2009;**61**:216-224

Mind-body therapies

- Meditation-mindfulness therapies

- Meditative movement approaches

(Yoga, Tai-Chi, Feldenkrais method, etc.)

Mind-body therapies

- Meditation-mindfulne
- [illegible]tement approaches

(Yoga, Tai-Chi, Feldenkrais method, etc.)

Based on physical movement integrated with mental relaxation and breathing techniques

Mind and body therapies

- They belong to the **big group of *nonpharmacological therapies*** which are fundamental for a multimodal approach to these patients.
- In some studies they appear even to be **effective in more domains with respect to pharmacological approaches**

Background

- Mind-Body therapies **use movement and concentration** to augment the relationship between the mind (mental activity) and body (motor control)

- This allows to intervene on **centrally-mediated pain mechanisms**, which have a pivotal role in nociplastic fibromyalgia pain.

Mindfulness

- **Mindfulness** is based on the principle of the non-judgemental acceptance of one's condition, thoughts and suffering, recognizing that nothing is intrinsically positive or negative.
- The effect of mindfulness approaches in fibromyalgia syndrome has been more and more studied, giving encouraging results

Mindfulness

The analyses showed small to moderate effects in favor of mindfulness- and acceptance-based interventions compared to controls in:

pain (SMD -0.46 [95% CI -0.75, -0.17]),

depression (SMD -0.49 [95% CI -0.85, -0.12]),

anxiety (SMD -0.37 [95% CI -0.71, -0.02]),

mindfulness (SMD -0.40 [-0.69, -0.11]),

sleep quality (SMD -0.33 [-0.70, 0.04])

health-related quality of life (SMD -0.74 [95% CI -2.02, 0.54])

PLOS ONE

RESEARCH ARTICLE

Mindfulness- and acceptance-based interventions for patients with fibromyalgia – A systematic review and meta-analyses

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Objectives

To analyze health effects of mindfulness- and acceptance-based interventions, including mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT) and acceptance and commitment therapy (ACT). Additionally, we aimed to explore content and delivery components in terms of procedure, instructors, mode, length, fidelity and adherence in the included interventions.

Methods

We performed a systematic literature search in the databases MEDLINE, PsychINFO, CINAHL, EMBASE, Cochrane Central and AMED from 1990 to January 2019. We included randomized and quasi-randomized controlled trials analyzing health effects of mindfulness- and acceptance-based interventions for patients with fibromyalgia compared to no intervention, wait-list control, treatment as usual, or active interventions. MBSR combined with other treatments were included. Predefined outcomes were pain, fatigue, sleep quality, psychological distress, depression, anxiety, mindfulness, health-related quality of life and work ability. The Template for Intervention Description and Replication (TIDieR) checklist and guide was used to explore content and delivery components in the interventions. Meta-analyses were performed, and GRADE was used to assess the certainty in the evidence.

Results

The search identified 4430 records, of which nine original trials were included. The vast majority of the participants were women. The analyses showed small to moderate effects in favor of mindfulness- and acceptance-based interventions compared to controls in pain (SMD -0.46 [95% CI -0.75, -0.17]), depression (SMD -0.49 [95% CI -0.85, -0.12]), anxiety (SMD -0.37 [95% CI -0.71, -0.02]), mindfulness (SMD -0.40 [-0.69, -0.11]), sleep quality (SMD -0.33 [-0.70, 0.04]) and health-related quality of life (SMD -0.74 [95% CI -2.02, 0.54])

- **Mindfulness-based stress reduction** was superior to TAU both at post-treatment (large effect sizes) and at follow-up (medium to large effect sizes), and MBSR was also superior to FibroQoL post-treatment (medium to large effect sizes), but in the long term, it was only modestly better (significant differences only in pain catastrophising and fibromyalginess)
- Immediately post-treatment, **the number needed to treat for 20% improvement in MBSR vs TAU and FibroQoL was 4.0 (95% confidence interval [CI] 5 2.1-6.5) and 5.0 (95% CI 5 2.7-37.3)**
- An unreliable number needed to treat value of 9 (not computable 95% CI) was found for FibroQoL vs TAU

Research Paper

PAIN

A randomized controlled efficacy trial of mindfulness-based stress reduction compared with an active control group and usual care for fibromyalgia: the EUDAIMON study

Adrián Pérez-Aranda[a,b,c,d], Albert Feliu-Soler[a,b,c,*], Jesús Montero-Marín[e], Javier García-Campayo[c,f], Laura Andrés-Rodríguez[a,b,c], Xavier Borràs[g], Antoni Rozadilla-Sacanell[h], Maria T. Peñarrubia-María[i,j,k], Natalia Angarita-Osorio[a,b,g], Lance M. McCracken[l], Juan V. Luciano[a,b,c]

Abstract

Fibromyalgia (FM) syndrome represents a great challenge for clinicians and researchers because the efficacy of currently available treatments is limited. This study examined the efficacy of mindfulness-based stress reduction (MBSR) for reducing functional impairment as well as the role of mindfulness-related constructs as mediators of treatment outcomes for people with FM. Two hundred twenty-five participants with FM were randomized into 3 study arms: MBSR plus treatment-as-usual (TAU), FibroQoL (multicomponent intervention for FM) plus TAU, and TAU alone. The primary endpoint was functional impact (measured with the Fibromyalgia Impact Questionnaire Revised), and secondary outcomes included "fibromyalginess," anxiety and depression, pain catastrophising, perceived stress, and cognitive dysfunction. The differences in outcomes between groups at post-treatment assessment (primary endpoint) and 12-month follow-up were analyzed using linear mixed-effects models and mediational models through path analyses. Mindfulness-based stress reduction was superior to TAU both at post-treatment (large effect sizes) and at follow-up (medium to large effect sizes), and MBSR was also superior to FibroQoL post-treatment (medium to large effect sizes), but in the long term, it was only modestly better (significant differences only in pain catastrophising and fibromyalginess). Immediately post-treatment, the number needed to treat for 20% improvement in MBSR vs TAU and FibroQoL was 4.0 (95% confidence interval [CI] = 2.1-6.5) and 5.0 (95% CI = 2.7-37.3). An unreliable number needed to treat value of 9 (not computable 95% CI) was found for FibroQoL vs TAU. Changes produced by MBSR in functional impact were mediated by psychological inflexibility and the mindfulness facet acting with awareness. These findings are discussed in relation to previous studies of psychological treatments for FM.

Keywords: Fibromyalgia, Mindfulness-based stress reduction, Mediational models, RCT

1. Introduction

Fibromyalgia (FM) is a disabling syndrome of unknown etiology that affects approximately 2% of the general population worldwide.[9] It is mainly characterized by chronic widespread pain, fatigue, stiffness, sleep problems, perceived cognitive dysfunction, and distress.[24,32] FM is associated with high health care and societal costs industrialized countries.[46,73]

Clinicians prescribe medications as the usual treatment for FM despite their limited benefits.[61,67] In fact, clinical guidelines are inconsistent regarding recommendations for pharmacotherapy for

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

A. Pérez-Aranda and J.V. Luciano contributed equally to this article and should be considered co-first authors.

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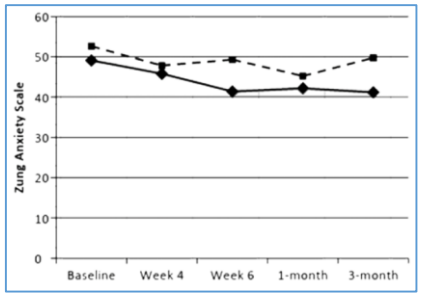
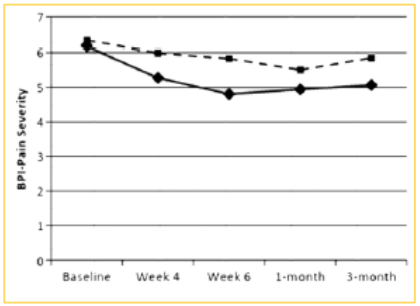
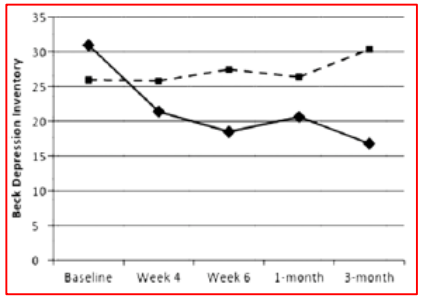






A Randomized, Controlled Trial of Wholistic Hybrid Derived From Eye Movement Desensitization and Reprocessing and Emotional Freedom Technique (WHEE) for Self-Treatment of Pain, Depression, and Anxiety in Chronic Pain Patients

Daniel Benor, MD[1], John Rossiter-Thornton, MD, FRCP[2], and Loren Toussaint, PhD[3]

WHEE
Wait

EMDR involves the back and forth movement of one's eyes from side to side while focusing the mind on troublesome issues in one's life (eg, pain, stress, trauma).

a convenience sample of 24 chronic pain patients (17 with chronic fatigue syndrome /fibromyalgia) were randomized into WHEE treatment and wait-list control groups for 6 weeks.

WHEE decreased anxiety ($P < .05$) ,depression ($P < .05$) and pain ($P < .05$) compared with the control group

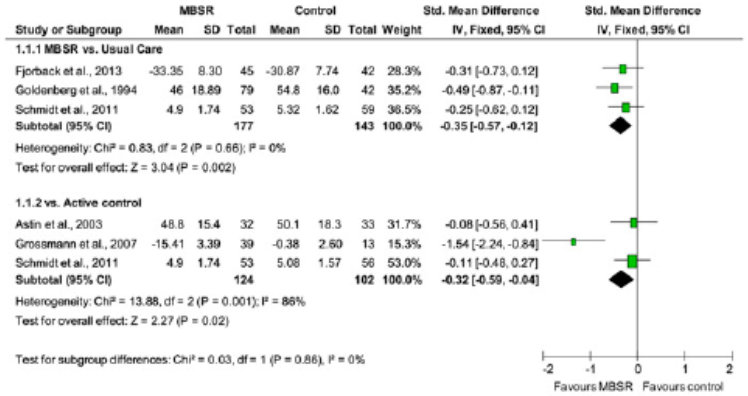
Journal of Evidence-Based Complementary & Alternative Medicine 2017, Vol. 22(2) 268-277

A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome

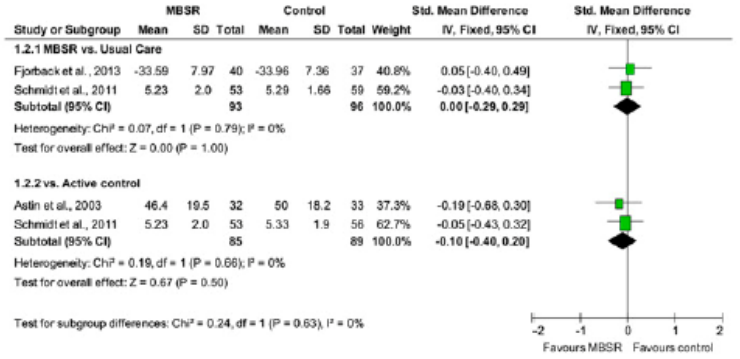
Romy Lauche [a,*], Holger Cramer [a], Gustav Dobos [a], Jost Langhorst [a], Stefan Schmidt [b,c]

Six trials were located with a total of 674 FMS patients

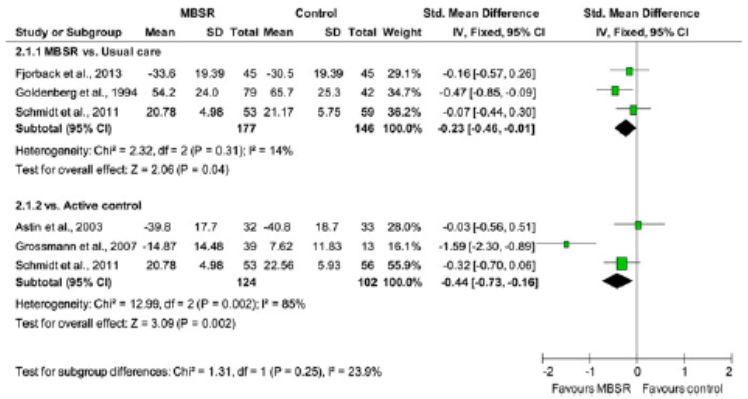
1) Quality of life, short-term



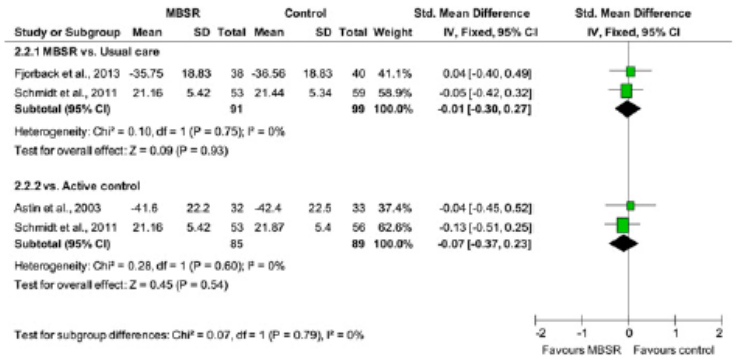
1) Quality of life, long-term



2) Pain, short-term



2) Pain, long-term



Journal of Psychosomatic Research 75 (2013) 500–510

Both groups registered statistically significant improvements across time for the Fibromyalgia Impact Questionnaire, Total Myalgic Score, Pain, and Depression, and no improvement in the 6 minute walk.

However, there was **no difference in either the rate or magnitude of these changes between the mind-body training group and the education control group**.

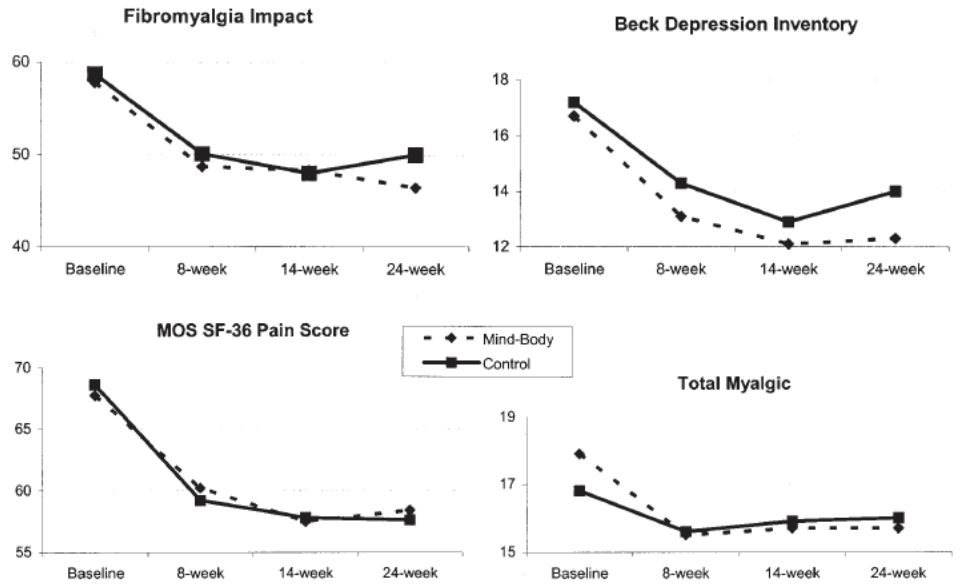


Figure 1. The salutary changes in test measures occurring by the 8th week in both study groups were largely maintained throughout the followup period.

The Efficacy of Mindfulness Meditation Plus Qigong Movement Therapy in the Treatment of Fibromyalgia: A Randomized Controlled Trial

JOHN A. ASTIN, BRIAN M. BERMAN, BARKER BAUSELL, WEN-LIN LEE, MARC HOCHBERG, and KELLY L. FORYS

ABSTRACT. ***Objective.*** To test the short and longterm benefits of an 8 week mind-body intervention that combined training in mindfulness meditation with Qigong movement therapy for individuals with fibromyalgia syndrome (FM).

Methods. A total of 128 individuals with FM were randomly assigned to the mind-body training program or an education support group that served as the control. Outcome measures were pain, disability (Fibromyalgia Impact Questionnaire), depression, myalgic score (number and severity of tender points), 6 minute walk time, and coping strategies, which were assessed at baseline and at 8, 16, and 24 weeks.

Results. Both groups registered statistically significant improvements across time for the Fibromyalgia Impact Questionnaire, Total Myalgic Score, Pain, and Depression, and no improvement in the number of feet traversed in the 6 minute walk. However, there was no difference in either the rate or magnitude of these changes between the mind-body training group and the education control group. Salutary changes occurring by the eighth week (which corresponded to the end of the mind-body and education control group sessions) were largely maintained by both groups throughout the 6 month followup period.

Conclusion. While both groups showed improvement on a number of outcome variables, there was no evidence that the multimodal mind-body intervention for FM was superior to education and support as a treatment option. Additional randomized controlled trials are needed before interventions of this kind can be recommended for treatment of FM. (J Rheumatol 2003;30:2257–62)

Key Indexing Terms:
MEDITATION MOVEMENT THERAPY FIBROMYALGIA

Fibromyalgia syndrome (FM) is characterized by chronic widespread musculoskeletal pain and multiple tender points[1]. In studies performed in the general population, prevalence ranges between 0.5% and 5%, with women showing significantly greater prevalence than men[2]. Patients with FM frequently present with multiple symptoms including depression, sleep disturbance, and fatigue, with resulting high disability and disruption in social and work roles as well as extensive use of medical services.

Causes of FM remain poorly understood, with treatment typically focused almost exclusively on symptom management[3-6]. Common therapeutic approaches include use of antidepressants (tricyclics and selective serotonin reuptake inhibitors)[7], as well as selected pain and sleep medications. There are significant side effects associated with a number of these pharmacological approaches, however, and the therapeutic benefits tend to be small and relatively shortlived[5,8]. Patient dissatisfaction with conventional pharmacologic and biomedical approaches to FM has also been suggested as one factor underlying the relatively high rates of use of complementary/alternative therapies by this population[9-12]. There is some evidence from 2 recent systematic reviews to suggest that 2 forms of these complementary/alternative therapies — aerobic exercise and an array of psychological/"mind-body" therapies (e.g., biofeedback, relaxation, cognitive-behavioral therapy) — may be effective adjuncts to pharmacologic treatment, particularly in terms of helping foster a greater sense of control and self-efficacy to meet the challenges of FM[13,14].

Results of a pilot study (n = 28) of an 8 week intervention in FM patients focusing on the practice of mindfulness meditation and Qigong movement therapy (described below) showed significant reductions in pain, fatigue, sleep disturbance, and depression, as well as reductions in tender point scores that persisted through 24 weeks[15]. However,

From the California Pacific Medical Center Research Institute, San Francisco, California, USA.

This study was carried out at the Complementary Medicine Program, University of Maryland School of Medicine, and funded by a grant from the National Center for Complementary and Alternative Medicine, National Institutes of Health (5 P50AT00084-03).

J.A. Astin, PhD, California Pacific Medical Center; B.M. Berman, MD; B. Bausell, PhD; W-L. Lee, PhD; M. Hochberg, MD, University of Maryland School of Medicine; K.L. Forys, MA, University of Maryland, Baltimore, Maryland, USA.

Address reprint requests to Dr. J.A. Astin, California Pacific Medical Center Research Institute, 2300 California Street, Room 207, San Francisco, CA 94115. E-mail: jastin@cooper.cpmc.org

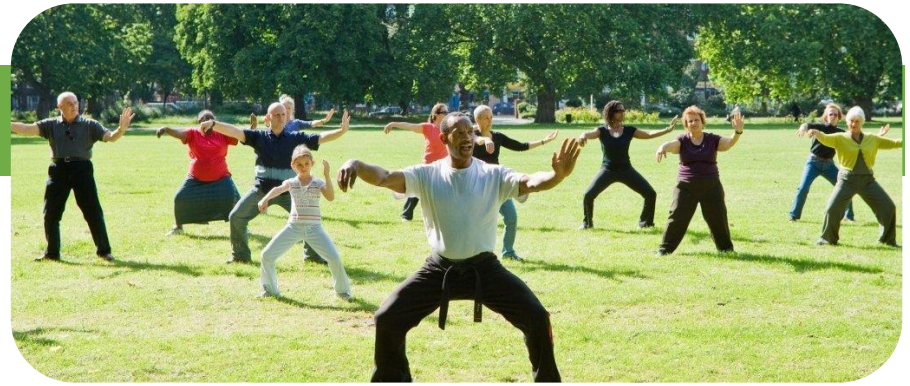
Submitted November 4, 2002; revision accepted February 13, 2003.

Movement-Based Therapies in Fibromyalgia

- YOGA: Yoga is a practice of physical postures, breathing techniques, and sometimes meditation derived from ancient India to promote physiologic and psychological well-being
- PILATES: Pilates is low-impact exercise based on holistic movement principles including concentration centering, control, breathing, precision, and flow
- TAI CHI: Tai chi is a Chinese, meditative, martial arts practice designed to gently strengthen and relax the body and mind. It is a system featuring coordinated movements, meditation and purposeful breathing that is believed to help unlock the body's Qi
- QIGONG: Qigong is another "moving" mindfulness practice that originated from traditional Chinese medicine Similar to tai chi, qigong uses the "mind" (or concentration) to coordinat breathing and smooth movements that promote the circulation of Qi

Phuphanich ME et al. Phys Med Rehabil Clin N Am 31 (2020) 577–591

FMS: TAI-CHI



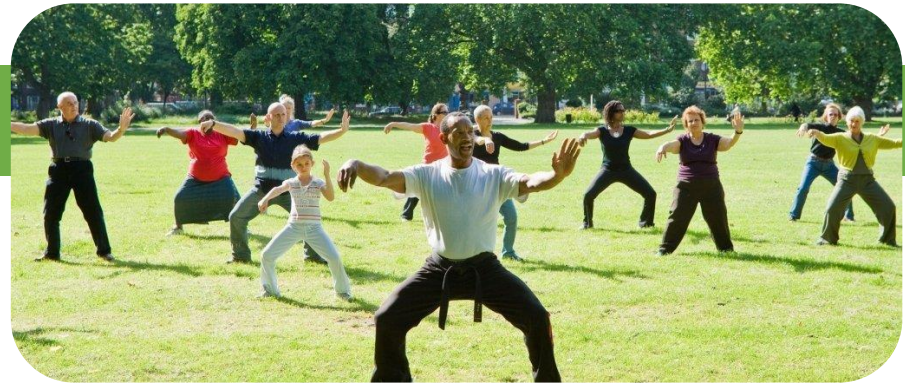
- Studio in singolo cieco, randomizzato, Tai-chi vs educazione al benessere e stretching. Nel gruppo Tai-chi sono stati evidenziati importanti miglioramenti nel punteggio totale FIQ e nella QoL. Miglioramenti mantenuti a 24 settimane, non sono stati osservati eventi avversi.

Wang C et al, NEJM 2010

- RCT, Tai-chi vs esercizio aerobico. Nel gruppo Tai-chi significativo miglioramento del FIQ-R rispetto all'esercizio aerobico

Wang C et al, BMJ 2018

FMS: TAI-CHI



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Wang C et al, NEJM 2010

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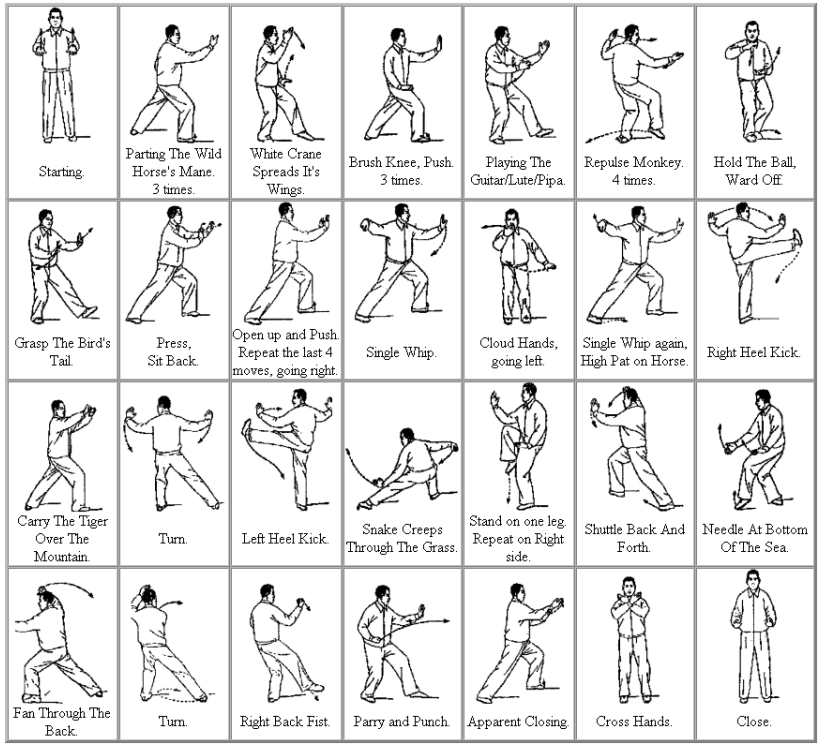
Wang C et al, BMJ 2018

Randomized Trial of Tai Chi for Fibromyalgia

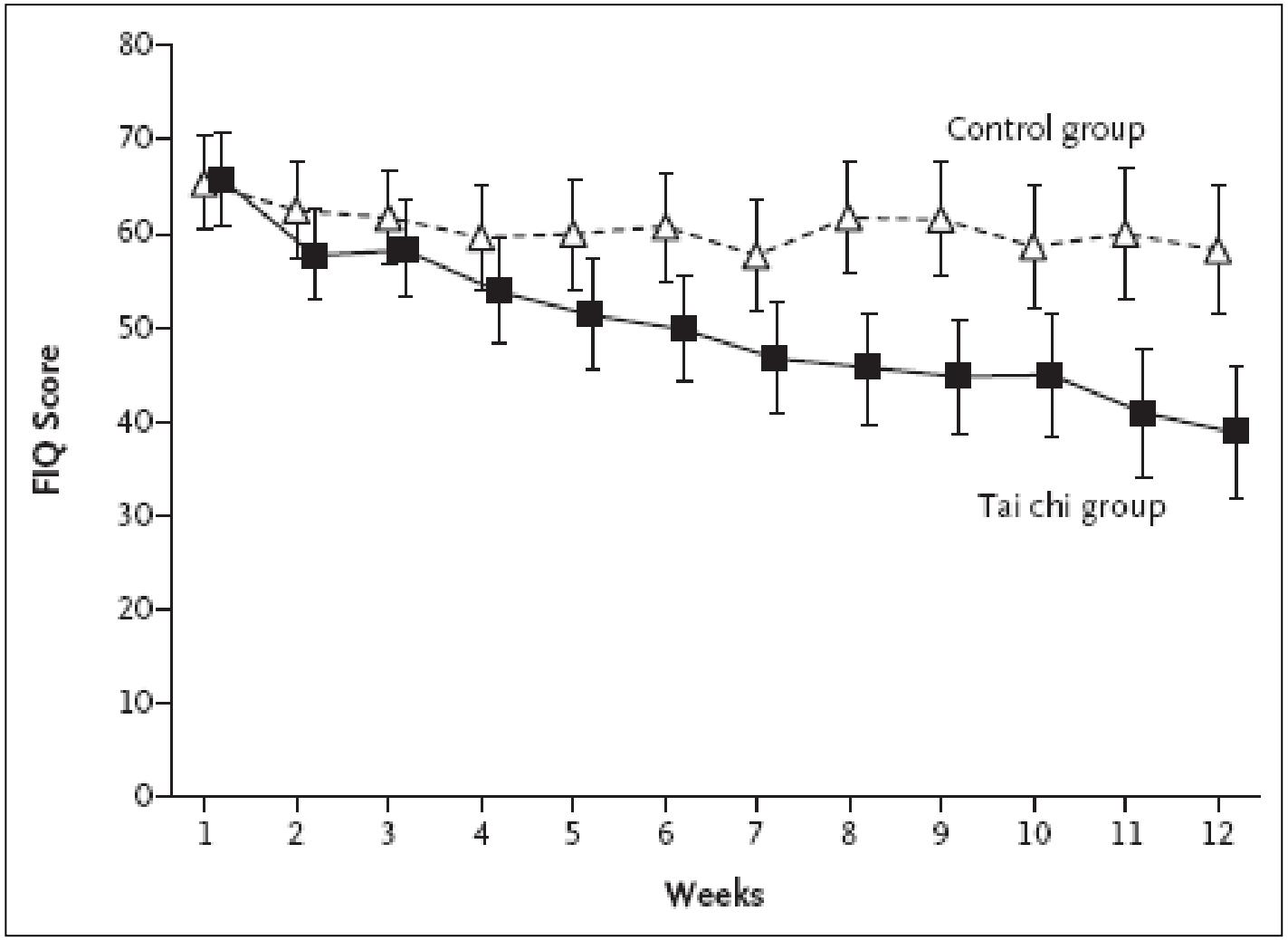
Chenchen Wang, M.D et al. N Engl J Med 2010: 19, 743-754



A Randomized Trial of Tai Chi for Fibromyalgia

Chenchen Wang, M.D et al. N Engl J Med 2010: 19, 743-754

FIQ score iin the 12 weks of treatment



Movement based therapy (Body Awareness Programs) in fibromyalgia

- FELDENKRAIS: the Feldenkrais method (FM), founded by a physicist and engineer, is a system tha uses movement exploration for somatic learning through 2 major techniques (awareness throug movement and functional integration). Series of movements force the practitioner to use body sensation and perceptual feedback to choose between favorable (easy, comfortable) and unfavorable (painful, straining) position

- BODY AWARENESS THERAPY (BAT): Body awareness is used as an overall concept for the use of the body. It includes body consciousness, body management and deepened body experience. If the individual i helped to increase sensory awareness in the practic of movements, a sufficient degree of sensory activatio can be achieved and emotional reactions ca take place

- MENSENDIECK SYSTEM: The system is based on learning and treatment in phases: 1) the cognitive phase—understanding what is to be done, 2) the associative phase—understanding how to do things, and 3) the automatize phase—changing and adopting a more muscularly efficient behavior without conscious thought.

Phuphanich ME et al. Phys Med Rehabil Clin N Am 31 (2020) 577–591

Body awereness (BA) in rehabilitation

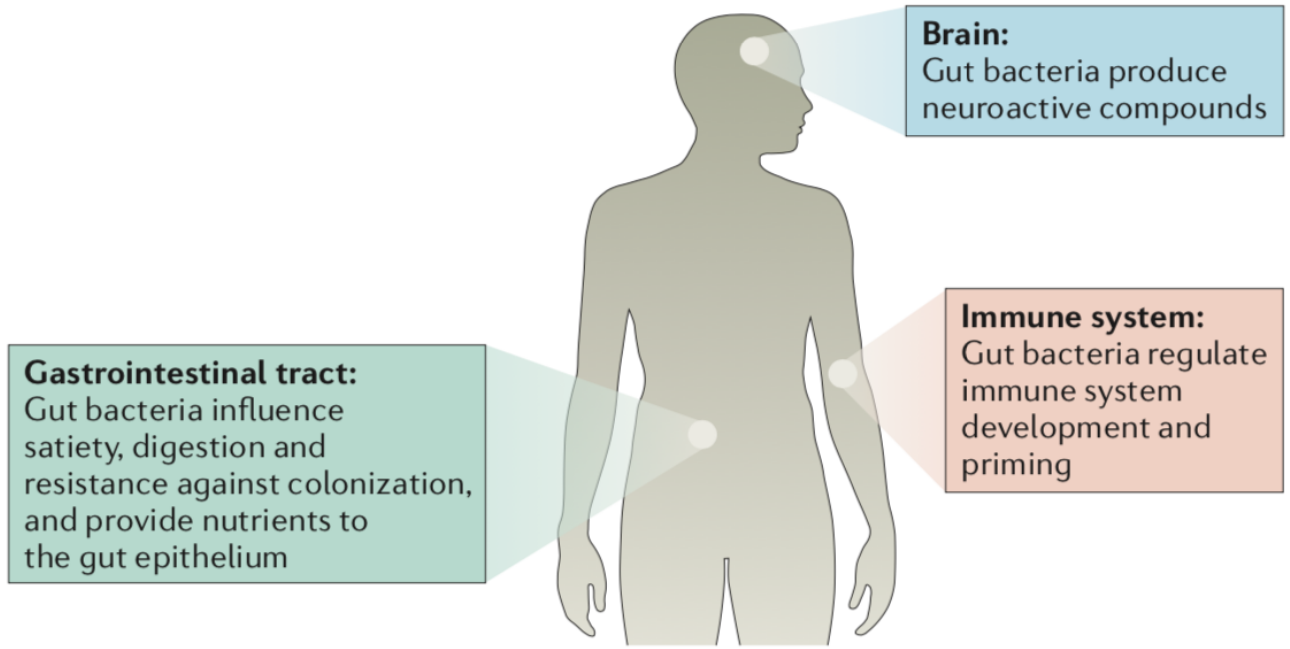
- Human movement and function are key concepts in rehabilitation and the study of human movement includes key phenomena.
- Movement awareness is a term that can how the movements are performed and experienced in relation to space, time and energy, as well as, identifying movement reactions in relation to internal, environmental and relational conditions.
- BA therapies refer to a group of interventions sharing a common perspective that focuses on the internal subjective experience of the body.
- While the classification of BA therapies remains unclear since there are other approaches and traditions in the field, physiotherapy works to build a frame that give coherence and consistency for movements and BA approaches.
- Eastern approaches such as t'ai chi, qi gong and yoga defined by some form of movement and body positioning, focusing on breathing and a cleared and calm state of mind with a goal of deep states of relaxation.

Trapianto di microbiota fecale

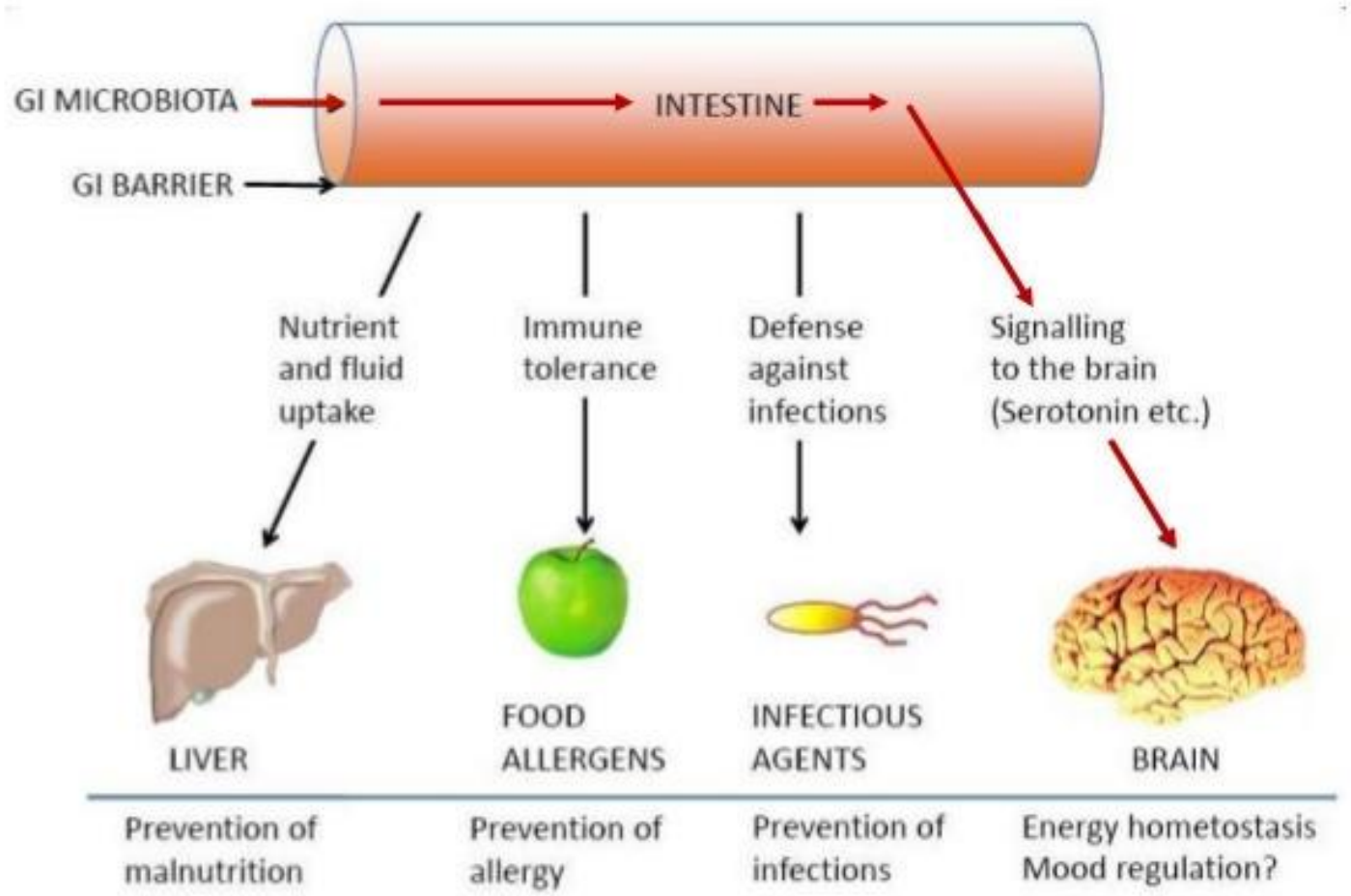
- Il **trapianto di microbiota fecale** (**FMT**) è il processo attraverso il quale le feci prelevate da un individuo sano vengono trasferite nell'intestino di una persona malata attraverso clistere, colonscopia o altri metodi. L'obiettivo di questa metodica è eliminare i microrganismi patogeni dall'intestino, ristabilendo una **comunità microbica sana**.
- Negli ultimi dieci anni c'è stato un crescente interesse nei confronti dei trapianti di microbiota come trattamento per una serie di condizioni, comprese le infezioni intestinali ricorrenti causate dal batterio *Clostridioides difficile*.

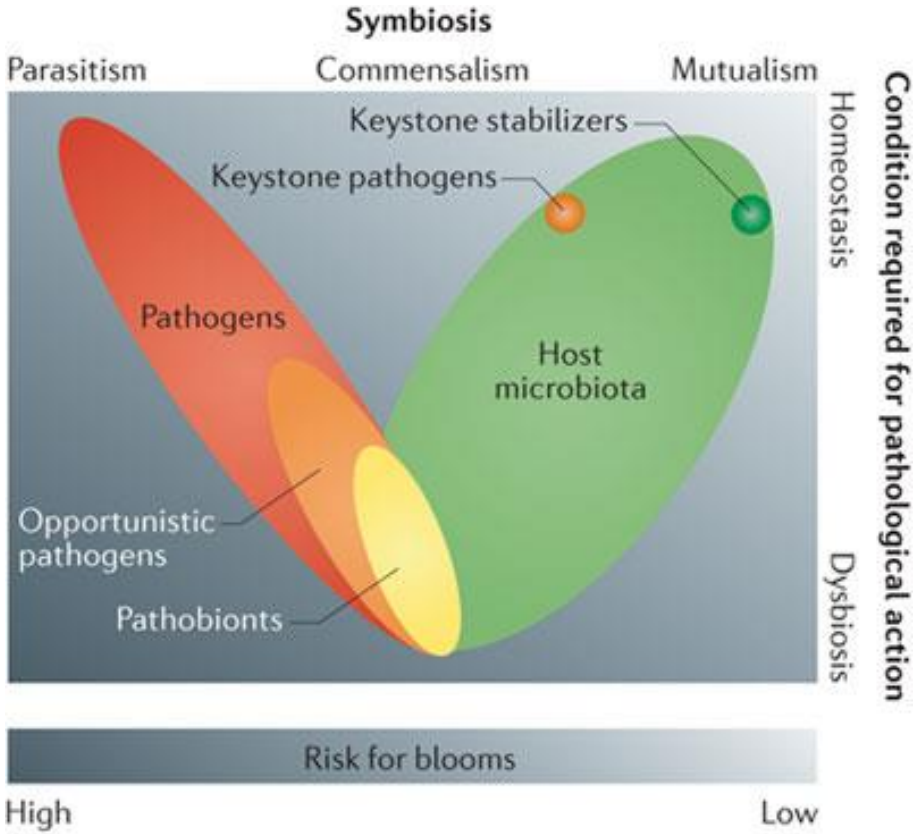
Box 2 | **Functions of the human gut microbiota**

- Digestion and energy harvesting from otherwise indigestible food components, by modulation of the absorptive capacity of the intestinal epithelium and production of enzymes that are absent in humans[185]
- Supporting and priming the immune system
- Providing nutrients to the gut epithelium (such as short-chain fatty acids), thereby exerting a trophic function and influencing the differentiation of gut epithelial cells[186]
- Resistance against colonization by potential pathogens by filling in all the available functional niches (that is, competition with the pathogen for physical space and nutrients) and maximizing the functional capacity of the entire ecosystem[187]
- Influencing satiety through the production of short-chain fatty acids via fermentation of fibres, which can affect the release of gastrointestinal satiety hormones, such as peptide YY and glucagon-like peptide[188]
- Gut bacteria are also thought to influence our state of mind by producing neuroactive compounds that act on the brain[189]

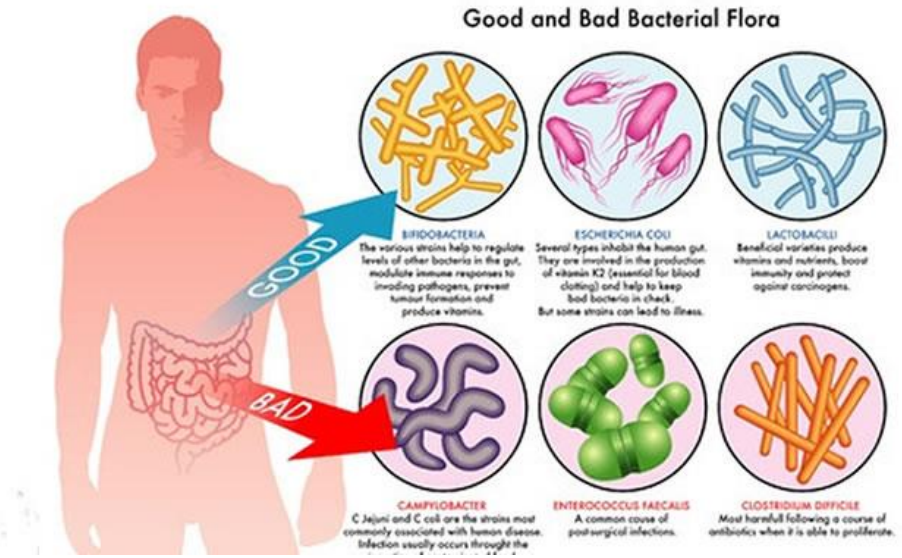


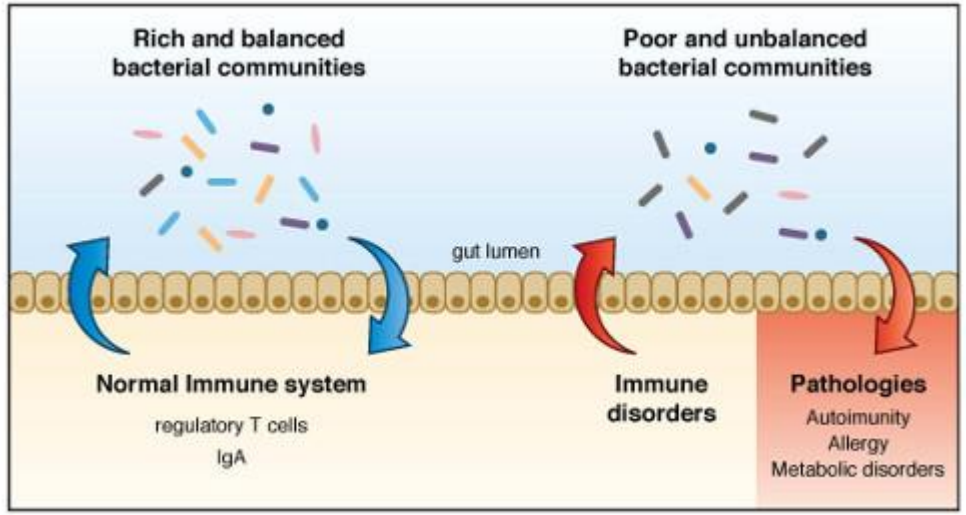
The microbiota-gut-brain axis





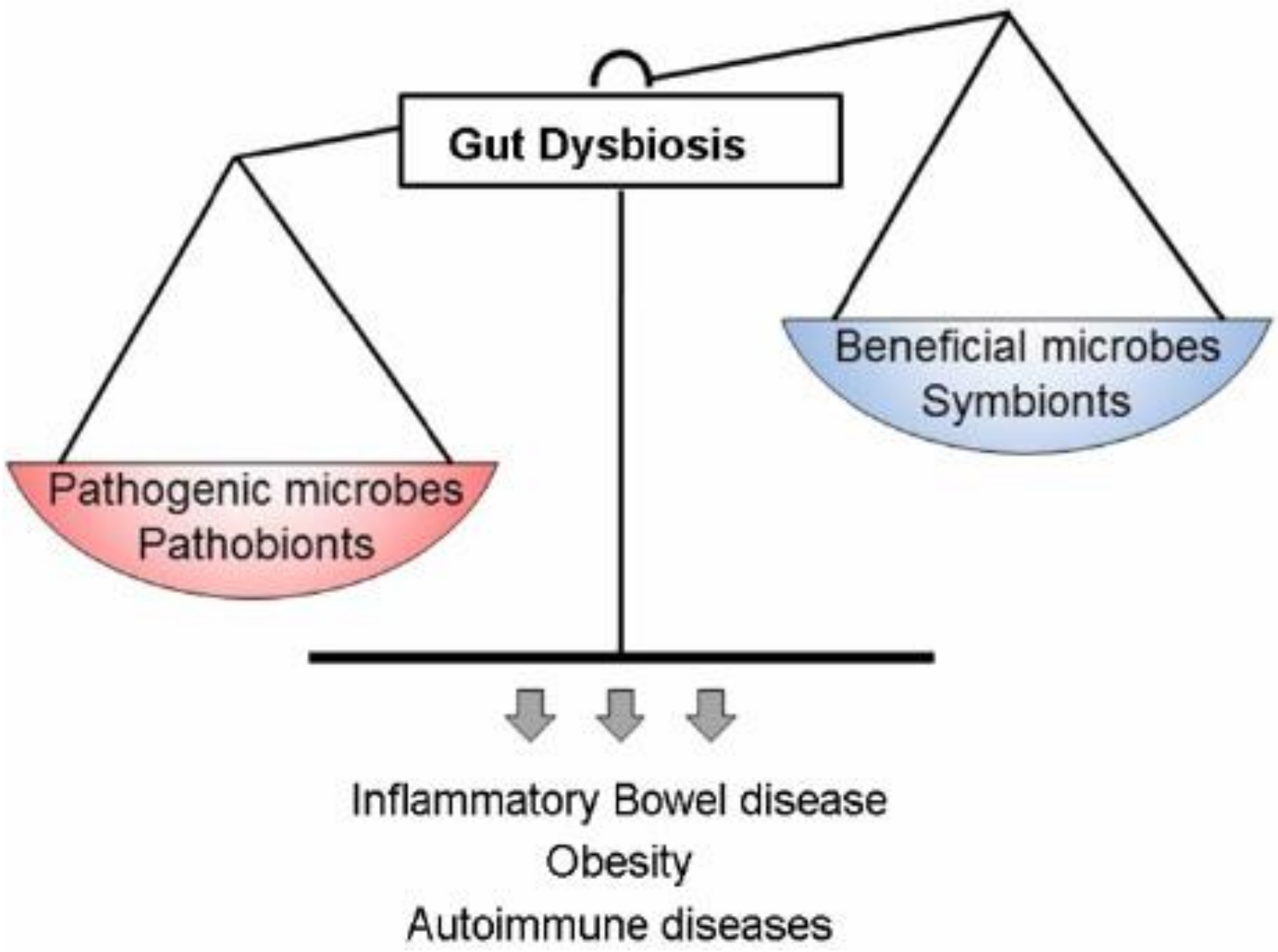
Balance between «good» versus «bad» bacteria determines disease suscptibility



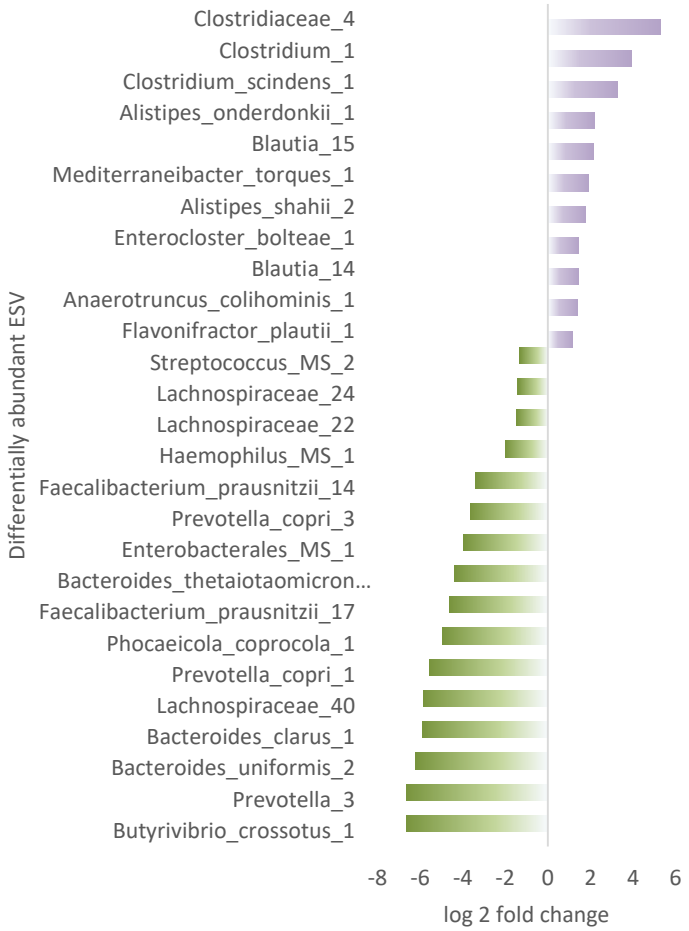


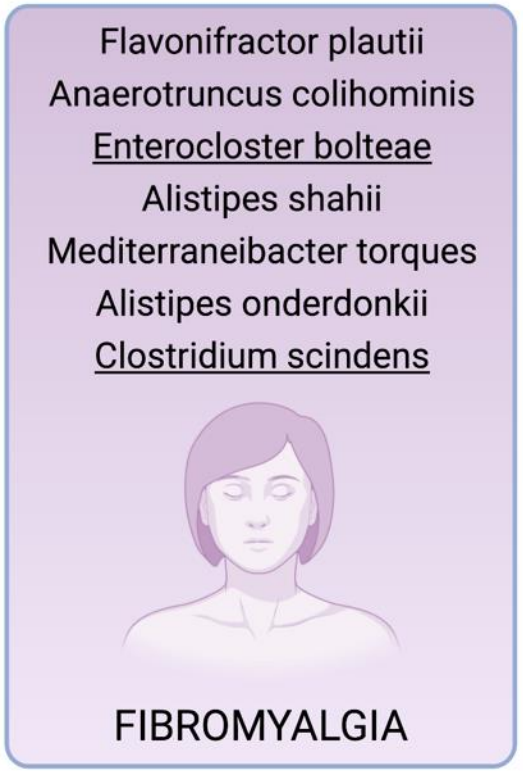
Health

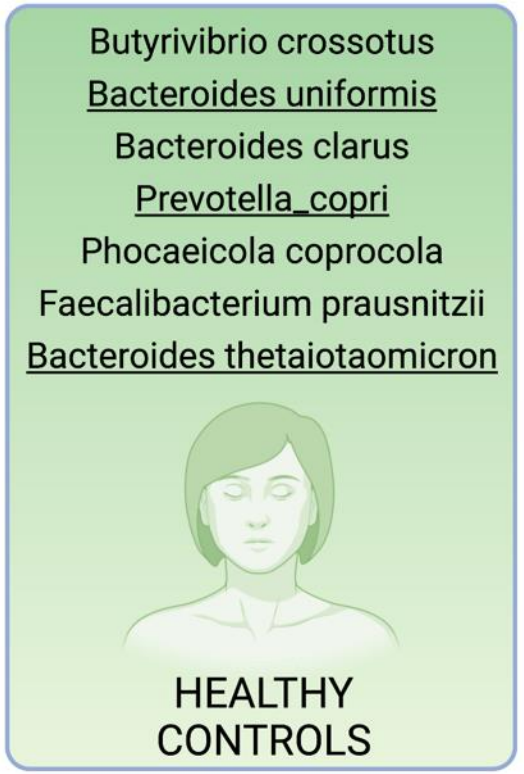
Disease


Gut Dysbiosis
Beneficial microbes
Symbionts
Pathogenic microbes
Pathobionts
Inflammatory Bowel disease
Obesity
Autoimmune diseases

Specific Bacterial Taxa Are Altered in Fibromyalgia

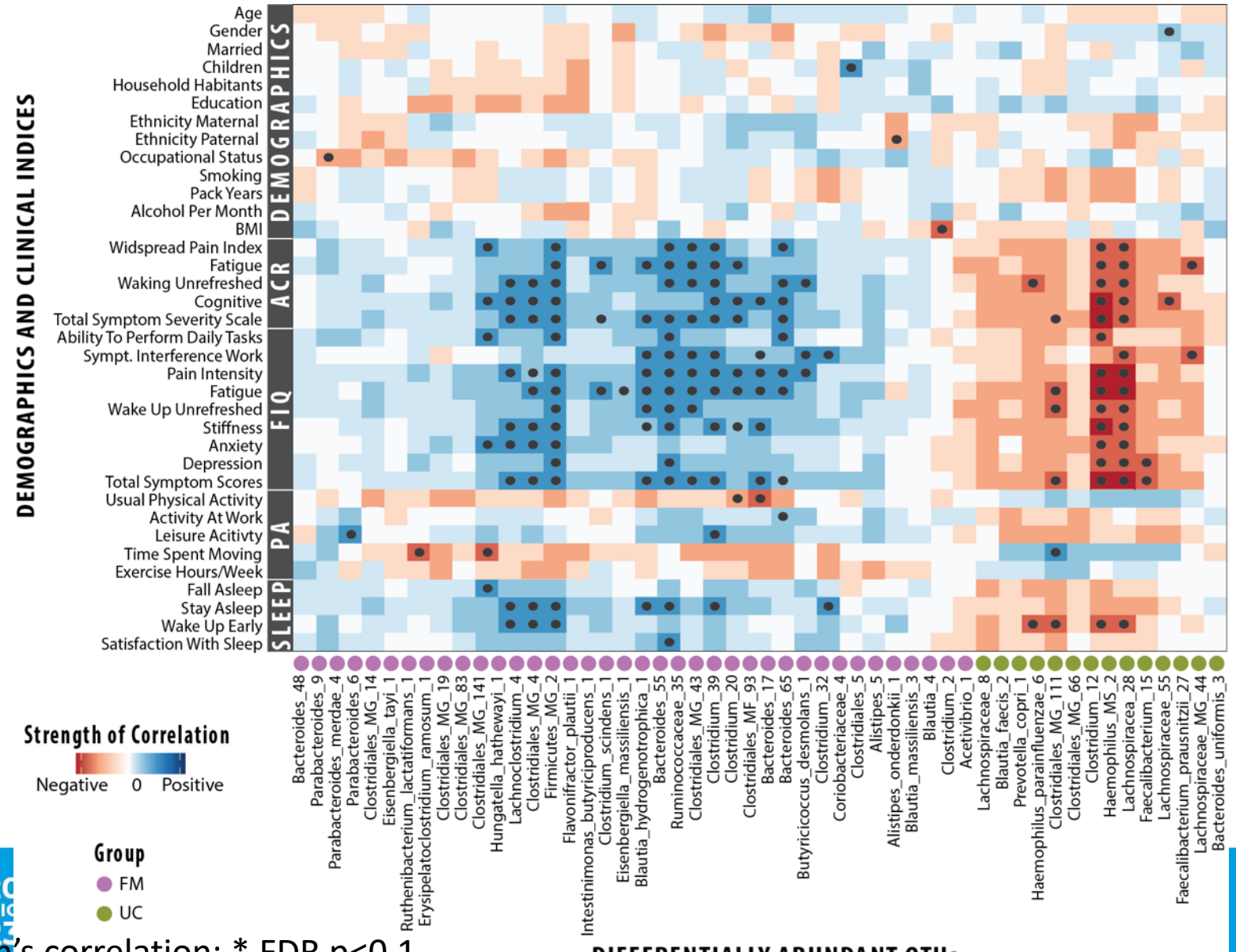






Minerbi et al., Pain 2019

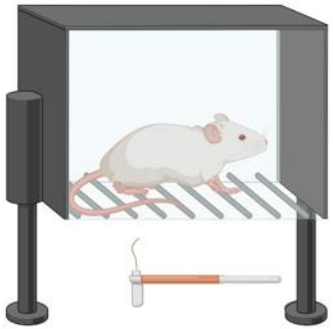
Some bacteria are correlated with symptoms severity

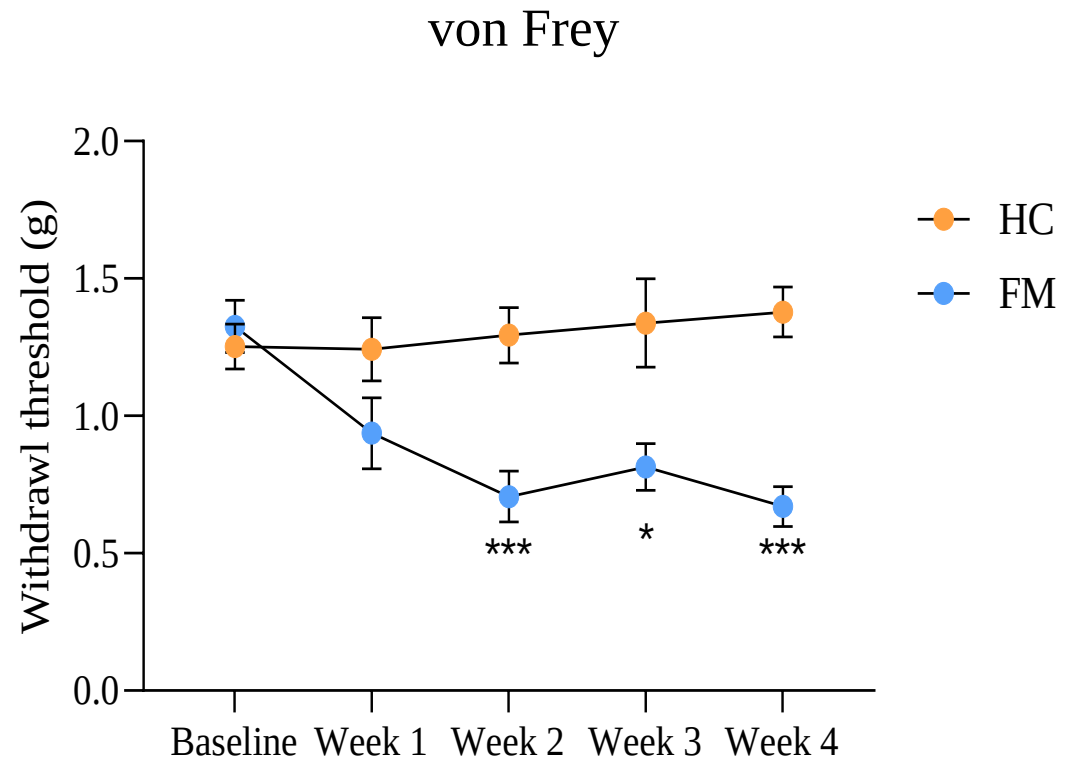


Pearson's correlation; * FDR p<0.1

Evoked Pain

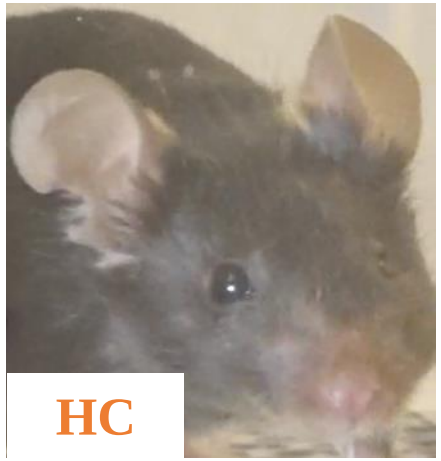
Days following FMT from humans with fibromyalgia, recipient mice show pain hypersensitivity

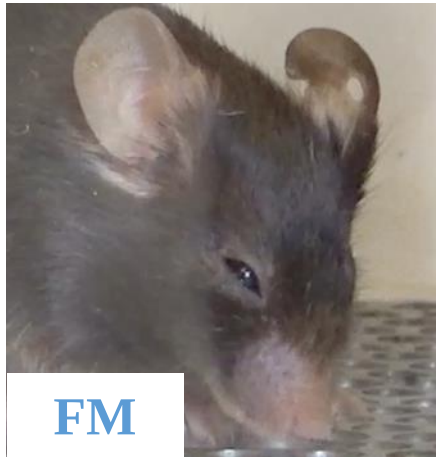


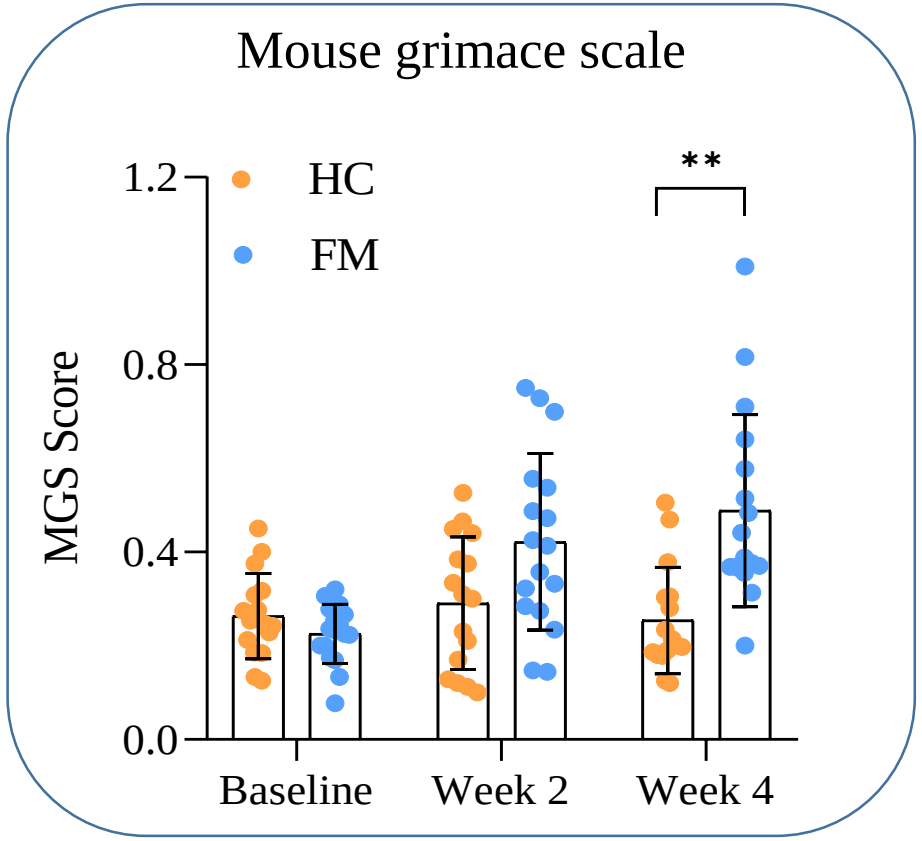


Khoutorsky and Minerbi, Unpublished data

Spontaneous Pain







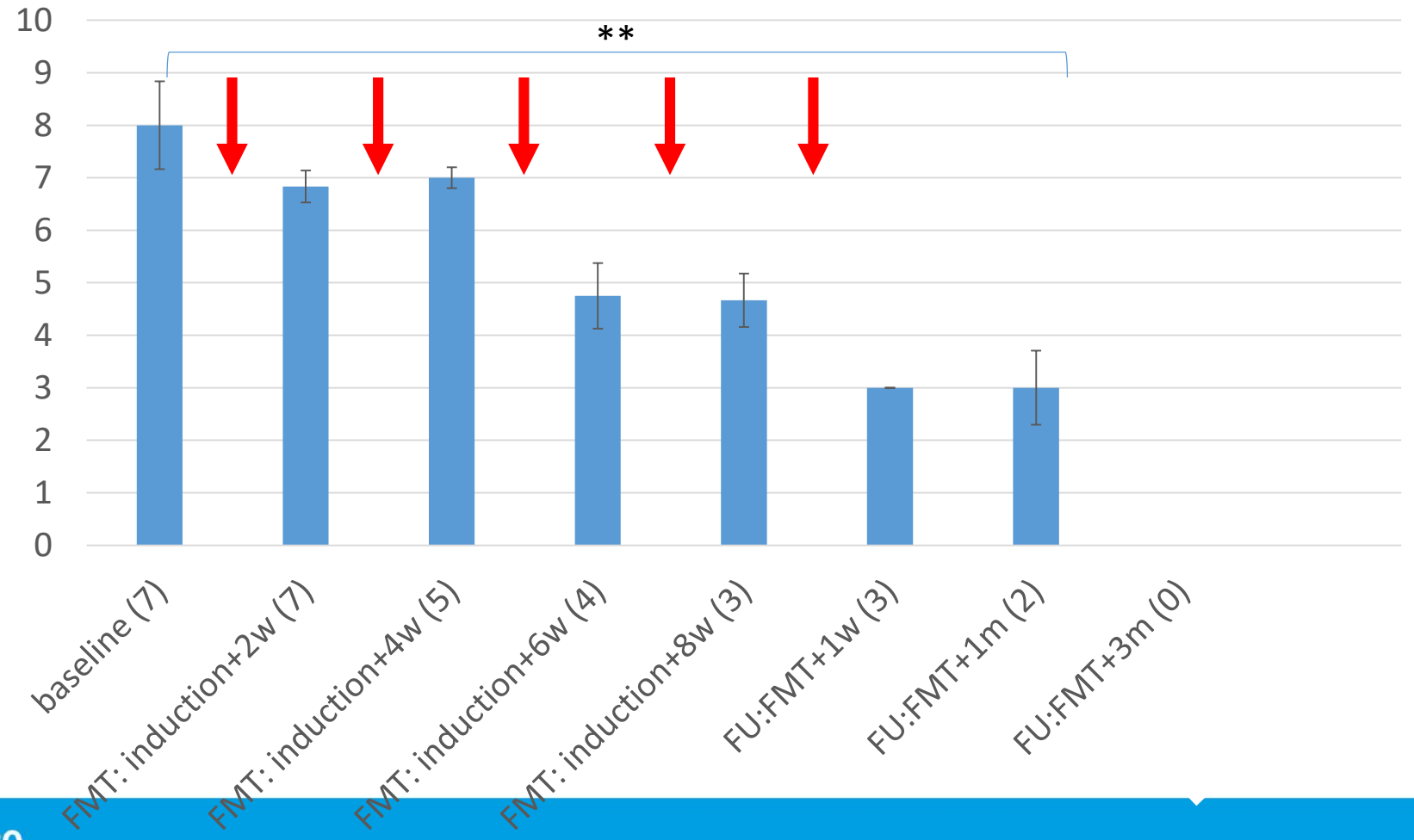
Khoutorsky and Minerbi, Unpublished data

Pilot Study – FMT in Women With Fibromyalgia




Pilot Study – FMT in Women With Fibromyalgia

Pain (NRS, mean±SEM)



(In parentheses – number of pts reaching the time point; p<0.001)

Neurophysiologie Clinique
Volume 51, Issue 4, August 2021, Pages 339-347

Original article

Repetitive transcranial magnetic stimulation (rTMS) versus transcranial direct current stimulation (tDCS) in the management of patients with fibromyalgia: A randomized controlled trial

Bijan Forogh, Hosnieh Haqiqatshenas, Tannaz Ahadi, Safoora Ebadi, Vajiheh Alishahi, Simin Sajadi

Effectiveness of High-Frequency Transcranial Magnetic Stimulation and Physical Exercise in Women With Fibromyalgia: A Randomized Controlled Trial

Get access

Ruth Izquierdo-Alventosa, PT, Marta Inglés, PT, PhD, Sara Cortés-Amador, PT, PhD, Lucia Gimeno-Mallench, PhD, Núria Sempere-Rubio, PT, PhD, Pilar Serra-Añó, PT, PhD

Physical Therapy, Volume 101, Issue 10, October 2021, pzab159,
https://doi.org/10.1093/ptj/pzab159

RESEARCH PAPER

Transcranial direct current stimulation of 3 cortical targets is no more effective than placebo as treatment for fibromyalgia: a double-blind sham-controlled clinical trial

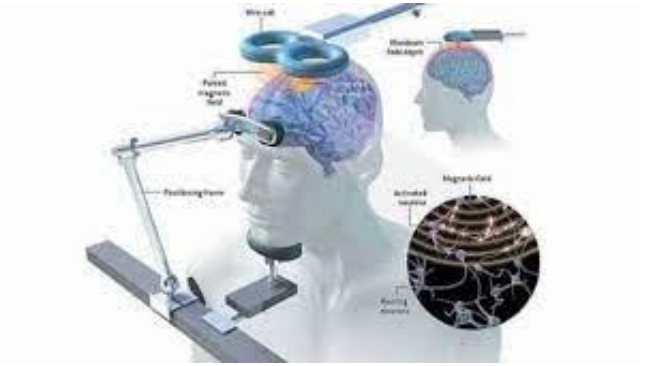
Samartin-Veiga, Noelia[a,*]; Pidal-Miranda, Marina[a]; González-Villar, Alberto J.[b]; Bradley, Claire[c,d,e]; Garcia-Larrea, Luis[c,d]; O'Brien, Anthony T.[f]; Carrillo-de-la-Peña, María T.[a]

Author Information

PAIN: July 2022 - Volume 163 - Issue 7 - p e850-e861
doi: 10.1097/j.pain.0000000000002493

TRANSCRANIAL

Stimolazione transcranica



- Negli ultimi anni, la neuro modulazione o stimolazione transcranica è stata proposta come possibile terapia per la fibromialgia.
- Si tratta di una tecnica non invasiva che utilizza correnti elettriche o campi magnetici per stimolare specifiche aree del cervello.
- Le tecniche più comuni utilizzate in questo contesto sono la stimolazione transcranica a corrente continua (tDCS) e la stimolazione magnetica transcranica (TMS).
- Entrambe le tecniche sono state proposte come possibili t
  fibromialgia, poiché possono modulare l'attività cerebrale
  dolore. Ambedue le tecniche possono essere attivatorie od i

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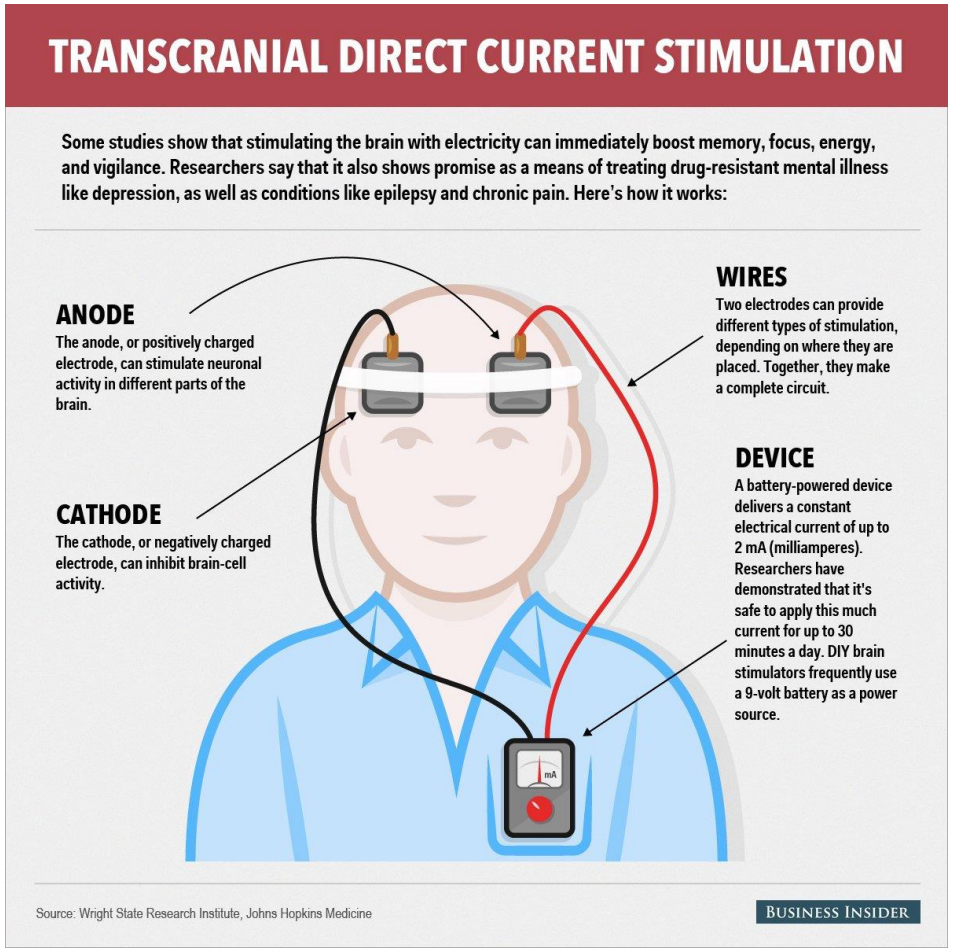
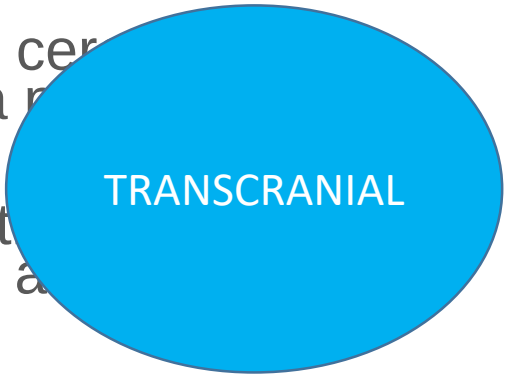
stimolazione transcranica a corrente continua (tDCS)



Stimolazione magnetica transcranica

Stimolazione transcranica

- La TMS può essere utilizzata per attivare o inibire specifiche regioni cerebrali, a seconda della frequenza di stimolazione utilizzata (1,5-2,5 Tesla).
- La stimolazione a bassa frequenza è generalmente utilizzata per inibire l'attività cerebrale, mentre la stimolazione ad alta frequenza è utilizzata per attivare l'attivita cerebrale.
- La tDCS utilizza una corrente continua a bassa intensità per modulare l'attività neurale. La stimolazione puo essere anodica (positiva) o catodica (negativa), a seconda dell'effetto desiderato.
- La stimolazione anodica viene utilizzata per aumentare l'attività cer
  zona stimolata , mentre la stimolazione catodica viene utilizzata r
  l'attivita cerebrale nella zona stimolata.
- Esistono anche altre varianti della tDCS, come ad esempio la st
  anodica-catodica alternata (tACS), che utilizza onde sinusoidali a
  frequenza per stimolare il cervello in modo non invasivo.



Stimolazione transcranica

- Una recente revisione sistematica di Conde-Antontòn e colleghi ha analizzato un totale di 14 studi per un totale di che 565 pazienti affetti da fibromialgia,
- I pazienti sono stati sottoposti a una o più sessioni di stimolazione transcranica, utilizzando tDCS o TMS.
- Le dimensioni del campione variavano notevolmente, con la maggior parte comprendente 30-50 persone. L'intervento analizzato è stato tDCS in 6 studi e TMS in 8. La frequenza e il numero di sessioni variavano tra gli studi.

Neurología 2023;xxx:xxx–xxx

NEUROLOGÍA

www.elsevier.es/neurologia

REVISIÓN

Efectos de la estimulación transcraneal por corriente directa y de la estimulación magnética transcraneal en pacientes con fibromialgia. Revisión sistemática

Á. Conde-Antón, I. Hernando-Garijo, S. Jiménez-del-Barrio, M.T. Mingo-Gómez, R. Medrano-de-la-Fuente y L. Ceballos-Laita*

Clinical Research in Health Sciences Group, Department of Surgery, Ophtalmology, Otorhinolaryngology, and Physical Therapy, Faculty of Health Sciences, University of Valladolid, Soria, Spain

Recibido el 6 de junio de 2020; aceptado el 19 de julio de 2020

PALABRAS CLAVE
Fibromialgia;
Estimulación por corriente directa transcraneal;
Estimulación magnética transcraneal

Resumen

Introducción: La fibromialgia (FM) es una patología crónica caracterizada por la presencia de dolor musculoesquelético generalizado que se asocia a trastornos psicológicos que afectan a la calidad de vida. En los últimos años, la estimulación transcraneal con corriente directa (tDCS) y la estimulación magnética transcraneal (TMS) se han estudiado para el abordaje del dolor crónico. El objetivo de esta revisión es determinar los efectos de la tDCS y la TMS en los síntomas característicos de los pacientes con FM.

Desarrollo: Se realizó una revisión sistemática acorde a los criterios PRISMA. Se realizaron búsquedas en las bases de datos Medline, Scopus, PEDro y Cochrane Library. Se seleccionaron ensayos clínicos aleatorizados que analizaran los efectos de estas intervenciones en el dolor, el umbral de dolor a la presión, la fatiga, la ansiedad y depresión, el catastrofismo y la calidad de vida en pacientes con FM. Se incluyeron 14 est

Conclusiones: La aplicación de tDCS en

trado disminuir el dolor a corto y

intervenciones ha mostrado mej

calidad de vida cuando se aplic

dorsolateral prefrontal. Los

concluyentes.

TRANSCRANIAL

* Autor para correspondencia.
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https://doi.org/10.1016/j.nrl.2020.07.024

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Stimolazione transcranica

- In sintesi, **la tDCS sembra essere la tecnica più efficace per ridurre il dolore nei pazienti con fibromialgia**, mentre **entrambe le tecniche, tDCS e TMS, possono migliorare la soglia al dolore a pressione, il catastrofismo, la qualità della vita e la funzione cognitiva quando applicate alla corteccia motoria, la fatica quando [illegible] corteccia dorsolaterale prefrontale**.
- Ulteriori ricerche sono necessarie per definire l'efficacia della [illegible]one transcranica nella fibromial- gia e per confermare i risultati ottenuti finora.

TRANSCRANIAL

Fitness

- **Fitness 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 fibromyalgia, although the commencement of training can be difficult for some patients because of deconditioning and psychological factors

Nutrizione e fibromialgia

Fibromyalgia (FM) is a chronic non-degenerative disease, whose **nutritional therapy seems controversial but promising**.

Pain and functional repercussion in FM patients seem to improve with **a hypocaloric diet,a raw vegetarian diet or a low FODMAPs diet,** as much as quality of life, quality of sleep,anxiety and depression and inflammatory biomarkers.

Existing studies in this subject are scarce and low quality, which does not allow conclusions to be drawn.

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REVIEW ARTICLE

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Dietary interventions in fibromyalgia: a systematic review

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ABSTRACT

Fibromyalgia (FM) is a chronic non-degenerative disease, whose nutritional therapy seems controversial. This systematic review aimed to synthesize the knowledge about the effect of dietary interventions on patient-reported outcomes (PRO) and inflammation in patients with FM. Six electronic databases – PubMed, BioMed Central, Cochrane library, EMBASE, LILACS and ISI – were searched for clinical trials, in which a dietary intervention in patients with FM diagnosed was conducted. Quality of evidence assessment was measured in accordance with GRADE methodology. Seven clinical trials – 3 randomized controlled trials, 1 unrandomized clinical trial and 3 uncontrolled clinical trials were identified. Dietary approaches included gluten-free diet ($n = 1$), raw vegetarian diet ($n = 2$), low Fermentable oligo-, di- and monossacharides, alcohols and polyols (FODMAPs) diet ($n = 1$), hypocaloric diet ($n = 2$) and monosodium glutamate- and aspartame-free diet interventions ($n = 1$). The major PRO were pain and functional repercussion, with 5 out of 7 studies reporting an improvement. The progress in secondary outcomes was reported for fatigue (2/5 studies), sleep quality (2/3 studies), depression and anxiety (3/6 studies), quality of life (4/5 studies), gastrointestinal symptoms (1/2 studies) and inflammatory biomarkers (1/1 study). However, according to Cochrane Risk of Bias, these studies had poor statistical quality. Well-designed studies should be performed to investigate the dietary interventions effect on FM.

KEY MESSAGES

- Fibromyalgia (FM) is a chronic non-degenerative disease, whose nutritional therapy seems controversial but promising.
- Pain and functional repercussion in FM patients seem to improve with a hypocaloric diet, a raw vegetarian diet or a low FODMAPs diet, as much as quality of life, quality of sleep, anxiety and depression and inflammatory biomarkers.
- Existing studies in this subject are scarce and low quality, which does not allow conclusions to be drawn.

ARTICLE HISTORY
Received 16 October 2018
Revised 4 December 2018
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KEYWORDS
Dietary interventions; fatigue; fibromyalgia; pain; systematic review

Introduction

Fibromyalgia (FM) is a chronic non-degenerative disease of unknown aetiology that mostly affects women, with a prevalence range between 0.5 and 2% worldwide [1] estimated at 1.7% in Portugal [2]. The diagnosis is based on the criteria of Rome III of the American College of Rheumatology (ACR), reviewed in 2010 [3].

The main symptoms of FM are musculoskeletal pain and chronic fatigue. Patients usually also refer nonrestorative sleep, morning stiffness, depression, anxiety [1] and gastrointestinal (GI) symptoms similar to irritable bowel syndrome (IBS) [4], strongly compromising their quality of life. All these patient's reported outcomes (PRO) are evaluated in clinical practice, through questionnaires which are considered subjective. However, changes in biomarkers, particularly inflammatory cytokines were also described. A meta-analysis with 25 clinical trials and 1255 FM patients revealed a higher plasma interleukin (IL)-6 in these patients, compared to healthy controls [5]. Additionally, several studies showed an association between FM and intestinal inflammation [4,6–8],

Gardoki-Souto et al. Trials (2021) 22:104
https://doi.org/10.1186/s13063-021-05042-w

Trials

STUDY PROTOCOL Open Access

Augmentation of EMDR with multifocal transcranial current stimulation (MtCS) in the treatment of fibromyalgia: study protocol of a double-blind randomized controlled exploratory and pragmatic trial

I. Gardoki-Souto[1,2,3], O. Martín de la Torre[4], B. Hogg[1,2,3], D. Redolar-Ripoll[4], A. Valiente-Gómez[1,2,3,5], L. Martínez Sadurní[6], J. M. Blanch[7], W. Lupo[1], V. Pérez[2,3,5], J. Radua[8,9,10], B. L. Amann[1,2,3,5] and A. Moreno-Alcázar[1,2,3*]

Abstract

Background: Fibromyalgia (FM) is a generalized, widespread chronic pain disorder affecting 2.7% of the general population. In recent years, different studies have observed a strong association between FM and psychological trauma. Therefore, a trauma-focused psychotherapy, such as eye movement desensitization and reprocessing (EMDR), combined with a non-invasive brain stimulation technique, such as multifocal transcranial current stimulation (MtCS), could be an innovative adjunctive treatment option. This double-blind randomized controlled trial (RCT) analyzes if EMDR therapy is effective in the reduction of pain symptoms in FM patients and if its potential is boosted with the addition of MtCS.

Methods: Forty-five patients with FM and a history of traumatic events will be randomly allocated to Waiting List, EMDR + active-MtCS, or EMDR + sham-MtCS. Therapists and patients will be kept blind to MtCS conditions, and raters will be kept blind to both EMDR and MtCS. All patients will be evaluated at baseline, post-treatment, and follow-up at 6 months after post-treatment. Evaluations will assess the following variables: sociodemographic data, pain, psychological trauma, sleep disturbance, anxiety and affective symptoms, and wellbeing.

Discussion: This study will provide evidence of whether EMDR therapy is effective in reducing pain symptoms in FM patients, and whether the effect of EMDR can be enhanced by MtCS.

Trial registration: ClinicalTrials.gov NCT04084795. Registered on 2 August 2019.

Keywords: Fibromyalgia, Eye movement desensitization and reprocessing, Multifocal transcranial current stimulation, Psychological trauma, Pain, Randomized controlled trial

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FMS: balneoterapia

Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials

- **HT**: evidenza da moderata a forte di una piccola riduzione del dolore, evidenza da moderata a forte di un piccolo miglioramento nella QoL, nessun effetto sui sintomi depressivi

- **BT in acqua minerale/termale**: moderata evidenza di una riduzione media del dolore, evidenza moderata per un miglioramento medio del QoL, nessun effetto significativo sui sintomi depressivi

- LG: **EULAR, APS, AWMF**

Naumann J et al, Arthritis Res Ther 2014

FMS: agopuntura

- Recenti revisioni sistematiche e meta-analisi di studi randomizzati controllati hanno riportato come l'agopuntura sia un trattamento efficace, sicuro e raccomandato per la gestione dei pazienti con FMS

- Altri studi hanno dimostrato come l'agopuntura vera era più efficace dell'agopuntura sham su dolore, qualità del sonno e QoL mentre evidenza che riduca la fatica non è stata ancora evidenziata

- LG: **EULAR**

Zhang XC et al, J Pain Res 2019

Journal of Pain Research

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REVIEW

Effect of Acupuncture on Pain, Fatigue, Sleep, Physical Function, Stiffness, Well-Being, and Safety in Fibromyalgia: A Systematic Review and Meta-Analysis

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Purpose: Fibromyalgia (FM) is a syndrome characterized by widespread pain, which caused huge economic and social burden. Acupuncture is often used to manage chronic pain. However, the efficacy of acupuncture in FM is still controversial. This study aimed to systematically review the effects of acupuncture on pain, fatigue, sleep quality, physical function, stiffness, well-being, and safety in FM.

Methods: We searched databases including PubMed, Embase, the Cochrane Library, Wanfang Database, Chongqing Weipu, and the China National Knowledge Infrastructure from inception to September 2021. Eligible studies included randomized or quasi-randomized controlled studies of acupuncture in patients with FM. Quantitative analysis was conducted using RevMan 5.3 software, and risk assessment was performed according to the Cochrane collaboration tool. Safety was quantitatively analyzed.

Results: A total of 13 articles were searched, of which 12 were analyzed quantitatively. Our meta-analysis found that acupuncture could alleviate pain (SMD: −0.42, 95% CI, −0.66, −0.17, $P<0.001$, $I^2=58\%$) and improve well-being (SMD: −0.86, 95% CI, −1.49, 0.24, P=0.007, $I^2=85\%$) at post-treatment. In addition, acupuncture showed long-term effects on reducing pain ($P=0.03$) and improving well-being ($P<0.001$). No evidence that acupuncture works on fatigue, sleep quality, physical function, or stiffness was found. No serious adverse events were detected in acupuncture treatment.

Conclusion: Moderate quality of evidence supports acupuncture in reducing pain in patients with FM. Therefore, acupuncture is recommended as a treatment for FM.

Keywords: fibromyalgia, acupuncture, pain, meta-analysis, systematic review

Introduction

Fibromyalgia (FM) is a diffuse pain syndrome with widespread pain, fatigue, and sleep disturbance as the main symptoms caused by the dysfunction of central nervous system sensory afferent processing.[1] FM is the third most common chronic musculoskeletal pain after low back pain and osteoarthritis, with an incidence of 2–3% in the general population worldwide.[2] FM can affect people of any age and is more common in women, obese people, and those with poor mental health.[3] Patients with FM are reported to have considerably higher rates of comorbidities and medical cost burdens than age - and sex-matched healthy individuals,[4,5] with average medical costs that are 30% higher than the control group.[5]

At present, no gold standard treatment for FM is available in the guidelines. The management of FM focuses on improving symptoms, that is, reducing pain and fatigue, improving sleep quality and physical function, and improving quality of life.[6,7] Given that pharmacological treatments are often associated with adverse reactions, guidelines recommend that non-pharmacological treatments be considered for the initial management of FM.[6,7] Acupuncture is an important component of complementary alternative medicine treatment. Studies indicate that analgesia can be achieved by releasing endogenous opioid or non-opioid substances to activate peripheral and central pain regulation systems[8–10]

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Review

Efficacy of Dry Needling and Acupuncture in Patients with Fibromyalgia: A Systematic Review and Meta-Analysis

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Abstract: Fibromyalgia (FM) is a syndrome that involves chronic pain, fatigue, sleep disturbance and impaired quality of life and daily functioning. In addition to medical and psychological therapies, other therapies including acupuncture and dry needling aim to reduce pain and disability in patients with FM. The aim of this study was to investigate the efficacy of dry needling and acupuncture in patients with FM regarding pain, function and disability in both the short and the long term. MEDLINE, PubMed, SCOPUS and Web of Science databases were systematically searched for randomized controlled trial studies evaluating efficacy data of dry needling or/and acupuncture treatments to improve pain, fatigue, sleep disturbance and impaired quality of life and/or daily function. A qualitative analysis including the methodological quality and a systematic data synthesis was performed. A total of 25 studies addressed the selection criteria. Most studies had an acceptable methodological quality. Four studies assessed the effect of dry needling, and twenty-one studies assessed the effect of acupuncture. In general, both interventions improved pain, anxiety, depression, fatigue, stiffness, quality of sleep and quality of life. However, both techniques were not compared in any study. Acupuncture and dry needling therapies seems to be effective in patients with FM, since both reduced pain pressure thresholds, anxiety, depression, fatigue, sleep disturbances and disability in the short term. It is still required to compare both techniques and their application in the long term.

Keywords: fibromyalgia; dry needling; acupuncture; chronic diseases; systematic review

Citation: Valera-Calero, J.A.; Fernández-de-las-Peñas, C.; Navarro-Santana, M.J.; Plaza-Manzano, G. Efficacy of Dry Needling and Acupuncture in Patients with Fibromyalgia: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2022**, *19*, 9904. https://doi.org/10.3390/ijerph19169904

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1. Introduction

Fibromyalgia (FM) is a condition that involves generalized chronic pain [1] associated with fatigue, sleep disturbance, depression and cognitive impairments [2,3]. This disease can affect people at different ages, but FM is most frequently found in middle-aged women [4]. In addition to gender and age, prior family history of FM increases the risk of suffering this condition. Therefore, this suggests a mixed genetic and lifestyle etiology [5], but the exact etiology is still unknown. Previous studies assessed the altered pain perception reporting a chronic and increased pain response to a painful stimulus (hyperalgesia) and pain caused by a stimulus which normally should not cause pain (allodynia) [6–8]. Gender differences were found in the intensity, frequency, duration and locations, female patients being more affected than male patients. Although pain perception is conditioned

FMS: agopuntura vs nutraceutica

- RCT, trattamento **nutrizionale in combinazione** (coenzima Q10, vitamina D, acido alfa-lipoico, magnesio e triptofano) vs **agopuntura.**
- Il supporto nutrizionale ha mostrato una riduzione del dolore statisticamente significativa 1 mese dopo l'inizio della terapia, rafforzato dopo 3 mesi con il mantenimento
- L'efficacia era più evidente nel gruppo agopuntura a tutti i momenti post-trattamento e al follow-up. Per quanto riguarda QoL, miglioramento in FIQ-R e i valori FSS sono stati rilevati in entrambi i gruppi
- **Conclusione**: l'approccio nutraceutico sembra essere un'opzione efficace per i pazienti con FMS. Confermata anche la nota validità dell'agopuntura.

Schweiger V et al, Nutrients 2020

4. Con quali aggettivi descriveresti il paz fibromialgico?

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LA FIBROMIALGIA NON TOGLIE UN'ORA DI VITA,
MA PUO' AVVELENARE OGNI ORA DELLA VITA

- L'evoluzione aggiuntiva dei sintomi: ora è come allora?
  - NON E' PIU' LO STESSO MALATO CHE AVREI VISITATO ALL'INIZIO DEI SINTOMI O IN ALTRI MOMENTI DEL LUNGO DECORSO

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    - SENSO DI INADEGUATEZZA
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    - RICADUTE MENTALI
- E' possibile «fuggire» dalla gabbia?

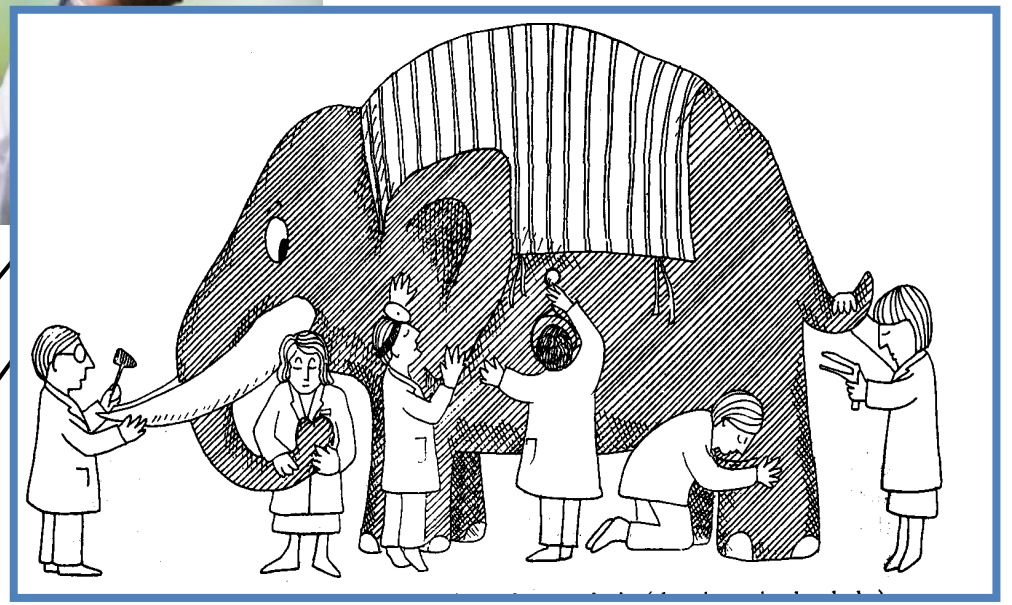
oms and Syndromes Related to ead chronic pain and Fibromyalgia

- Memory and cognitive difficulties
- ENT complaints (sicca sx, vasomotor rhinitis, accommodation problems)
- Vestibular complaints

Idiopathic low back pain

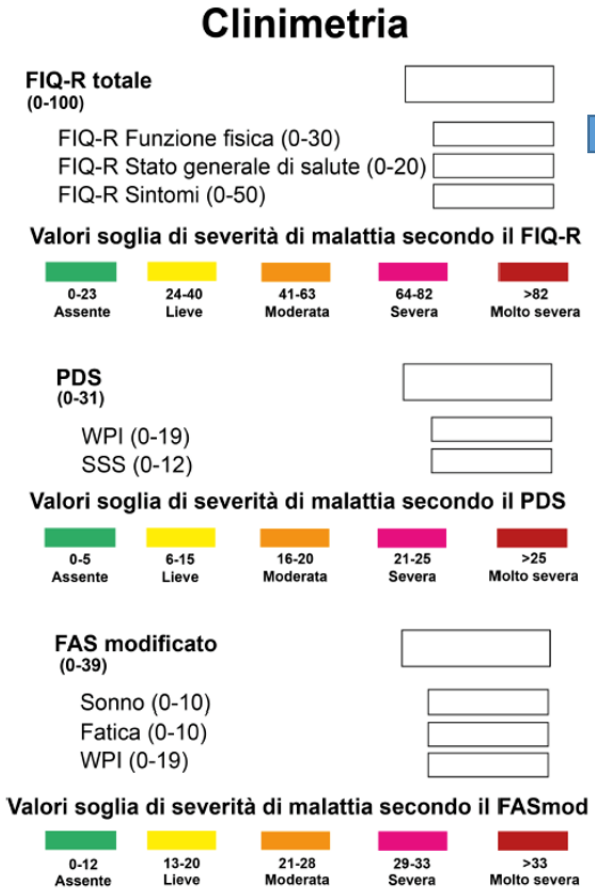
Irritable bowel syndrome

Nondermatomal paresthesias



Aaron et al. *Arch Int Med.* 2000;160:221-227.

CON CHE COSA CORRELA LA DISABILITA'?



197 PERSONE	PDS severo	FAS severo	Zung alto	STAY grave	Insonnia grave	Ritardo diagnosi
FIQ-R LIEVE (53%)	44%	20,5%	14%	22%	49%	7,1 anni
FIQ-R SEVERO (47%)	81%	73%	42%	41%	81%	7,7 anni

LA DISABILITA' MAGGIORE CORRELA CON MAGGIORE SEVERITA' DI MALATTIA E CON MAGGIORE GRAVITA' DI ANSIA, DEPRESSIONE ED INSONNIA.

GRUPPO DI STUDIO ABAR

EULAR revised recommendations for the management of fibromyalgia

G J Macfarlane,[1] C Kronisch,[1,2] L E Dean,[1] F Atzeni,[3] W Häuser,[4,5] E Fluß,[1] E Choy,[6] E Kosek,[7] K Amris,[8] J Branco,[9] F Dincer,[10] P Leino-Arjas,[11] K Longley,[12] G M McCarthy,[13] S Makri,[14] S Perrot,[15] P Sarzi-Puttini,[16] A Taylor,[17] G T Jones[1]

Macfarlane GJ, et al. Ann Rheum Dis 2017;76:318–328. doi:10.1136/annrheumdis-2016-209724

Tabella 3 Raccomandazioni

Raccomandazione	Livello di evidenza	Grado	Forza della raccomandazione	Accordo (%)*
Principi generali				
Una gestione ottimale richiede una diagnosi tempestiva. La piena comprensione della fibromialgia richiede una valutazione completa del dolore, della funzione e del contesto psicosociale. Deve essere riconosciuta come una condizione complessa ed eterogenea in cui è presente un'elaborazione anomala del dolore e altre caratteristiche secondarie. In generale, la gestione della FM dovrebbe assumere la forma di un approccio graduale.	IV	D		100
La gestione della fibromialgia deve mirare a migliorare la qualità di vita correlata alla salute, bilanciando i benefici e i rischi del trattamento, che spesso richiede un approccio multidisciplinare con una combinazione di modalità di trattamento non farmacologiche e farmacologiche personalizzate in base all'intensità del dolore, alla funzione, alle caratteristiche associate (come la depressione), all'affaticamento, ai disturbi del sonno e alle preferenze del paziente e alle comorbidità; attraverso un processo decisionale condiviso con il paziente. La gestione iniziale dovrebbe concentrarsi sulle terapie non farmacologiche.	IV	D		100
Raccomandazioni specifiche				
Gestione non farmacologica				
Esercizio aerobico e di rafforzamento	Ia	A	Forte per	100
Terapie cognitivo-comportamentali	Ia	A	Debole per	100
Terapie multicomponente	Ia	A	Debole per	93
Terapie fisiche definite: agopuntura o idroterapia.	Ia	A	Debole per	93
Terapie di movimento meditativo (qigong, yoga, tai chi) e riduzione dello stress basata sulla mindfulness	Ia	A	Debole per	71-73
Gestione farmacologica				
Amitriptilina (a basso dosaggio)	Ia	A	Debole per	100
Duloxetina o milnacipran	Ia	A	Debole per	100
Tramadolo	Ib	A	Debole per	100
Pregabalin	Ia	A	Debole per	94
Ciclobenzaprina	Ia	A	Debole per	75

*Percentuale del gruppo di lavoro che ha ottenuto un punteggio di almeno 7 su una scala numerica da 0 a 10 per valutare l'accordo.

Raccomandazioni

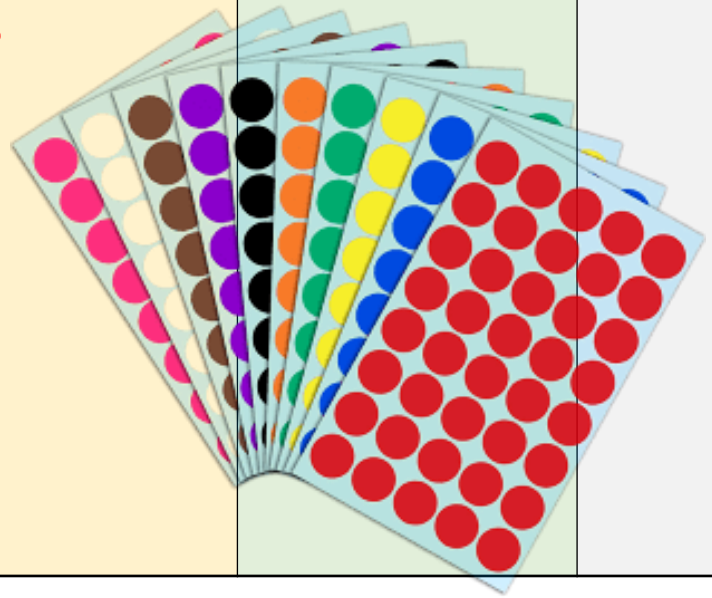
Diagnosi precoce
Trattamenti con e senza farmaci
Educazione e condivisione con il paziente
Considerare la salute mentale
Pochi farmaci sono utili
Approccio MULTIDISCIPLINARE

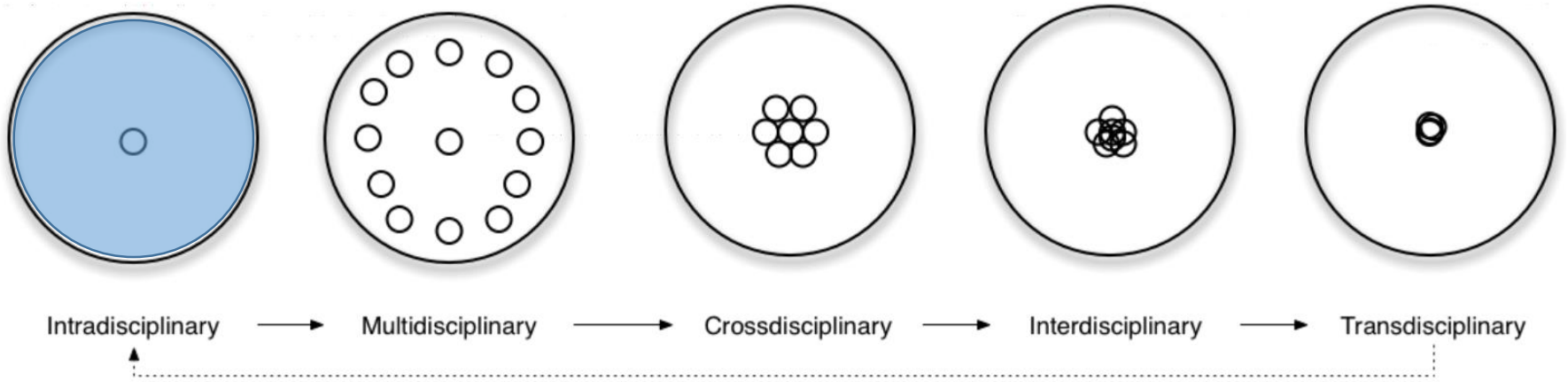
Trattamento non farmacologico

ESERCIZIO AEROBICO E STRETCHING
PSICOTERAPIA COGNITIVO-COMPORTAMENTALE
AGOPUNTURA, YOGA,THAI CHI, PILATES
MEDITAZIONE E MINDFULNESS

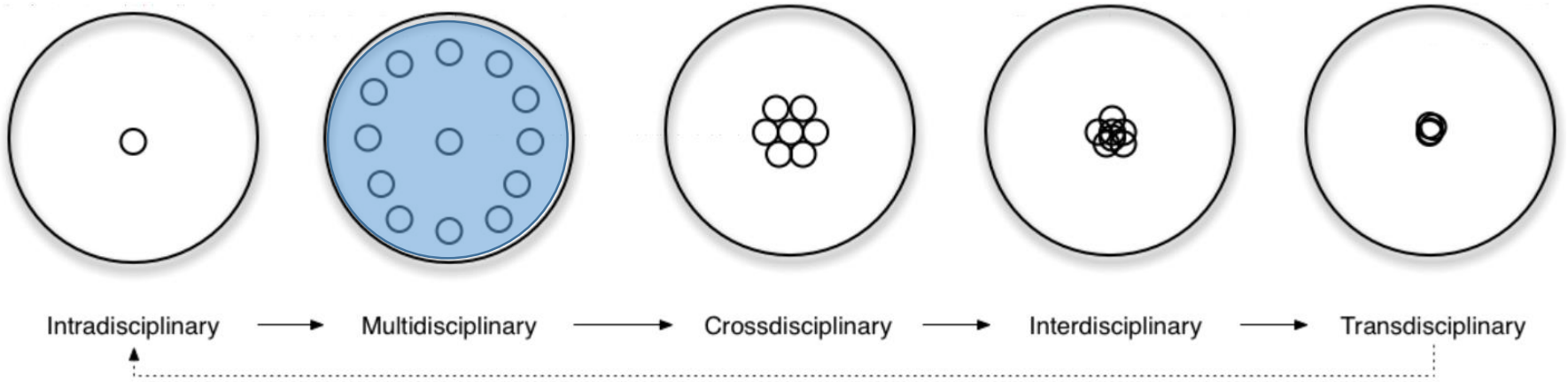
5. Quale ritieni essere il termine più appropriato?

5. Quale ritieni essere il termine più appropriato?

Intradisciplinare	Crossdisciplinare	Multidisciplinare	Interdisciplinare	Transdisciplinare
		1 solo bollino 		

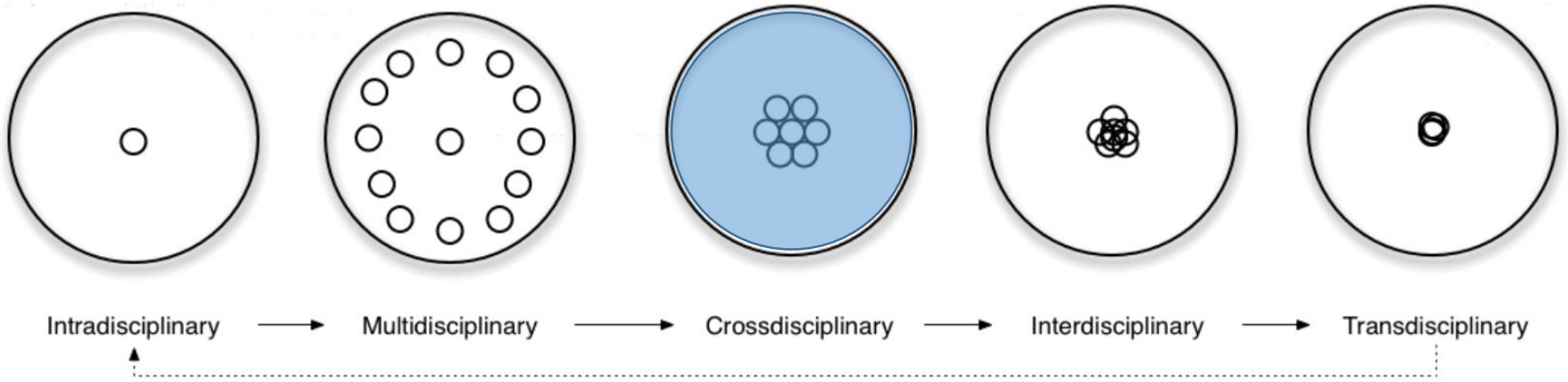


Intradisciplinare: lavorare all'interno di un'unica disciplina



Intradisciplinare: lavorare all'interno di un'unica disciplina

Multidisciplinare: persone di differenti discipline che lavorano insieme,
ognuna attingendo alla propria conoscenza disciplinare



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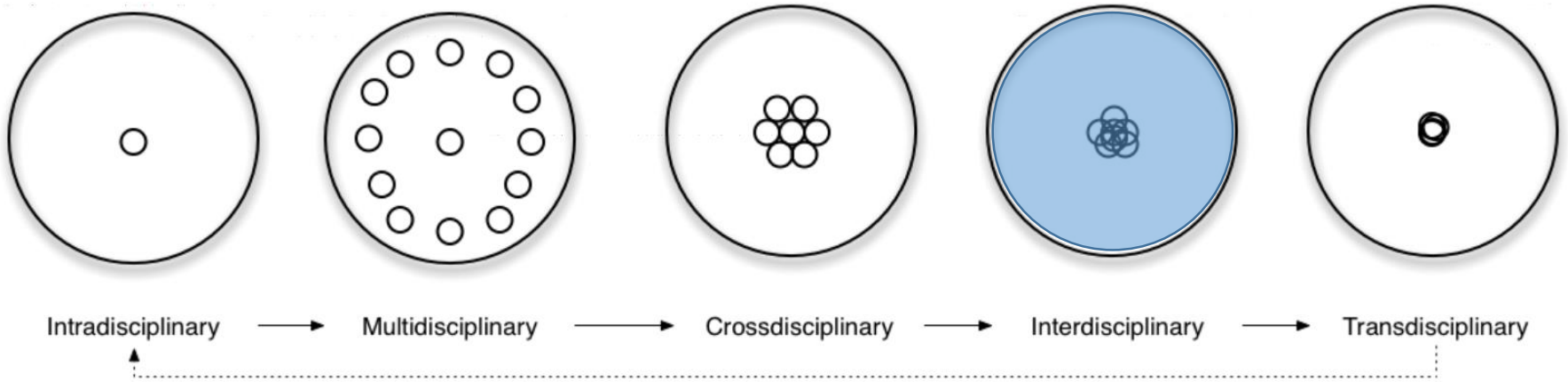
Multidisciplinare: persone di differenti discipline che lavorano insieme, ognuna attingendo alla propria conoscenza disciplinare

Crossdisciplinare: vedere una disciplina dalla prospettiva di un'altra



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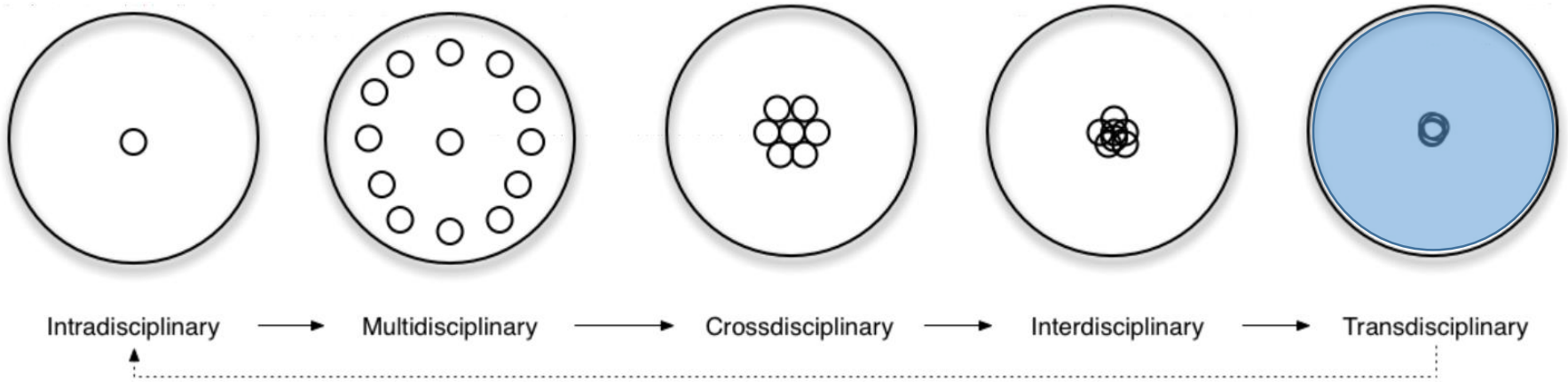
Interdisciplinare: integrazione di conoscenze e metodi di diverse discipline, utilizzando una vera sintesi di approcci



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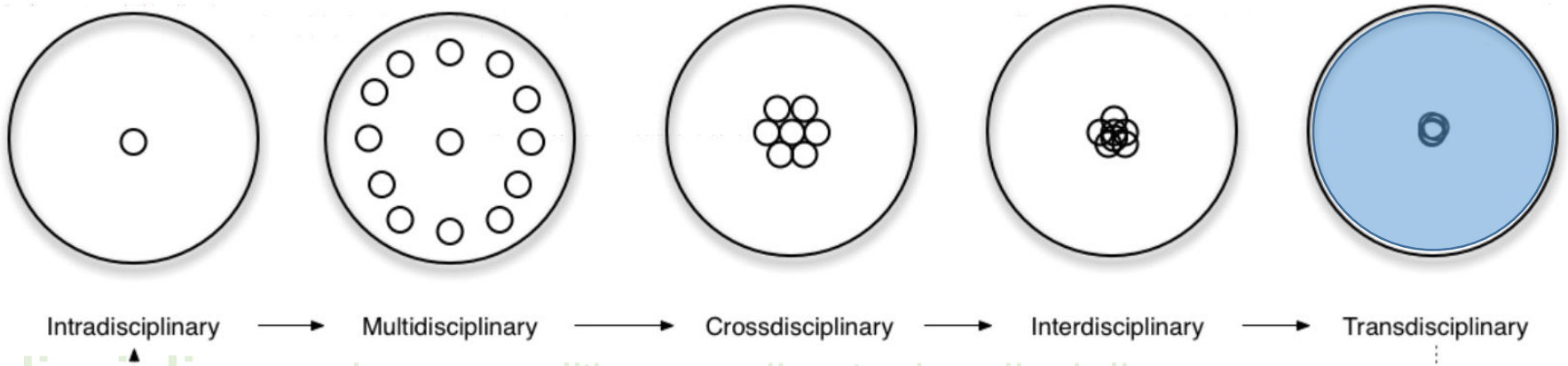
Transdisciplinare: creare un'unità di quadri intellettuali al di là delle prospettive disciplinari



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Interdisciplinare: integrazione di conoscenze e metodi di diverse discipline,

utilizzando una vera sintesi di approcci

Transdisciplinare: creare un'unità di quadri intellettuali al di là delle prospettive disciplinari

Approccio interdisciplinare

Educazione del paziente

Self-management

Area farmacologica

Area non farmacologica

farmaci

riabilitazione

Approccio psicologico

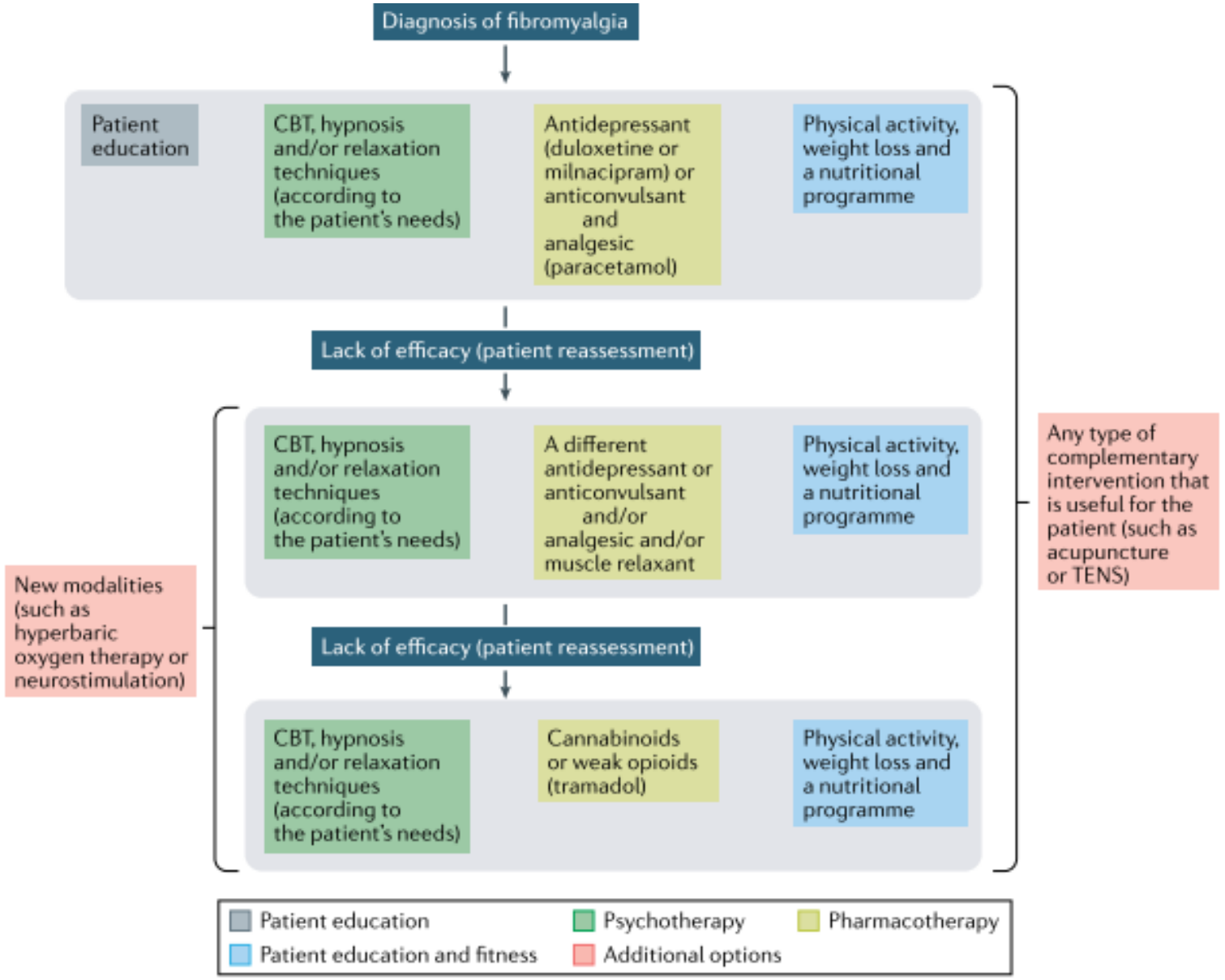
Terapie complementari e alternative

6. Di quali competenze ritieni di non poter fare a meno?

Approccio interdisciplinare

- Lastly, it is always important to state that managing FMS is about more than just pharmacological therapy
- As many patients and physicians have come to understand (and as reflected in the current guidelines) treating FMS will most probably continue to strive to combine pharmacotherapy with many nonpharmacological tools, ranging from exercise to neurofeedback and all that lie in between
- **Thus is the art of treating FMS**.

Tzadok R, Ablin JN. Current and Emerging Pharmacotherapy for Fibromyalgia. Pain Res Manag. 2020 Feb 11;2020:6541798.



Sarzi-Puttini, P., Giorgi, V., Marotto, D. *et al. Nat Rev Rheumatol* **16,** 645–660 (2020).

Non-pharmacological interventions, Patient reported outcomes, Fibromyalgia

PHARMAKON OR THE ART THAT HEALS: TRANS-DISCIPLINARY ARTISTIC-TRANSFORMATIVE WORKSHOPS FOR FIBROMYALGIA SYNDROME

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Background:

Fibromyalgia syndrome (FMS) is a widespread chronic pain syndrome with many associated symptoms. It is frequently related to a traumatic event (1), strong and of short duration, or slight but protracted over time. A multidisciplinary therapeutic approach is recommended by international guidelines. The transformative experience (TE) allows for a profound and immediate change that differs from linear and gradual psychological change; this helps create novel responses to the same initial thoughts and actions, thereby breaking the maladaptive emotional/behavioral loop elicited by chronic stress and trauma (2), creating a sort of "virtuous" cycle, adaptive rather than maladaptive and long-lasting. In this study, TE was specifically elicited through transformative art (TA), an intrinsically transdisciplinary tool, in different ways in the three arms of the study.

Objectives:

Validation of the efficacy (in terms of quality of life and sleep, self-esteem, self-efficacy) of transdisciplinary artistic-transformative pathways in patients with FMS.

Methods:

Prospective observational study lasting 8 months (February-October, 2021), in which the effectiveness of three different TA workshops in patients with FMS was evaluated: in group 1 participants were encouraged to review their autobiography and illness in a humorous sense; in group 2 participants were guided to express their own realities of chronically ill patients in poetry; group 3 was based on the guided narration of works of art according to visual thinking strategies integrated with the principles of narrative medicine. Patients were divided into the three laboratories according to their preference. Tests were administered at baseline and post-workshop. The activities took place entirely online.

Results:

109 FM patients completed the study (n=3 males, mean age 52.9, mean years from diagnosis 11.2 [SD 8.6]). No differences were found among the three groups at baseline in terms of clinimetric variables. Data analysis made by a Wlicoxon non-parametric test (WNPT) of the three groups in conjunction showed a statistically significant improvement of the Pittsburgh Sleep Quality Index (PSQI) ($p<0.05$), Response to Stressful Experiences Scale (RSES) ($p<0.05$), World Health Organization-Five Well-Being Index (WHO-5) ($p<0.001$) and Global Health scale (GH) ($p<0.05$). No significant difference was found for The Mindful Attention Awareness Scale (MAAS) ($p=0.2663$). A WPNT was performed to compare baseline and final results of the three groups separately. The best performance was seen in Group 1, since patients ameliorated in almost all parameters: PSQI ($p<0.05$), GH ($p<0.05$), SAP dimension 1 ($p<0.05$), 2 ($p<0.05$) and 4 ($p<0.05$), WHO-5 ($p=0.0013$). MAAS ($p=0.895$), RSES ($p=0.0673$) and SAP dimension 3 ($p=0.0573$) resulted nonsignificant, although very close to significance. Sleep ($p<0.05$) and the 3rd dimension of SAP ($p<0.05$) improved in patients of Group 2; whilst self-esteem ($p<0.05$) and WHO-5 ($p<0.05$) did in Group 3.

Conclusion:

Our research shows that art, experienced as TA, leads to significant improvements of the psychophysical condition of FMS patients. TA can be seen as a crucial mediator for overcoming the trauma/stressors, probably through the generation of "pivotal mental states" (PIMS), defined as a "hyper-plastic state aiding rapid and deep learning that can mediate psychological transformation" (3).

References:

1. Miró, E., Martínez, M.P., Sánchez, A.I. and Cáliz, R. (2020), Clinical Manifestations of Trauma Exposure in Fibromyalgia: The Role of Anxiety in the Association Between Posttraumatic Stress Symptoms and Fibromyalgia Status. JOURNAL OF TRAUMATIC STRESS, 33: 1082-1092
2. Christopher M. (2004) A broader view of trauma: A biopsychosocial-evolutionary view of the role of the traumatic stress response in the emergence of pathology and/or growth. Clinical Psychology Review; 24(1):75-98.
3. Brouwer, Ari, and Robin Lester Carhart-Harris. "Pivotal mental states." Journal of Psychopharmacology 35.4 (2021): 319-352.

Technician and specialist specific support

They will support the patient in any aspect of his or her disease

- ***Nurse***
- ***Psychiatrist, psychologist***
- ***Physiatrist, physical terapist***
- ***Integrative medicine specialist***
- ***Nutritionist***
- ***Patients associations***

Nursing care

- **The "case manager" nurse** is the professional figure able to guarantee the organization and management of these paths.
- An expert, adequately trained nurse as well as being a powerful ally of rheumatic patients is a valuable and indispensable collaborator of the specialist, can carry out numerous activities - such as **clinimetric evaluation, counseling and patient education.**
- Of no less importance is the organization of the care path, i.e., **managing of appointments, helping in achieving compliance with drug administration, updating of clinical documentation and planning of hospitalization and related workloads.**
- In addition, the nurse can organize, in collaboration with the specialist, the activities that may become necessary if **adverse events** appear or if risky situations are present during treatment with different drugs.

Associazione Italiana Sindrome Fibromialgica · Odv

Italian Association Fibromyalgia Syndrome-Odv (voluntary organization)

Supplement Clin Exp Rheumatol
March 2015

Working with patients association

- Continuous education
- Self-help group
- Volonteering

a) Special relaxing tecnicques
b) Feldenkreist
c) Tai-Chi
d) Yoga
e) Meditation
f) Nordic walking

Associazione Italiana Sindrome Fibromialgica - Onlus

Mass-media education

Friends or foes of the patients affected by fibromyalgia syndrome

Evidence-based vs fake-based treatment proposal

Self-help groups,, efficient sections , educated health care personnel

EULAR revised recommendations for the management of fibromyalgia

G J Macfarlane,[1] C Kronisch,[1,2] L E Dean,[1] F Atzeni,[3] W Häuser,[4,5] E Fluß,[1] E Choy,[6] E Kosek,[7] K Amris,[8] J Branco,[9] F Dincer,[10] P Leino-Arjas,[11] K Longley,[12] G M McCarthy,[13] S Makri,[14] S Perrot,[15] P Sarzi-Puttini,[16] A Taylor,[17] G T Jones[1]

A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non- pharmacological management for fibromyalgia.

A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning.

The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Working group members

Macfarlane GJ, et al. Ann Rheum Dis. 2017 Feb;76(2):318-328.

Management recommendations flowchart

History and physical exam

↓

Diagnosis of fibromyalgia → If needed to exclude treatable comorbidities:
Laboratory and/or radiological exams
Referral to other specialists

↓

Patient education and information sheet

if insufficient effect

↓

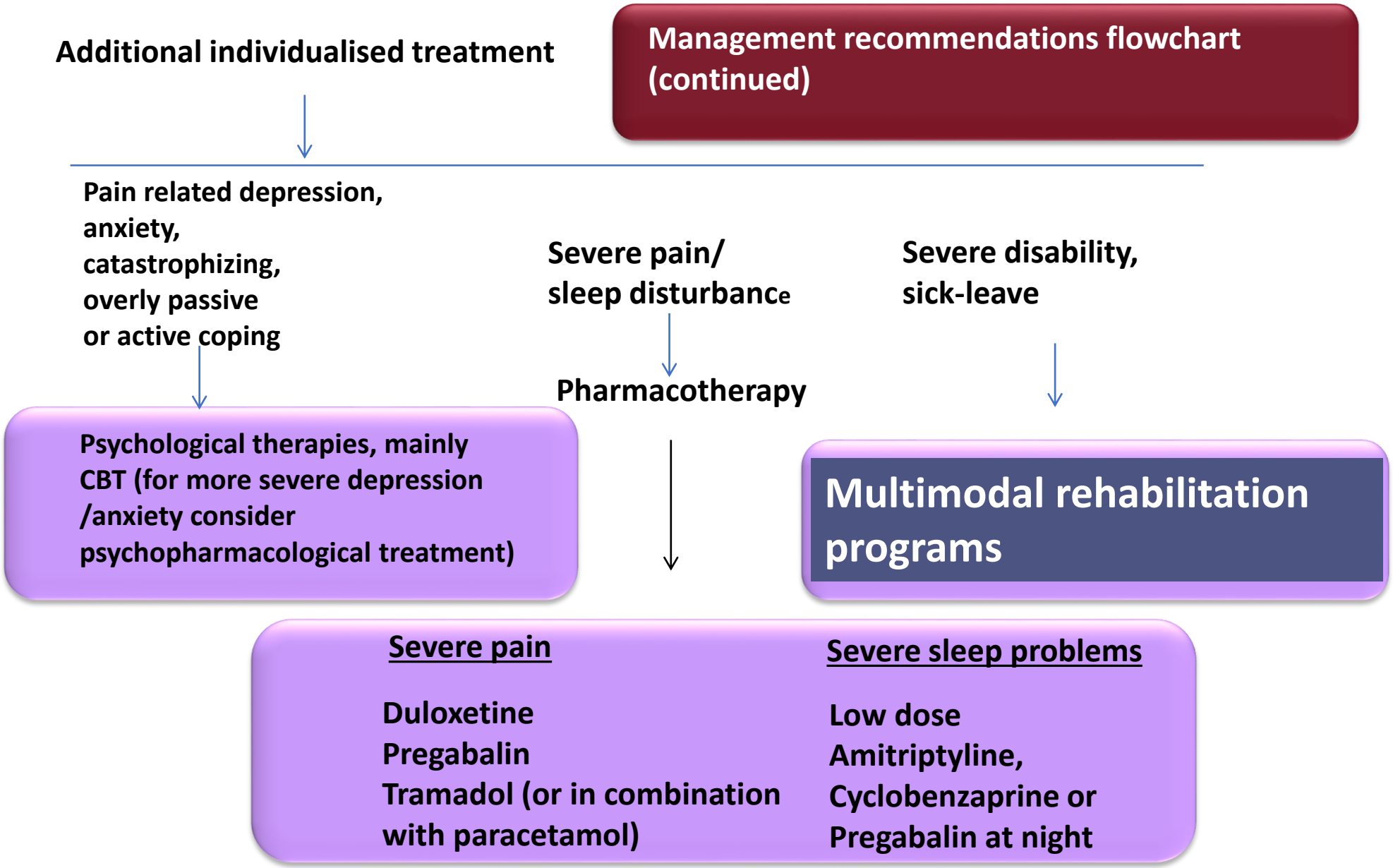
Physical therapy with individualised graded physical exercise
(can be combined with other non-pharmcological therapies
recommended such as hydrotherapy, acupuncture)

if insufficient effect

↓

Reassessment of patient to tailor individualised treatment

Macfarlane, G. J. et al. EULAR revised recommendations for the management of fibromyalgia. Ann. Rheum. Dis. 76, 318–328 (2017).



Macfarlane, G. J. et al. EULAR revised recommendations for the management of fibromyalgia. Ann. Rheum. Dis. 76, 318–328 (2017).

Management recommendations flowchart (continued)

Additional individualised treatment

Pain related depression, anxiety, catastrophizing, overly passive or active coping

→ **Psychological therapies, mainly CBT (for more severe depression /anxiety consider psychopharmacological treatment)**

Severe pain/ sleep disturbance

→ **Pharmacotherapy**

Severe disability, sick-leave

→ **Multimodal rehabilitation programs**

Severe pain

- Duloxetine
- Pregabalin
- Tramadol (or in combination with paracetamol)

Severe sleep problems

- Low dose Amitriptyline, Cyclobenzaprine or Pregabalin at night

Are there effective treatments for FM?

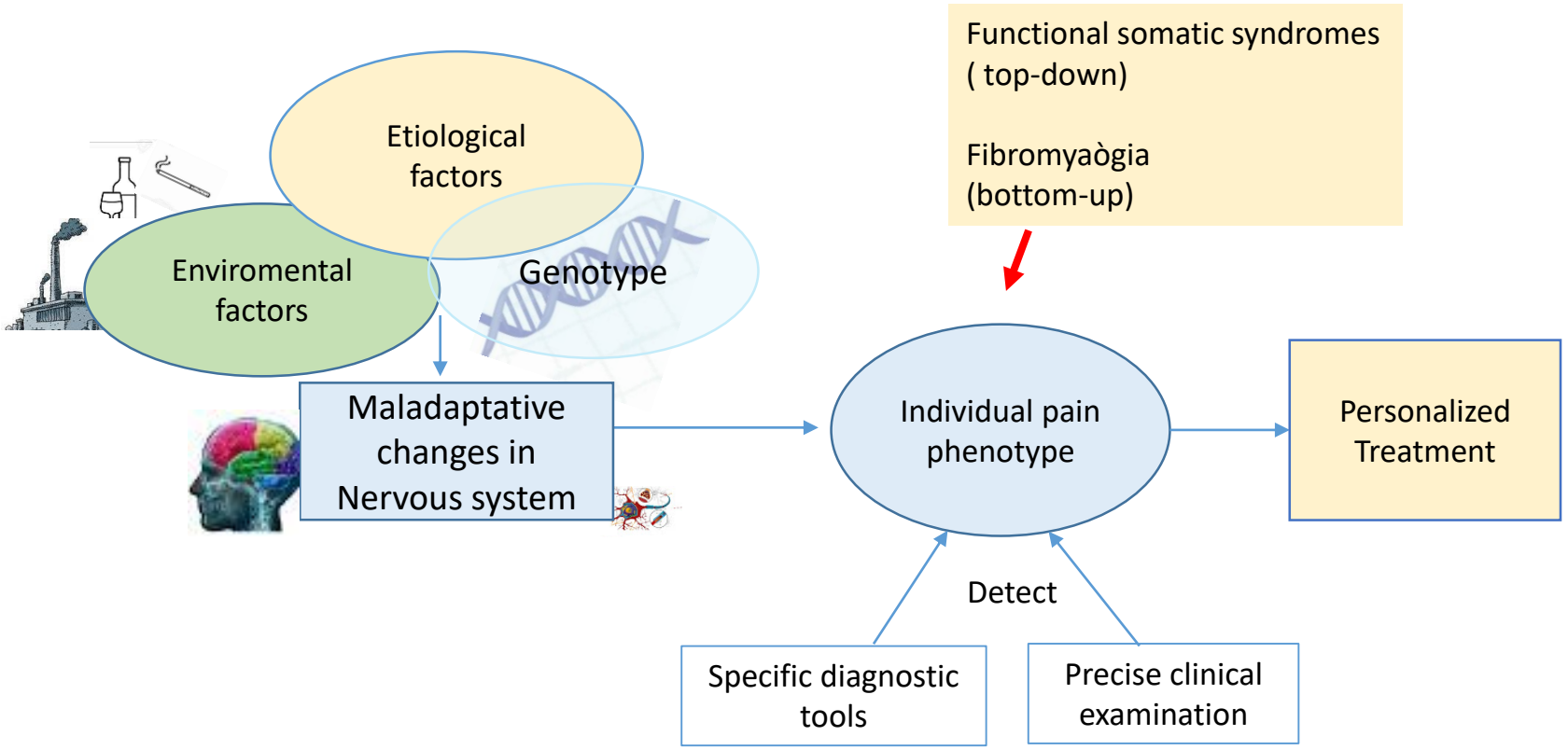
Management strategies for FM fall short of the mark:

- no recommended ideal health care setting,
- no universally accepted treatment algorithm or gold standard,
- uncerteinties of suggested duration of treatments.

1. The concept of **intensive treatments or tight control** is at this time outside the scope of this dialogue.
2. Many interventions show statistical significance, but clinically meaningful and **continued effect remains questionable**.

Arthritis Care & Research, 2017; 69:462–466

Future agenda



Individual pain phenotype requires personalized treatment

Modified from von Hehn et al. Neuron. 2012 ; 73(4):638-652

Comparison of APS and EULAR Guidelines for Fibromyalgia - FM Management

	Nonpharmacologic Therapy	Pharmacologic Therapy	Limitations of study Analysis
APS (American Pain Society)	Strong evidence: Patient education CBT Aerobic exercise Multidisciplinary therapy Moderate evidence: Strength training Acupuncture Hypnotherapy Biofeedback Balneotherapy	**Strong evidence**: **Amitriptyline 25-50 mg/d** **Cyclobenzaprine 10-30 mg/d** Moderate evidence: SNRIs (milnacipran, duloxetine; mixed evidence for venlafaxine) SSRI (fluoxetine 20-80 md/d) Tramadol 200-300 mg /d Anticonvulsant (pregabalin 300-450 mg /d)	Heterogeneous treatments in studies Study durations generally short term Some studies unblinded and/or uncontrolled Outcomes measures often exclusively pain without assessment of improvements in patient global, physical function, etc All studies predated FDA approvals of 3 FM pharmacotherapies Some agents listed still lack FDA approval for FM
EULAR (European League Against Rheumatism)	Balnotherapy (Grade B) Individually tailored exercise including aerobic ans strength training (Grade C) CBT (Grade D) Others: relaxation, rehabilitation, physiotherapy, and/or psycologic aupport (Grade C)	Tramadol (Grade B) Analgesics (paracetamol/acetaminophen, weak opioids (Grade D) **Antidepressants (amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindole) (Grade A)** **Tropisetron, pramipexole, pregabalin (Grade A)**	Outcome measures other than pain by visual analog scale and function by FIQ specifically excluded Other limitations similar to those of APS above

Burckhardt CS et al America Pain Society, 2005, Goldenberg DL et al JAMA 2004, Carvile SF et al Ann Rheum Dis 2008, Lyrica prescribing information

The Canadian guideline

- Management of FMS should be **centered in the primary care setting** with knowledgeable healthcare professionals, or augmented by access to a multidisciplinary team or team member to provide support and reassurance
- **Specialist consultation**, including referral to a sleep specialist or psychologist could be required **for selected subjects**
- **Continued care by a specialist was not recommended** and could be reserved for those patients who had failed management in primary care or had more complex comorbidities

M. A. Fitzcharles, P. A. Ste-Marie, D. L. Goldenberg et al., "2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary," Pain Research&Management, vol. 18, no. 3, pp. 119–126, 2013.

The German guideline

- **a treatment approach adapted to the severity of FMS**
- treatment and its coordination should, if possible, be performed by **a doctor who has the necessary knowledge and experience in the treatment of FM**S (e.g., pain medicine, psychosomatic medicine, and rheumatology).

(i)Mild FMS: advice to continue increase physical, mental, and social activities (no specialist care, no recommendation for additional therapies).

(ii) Moderate FMS: aerobic exercise; timely limited psychological (specialist care), and/or drug therapy.

(iii) Severe FMS or moderate FMS without response to therapies mentioned above: day clinic or inpatient multicomponent therapy including psychotherapeutic and/or psychiatric therapy of mental comorbidities.

(iv) Long-term management for all FMS: self-management without drugs.

W. Eich, W. H¨auser, B. Arnold et al., “Fibromyalgia syndrome. general principles and coordination of clinical care and patient education,” Schmerz, vol. 26, no. 3, pp. 268–275, 2012 (German).

Ablin J, et al.Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. Evid Based Complement Alternat Med 2013;2013:485272

The Israeli guideline

- a stepwise treatment approach depending on the response of the patient on first choice treatment options .
- The Israeli guideline did not specify which specialty should treat FMS-patients

Step 1

(i) Education and explanation regarding the essence of the disorder and the principals of treatment.

(ii) Instructions regarding graded aerobic exercise, adjusted to the functional level, and general health level of the patient.

(iii) Referral to hydrotherapy/aquatic exercise.

(iv) Start low dose amitriptyline 10–25 mg at bedtime.

(v) Refer for cognitive-behavioral treatment

J. N. Ablin, H. Amital H, M. Ahrenfeld et al., “Guidelines for the diagnosis and treatment of the fibromyalgia syndrome,” Harefuah, 2013, http://www.ima.org.il/Ima/FormStorage/

Ablin J, et al.Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. Evid Based Complement Alternat Med 2013;2013:485272.

The Israeli guideline

Step 2

Recommendations included in step 2 are based on a reassessment of the fibromyalgia patient's condition, about 12 weeks after initiating treatment.

(i) Treatment with a SNRI medication (duloxetine, milnacipran) instead of amitriptyline or addition of an SSRI medication (e.g., fluoxetine) together with treatment with Amitriptyline.

(ii) Start treatment with pregabalin to improve sleep quality and reduce pain.

(iii) Refer for balneotherapy.

(iv) Add complimentary medicinemodalities: TaiChi and Yoga

J. N. Ablin, H. Amital H, M. Ahrenfeld et al., "Guidelines for the diagnosis and treatment of the fibromyalgia syndrome," Harefuah, 2013, http://www.ima.org.il/Ima/FormStorage/

Ablin J, et al.Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. Evid Based Complement Alternat Med 2013;2013:485272.

Still a long road to run?

- Poorly treated FM has an immediate impact on physical and psychological well-being, with long-term consequences an emerging reality.

Future study should be focused on

- **identifying persons at risk for FM**
- consider **prevention strategies**
- Tailor specific therapies for the patient
- **Create specific FM treatment centers** with the availability of the moltitude of treatments which could be potentially prescribed in a personalized multicomponent strategy
- the availability and costs/reimbursement of treatments must be considered.

Hauser W, Clauw D, Fitzcharles MA. Treat-to-Target Strategy for Fibromyalgia: Opening the Dialogue. Arthritis Care Res 2017; 69: 462-466

Future agenda

Fibromyalgia interdisciplinary treatment centers

- Rheumatologist or pain specialist (diagnosis and pharmacological treatment)
- Fitness evaluation and Exercise program (physical therapist)
- Nutritional problems (dietologist or nutritionist)
- Psycotherapy (psychiatrist and/or psychologist)

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