Ospedale Niguarda

Sistema Socio Sanitario Regione Lombardia

XII EDIZIONE

MALATTIA DOLORE E RETE TERRITORIALE

IL DIRITTO DEL PAZIENTE AD ESSERE CREDUTO

RED

RETE TERAPIA DEL DOLORE - MILANO

FINALE

MILANO 23 › 24 MARZO 2017

AULA MAGNA · OSPEDALE NIGUARDA

Diagnosi e cura farmacologica della sindrome fibromialgica

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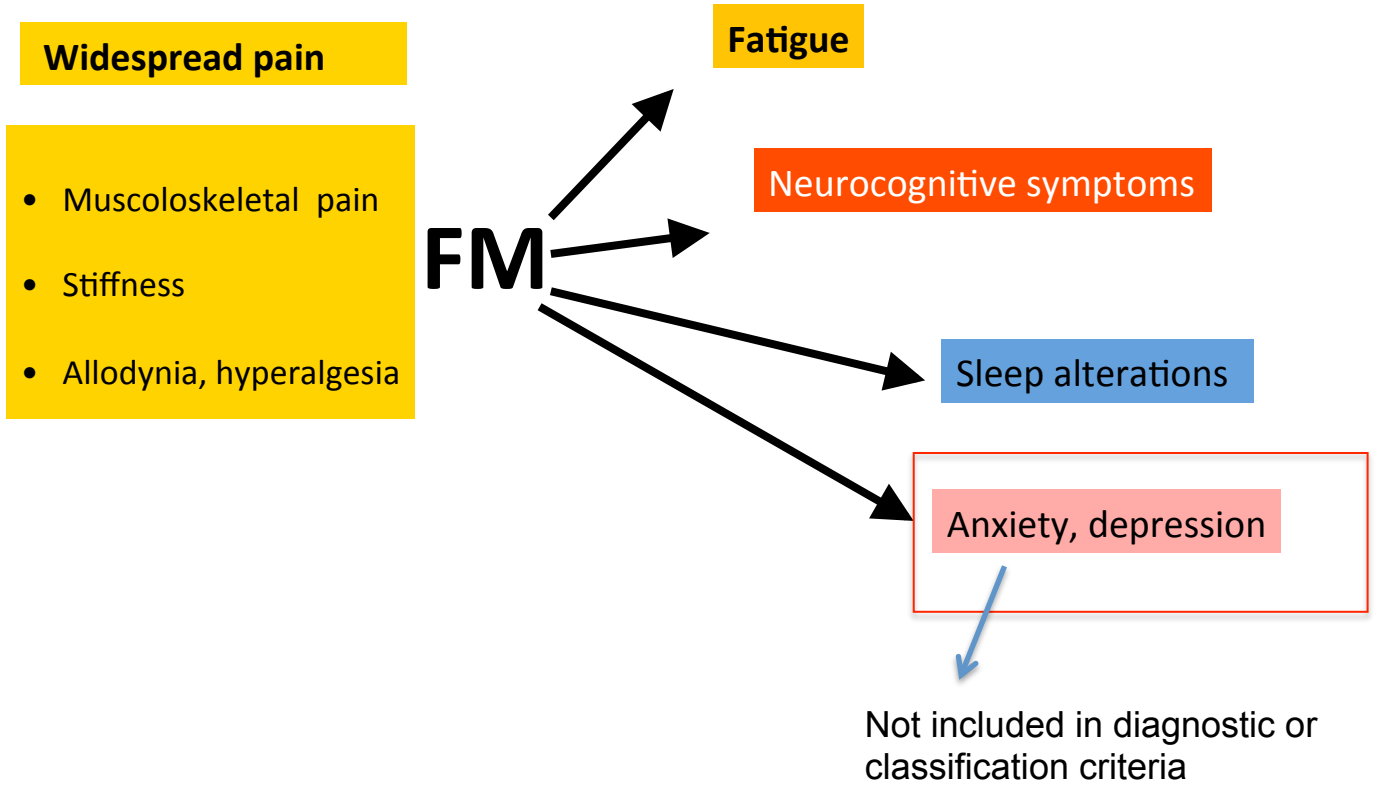
Polo Universitario L. Sacco -Milano

FM is a syndrome characterized by chronic widespread pain associated with a variety of ancillary symptoms



Fibromialgia-background

- è un'entità clinica distinta o piuttosto un complesso spettro di problemi?
- Sovrapposizione tra differenti sindromi e sintomi?
- Variazioni considerevoli in termini di severità e sintomi da paziente a paziente e perciò quadro clinico eterogeneo o omogeneo complessivamente?

Epidemiologia del dolore cronico diffuso e della fibromialgia

- La prevalenza del dolore cronico diffuso nella maggior parte dei paesi industrializzati interessa il 10-11% della popolazione.

  Wolfe F et al J Rheumatol 1995;22:151-156

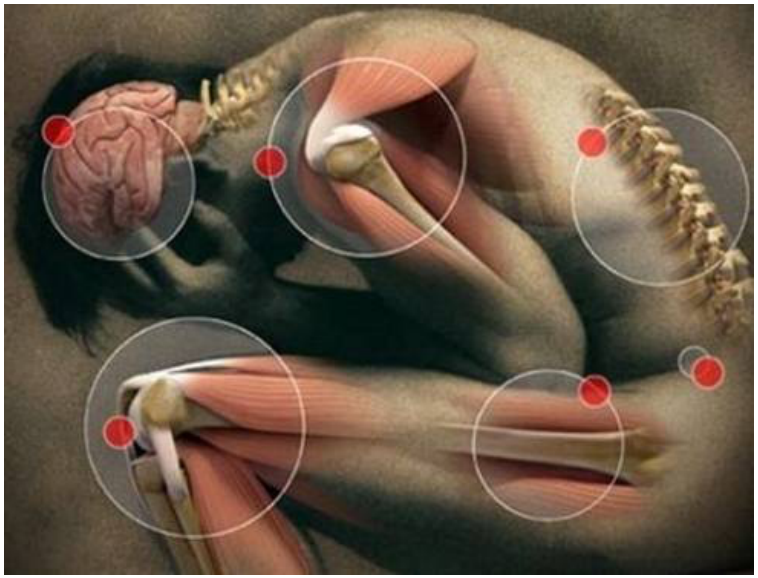
  Croft P et al J Rheumatol 1993;20:710-713

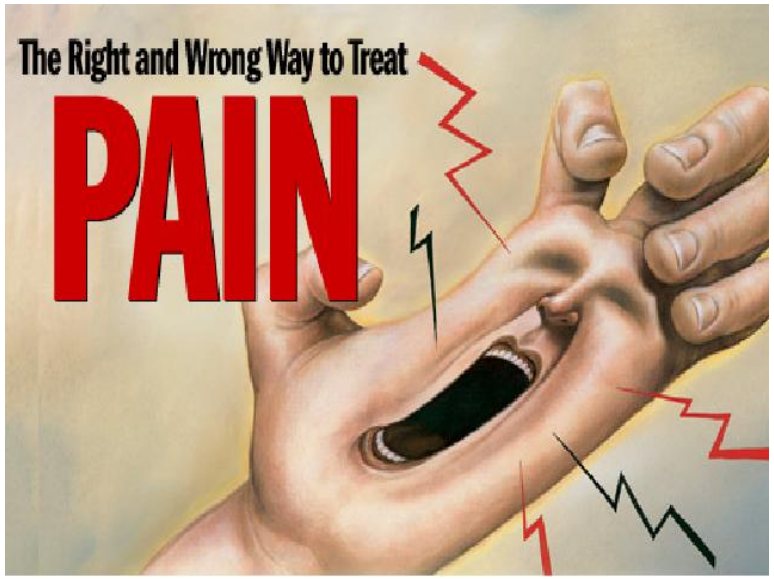
- La prevalenza della Fibromialgia, utilizzando i criteri classificativi ACR 1990 interessa il 2-5% della popolazione

  Wolfe F et al Arthritis Rheum 1995;38:19-28

  Croft P et al Br Med J 1994;309:696-699

Why are so important diagnostic/classification criteria in chronic widespread pain ?





Chronic widespread pain – fibromyalgia

- A need of uniform classification and to weigh the variety of symptoms

- A need of fully understsnd the etio-pathogenetic mechanisms

Chronic widespread pain—the need for a standard definition

Stephen Butler[a,b,c,*], Tormod Landmark[d], Mari Glette[a], Petter Borchgrevink[a,d], Astrid Woodhouse[d,e]

A PubMed search up to January 2015 revealed 1527 citations using the search words "chronic,widespread, pain." All 1527 abstracts (and full texts when needed) were reviewed to verify if CWP was indeed the subject of the articles.

Critical sorting identified 735 articles, which actually used the term "chronic widespread pain" spanning the years 1986 to 2014.

The full text of the most recent 100 articles published up to 2015 describing studies on CWP was read to evaluate the status of current research on CWP and FMS.

Articles on CWP	Definition
22 articles	No definition of CWP
47 articles	ACR 1990 definiton but not clearly interpreted
10 articles	ACR 1990 criteria used
15 articles	New ACR 2010 criteria
4 articles	ACR 1990 + ACR 2010
2 articles	ICD-10 definiton

Pain 157 (2016) 541–543

Chronic widespread pain—the need for a standard definition

Stephen Butler[a,b,c,*], Tormod Landmark[d], Mari Glette[a], Petter Borchgrevink[a,d], Astrid Woodhouse[d,e]

The effect of definition on prevalence

Prevalence of chronic widespread pain according to different criteria.

Variable	Total N = 6409 (%)
Two or more quadrants* and axial skeletal pain†	584 (9.1)
Three or more quadrants and axial pain	534 (8.3)
Four quadrants and axial pain	312 (4.9)

* Presence of pain in 2 or more quadrants where the quadrants are both upper and lower and bilateral. Pain must have been present for at least 6 months.

† Axial skeletal pain: pain in cervical spine or anterior chest or thoracic spine or low back.

Pain 157 (2016) 541–543

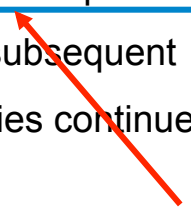
Chronic widespread pain—the need for a standard definition

Stephen Butler[a,b,c,*], Tormod Landmark[d], Mari Glette[a], Petter Borchgrevink[a,d], Astrid Woodhouse[d,e]

The effect of definition on prevalence

There are multiple studies linking both CWP and FMS to other parameters such as **depression, quality of life, activity levels, sleep**, etc. Interpreting the clinical, social, and health economic significance of FMS is very dependent on a clear definition for CWP as used to diagnose FMS.

This could become less of a problem using the new ACR criteria for the diagnosis of FMS from 2010 and their subsequent modification or using the London criteria but most currently published studies continue to use the ACR 1990 definition



or more than a problem ?

Pain 157 (2016) 541–543

Best Practice & Research Clinical Rheumatology xxx (2011) 1–2

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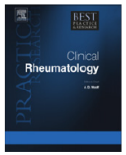
Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh



Preface

Chronic widespread pain or fibromyalgia? That is the question

Piercarlo Sarzi-Puttini [a,*], Fabiola Atzeni [a,b], Philip Mease [c,d]

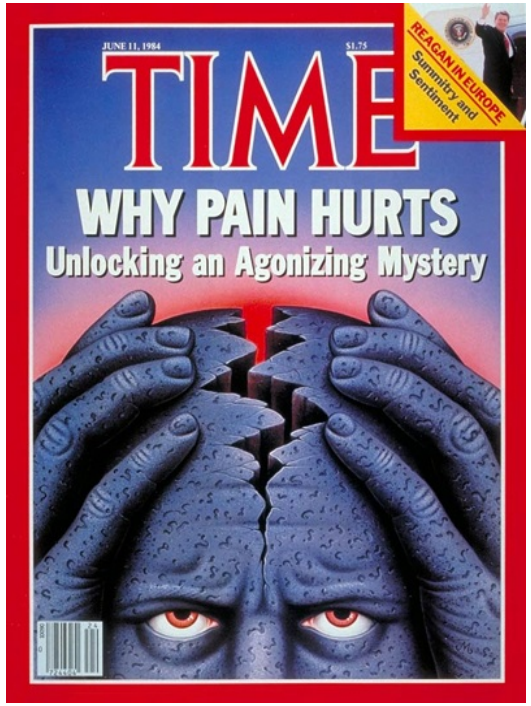
[a] Rheumatology Unit, L. Sacco University Hospital, 20127 Milan, Italy
[b] Centre for Experimental Medicine & Rheumatology, William Harvey Research Institute, Barts and the London School of Medicine & Dentistry, London, UK
[c] Rheumatology Research, Swedish Medical Center, Swede
[d] University of Washington School of Medicine, Seattle, WA, USA

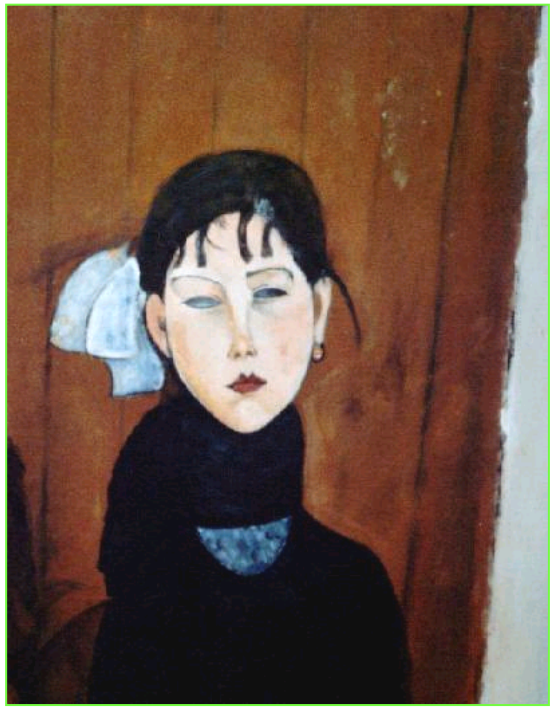
What should these different types of pain syndrome be called?

- **Topographical definition can be used if the pain is localised,**
- **CWP if the pain is regional or diffuse but there are few ancillary symptoms,**
- **the term FM can be used if there are many ancillary symptoms.**

- **This is the type of terminology we have for now**, until there are better and perhaps more objective measures, such as neuroimaging techniques, to characterise chronic pain patients.

How to diagnose chronic pain syndromes?





Caratterizzazione meccanicista del dolore

Periferico (nocicettivo)	Periferico Neuropatico	Centrale neuropatico o Dolore "centralizzato"

▪ Infiammazione o danno meccanico nei tessuti
▪ Responsivo ai FANS e agli oppioidi
▪ Responde alle terapie specifiche
▪ Esempi classici
  ▪ Osteoartrosi
  ▪ Artrite reumatoide
  ▪ Dolore da cancro
	▪ Danno o disfunzione del nervi periferici
	▪ Risponde sia alle terapie farmacologiche che agiscono perifericamente che a livello del sistema nervoso centrale
	▪ Esempi classici
	  ▪ Dolore da neuropatia diabetica
	  ▪ Nevralgia post-erpetica
		▪ Caratterizzato da un disturbo centrale nella processazione del dolore (diffusa iperalgesia/allodinia)
		▪ Responsivo alle molecole neuroattive che modifichino la concentrazione dei neurotrasmettitori coinvolti nella trasmissione del dolore
		▪ Esempi classici
		  ▪ Fibromialgia
		  ▪ Colon irritabile
		  ▪ Disfunzione temporomandibolare
		  ▪ Cefalea muscolo-tensiva

ACTTION-APS Pain Taxonomy (AAPT) for Chronic Pain

Peripheral nervous system	Complex regional pain syndrome Painful peripheral neuropathies associated with diabetes, impaired glucose tolerance, and human immunodeficiency virus Postherpetic neuralgia Posttraumatic neuropathic pain, including chronic pain after surgery Trigeminal neuralgia
Central nervous system	Pain associated with multiple sclerosis Poststroke pain Spinal cord injury pain
Spine pain	Chronic axial musculoskeletal low back pain Chronic lumbosacral radiculopathy
Musculoskeletal pain	Fibromyalgia and chronic myofascial and widespread pain Gout Osteoarthritis Rheumatoid arthritis Spondyloarthropathies
Orofacial and head pain	Headache disorders (see International Classification of Headache Disorders) Temporomandibular disorders
Abdominal, pelvic, and urogenital pain	Interstitial cystitis Irritable bowel syndrome Vulvodynia
Disease-associated pain conditions not classified elsewhere	Pain associated with cancer: cancer-induced bone pain, chemotherapy-induced peripheral neuropathy, and pancreatic cancer pain Pain associated with sickle cell disease

The Journal of Pain, Vol 17, No 9 (September), Suppl. 2, 2016: pp T1-T9

ICD (International Classification of Diseases)-10 Version: 2016

Other soft tissue disorders (M70-M79)

M79.7 Fibromyalgia

- Fibromyositis
- Fibrositis
- Myofibrositis

PAIN

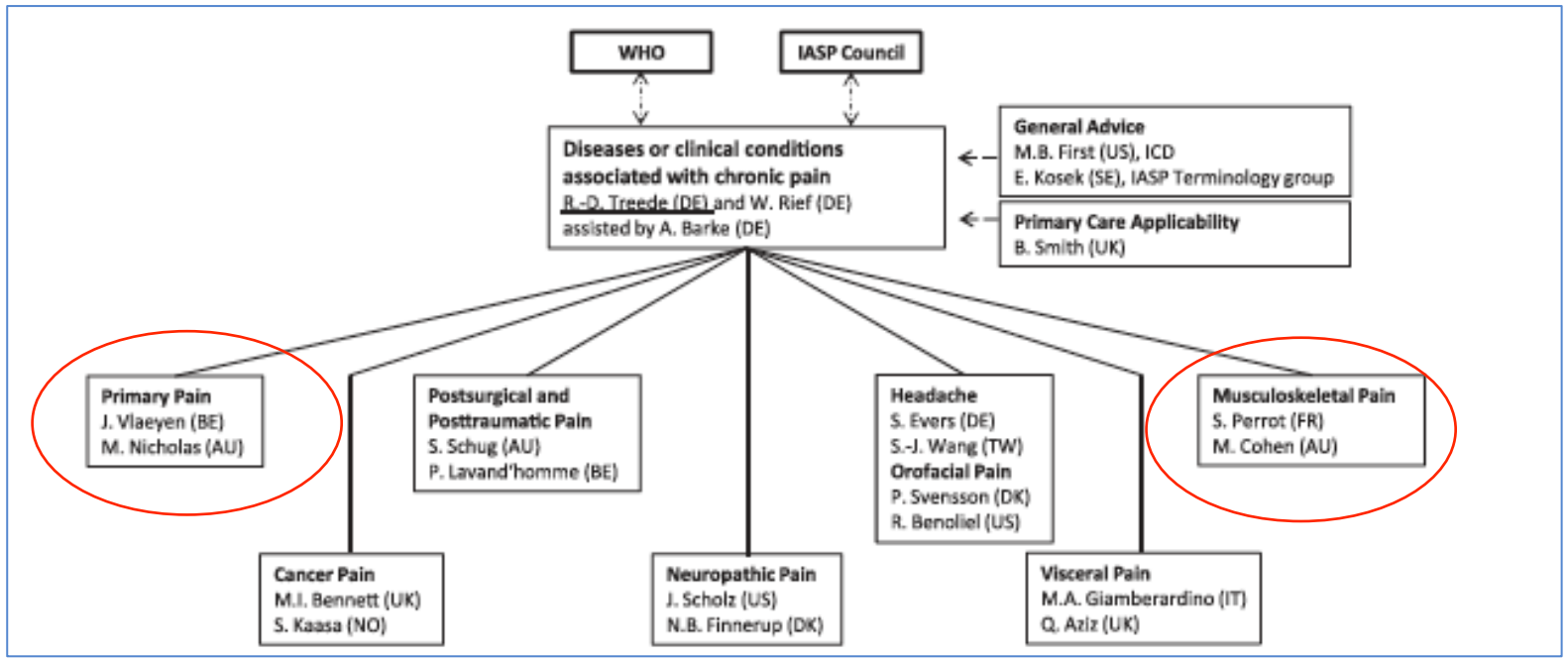
OPEN

A classification of chronic pain for *ICD-11*

Rolf-Detlef Treede[a], Winfried Rief[b], Antonia Barke[b,*], Qasim Aziz[c], Michael I. Bennett[d], Rafael Benoliel[e], Milton Cohen[f], Stefan Evers[g], Nanna B. Finnerup[h], Michael B. First[i], Maria Adele Giamberardino[j], Stein Kaasa[k], Eva Kosek[l], Patricia Lavand'homme[m], Michael Nicholas[n], Serge Perrot[o], Joachim Scholz[p], Stephan Schug[q], Blair H. Smith[r], Peter Svensson[s,t], Johan W.S. Vlaeyen[u,v], Shuu-Jiun Wang[w]

The IASP Task Force, has developed a new and pragmatic **classification of chronic pain for the upcoming 11th revision of the ICD**.

The goal is to **create a classification system** that is applicable in primary care and in clinical settings for specialized pain management.



Treede RD et al. 2015; 156 :1003–1007

Chronic pain

- Chronic pain (persistent or recurrent pain lasting longer than 3 months)

1. **Chronic primary pain**

- 1.1. Widespread chronic primary pain (including fibromyalgia syndrome)
- 1.2. Localized chronic primary pain (including nonspecific back pain, chronic pelvic pain)
- 1.x. Other chronic primary pain
- 1.z. Chronic primary pain not otherwise specified

7. **Chronic musculoskeletal pain**

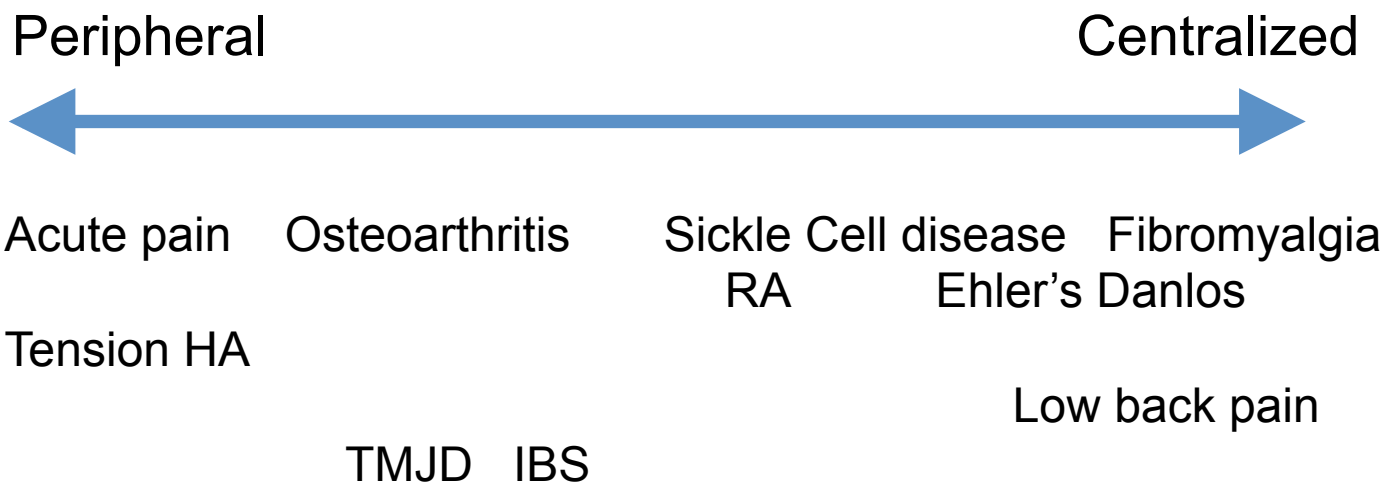
- 7.1. Chronic musculoskeletal pain from persistent inflammation
- 7.2. Chronic musculoskeletal pain from structural osteoarticular changes

Treede RD et al. 2015; 156 :1003–1007

Do causal and pathogenetic hypothesis influence classification/diagnostic criteria?

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain



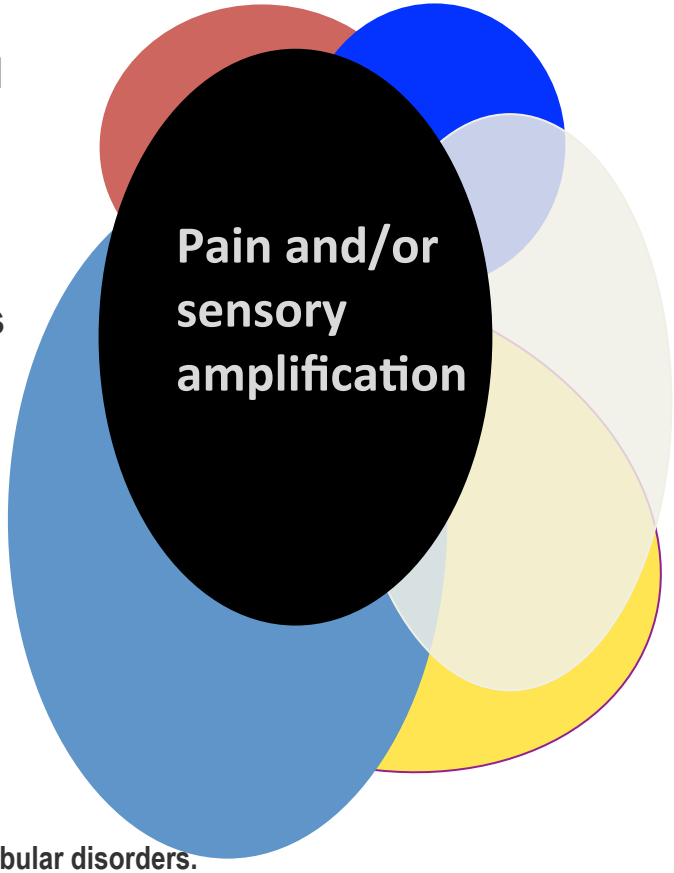
Overlap Between Systemic Syndromes

Chronic Fatigue Syndrome (CFS)

- 1% of population
- Fatigue and 4 of 8 "minor criteria"

Fibromyalgia

- 2%-4% of population
- Defined by widespread pain and tenderness



Psychiatric Disorders

- Major depression
- OCD
- Bipolar
- PTSD
- GAD
- Panic attack

Regional Pain Syndromes

- Irritable bowel [IBS]
- Interstitial cystitis/ Painful bladder syndrome
- TMJD
- Idiopathic low back pain
- Tension HA
- Vulvodynia

Somatoform Disorders

- 4% of population
- multiple unexplained symptoms — no "organic" findings

LBP = low back pain; TMD = temporomandibular disorders.
Clauw and Chrousos. *Neuroimmunomodulation*. 1997;4:134-53.

American Pain Society
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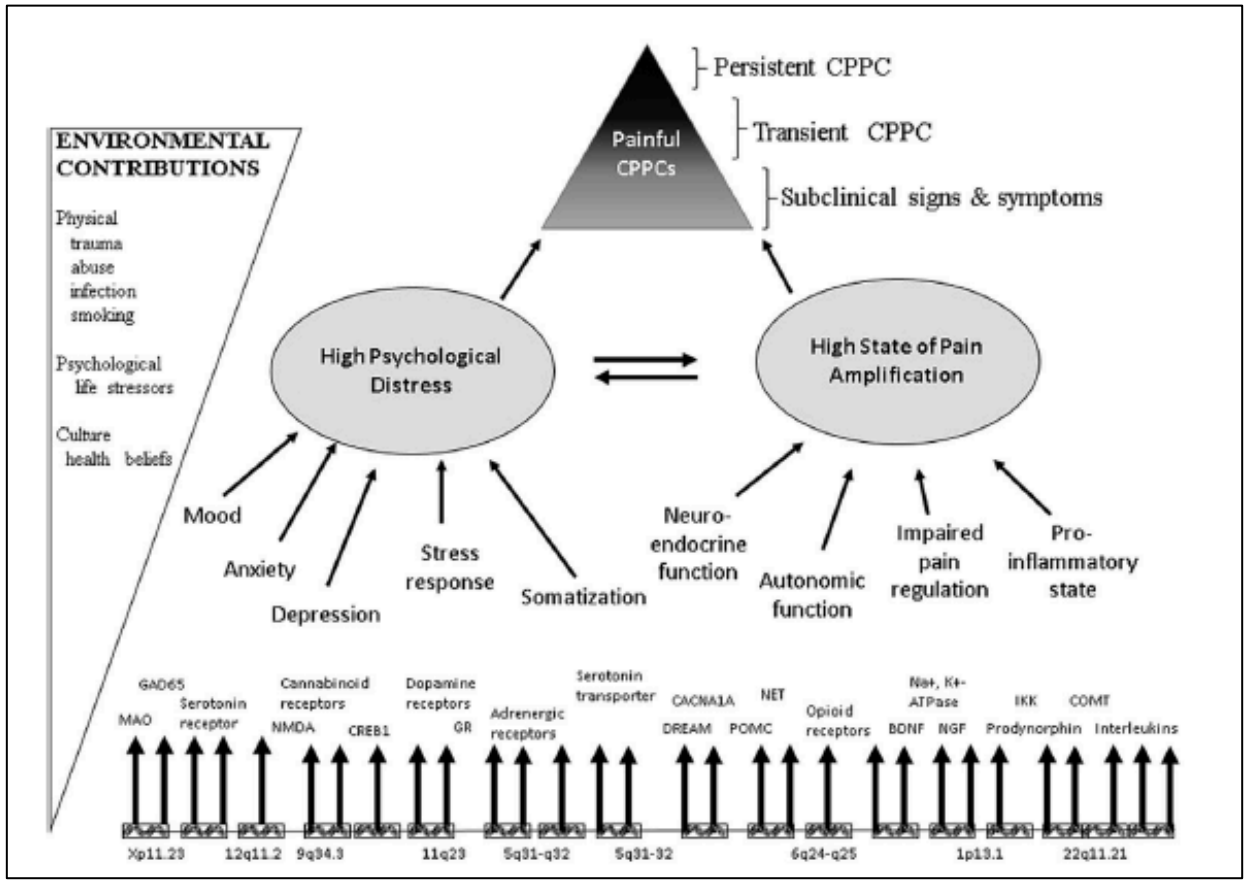
Available online at www.jpain.org and www.sciencedirect.com

Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification

William Maixner,*,† Roger B. Fillingim,† David A. Williams,§ Shad B. Smith,*,† and Gary D. Slade*,¶,‖

Common Chronic Overlapping Conditions

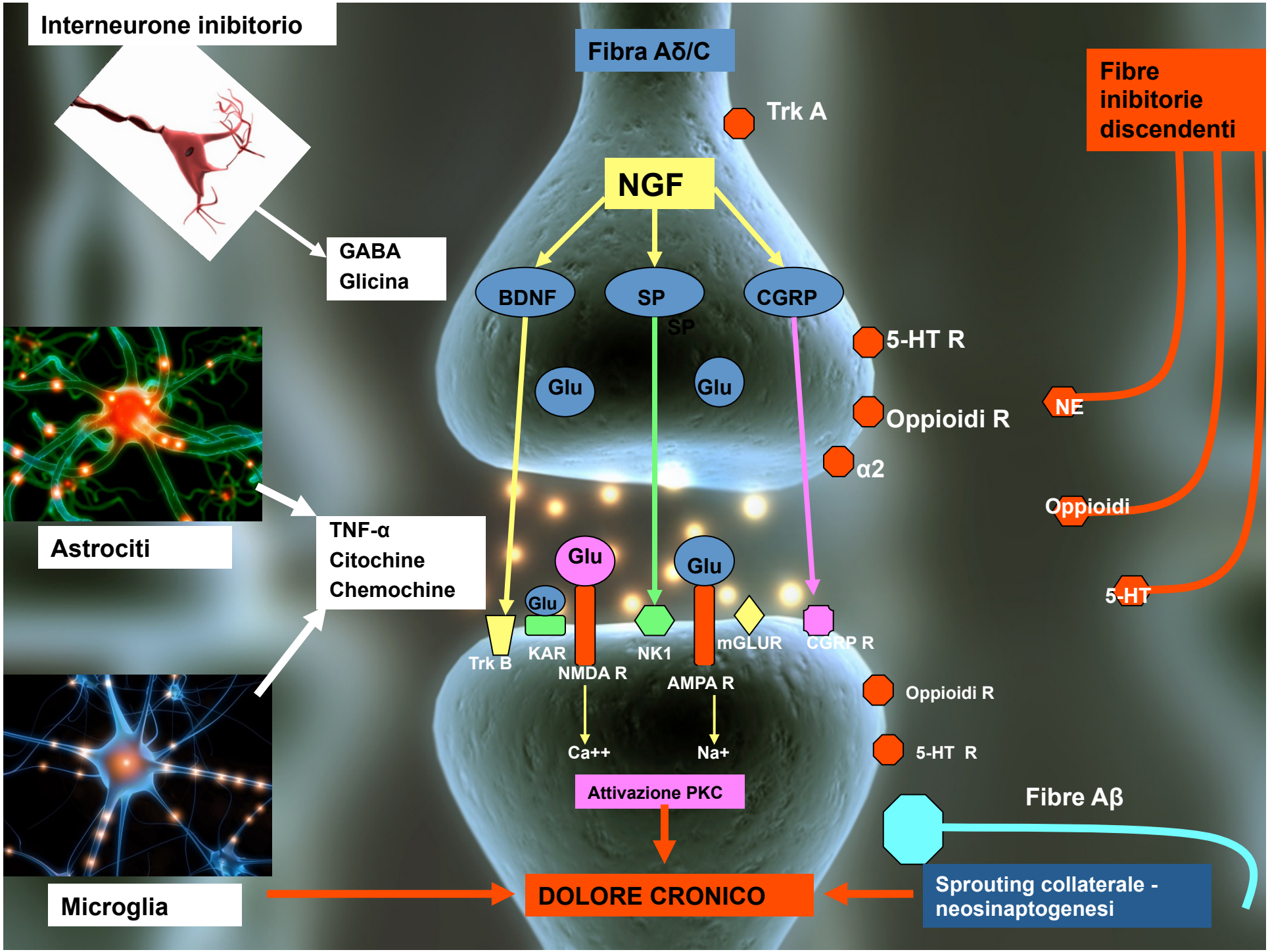


This model depicts likely determinants that contribute to the risk of onset and maintenance of common chronic overlapping pain conditions (COPCs).

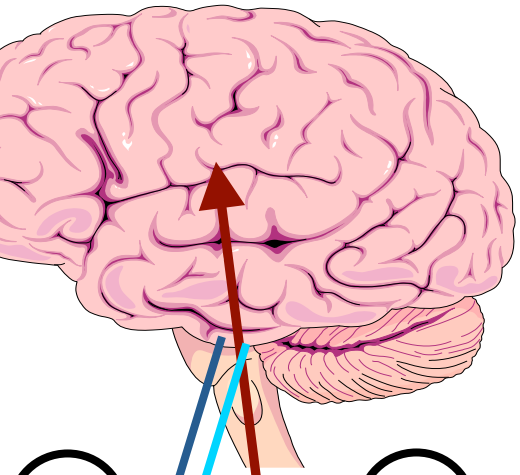
These factors are determined by genetic variability and environmental events that determine an individual's psychological profile and pain amplification status.

CRONICIZZAZIONE DEL DOLORE

1. **Modello biomedico:** modificazioni permanenti delle strutture nervose deputate alla percezione, trasmissione e processazione degli stimoli nocicettivi (PAIN MATRIX)

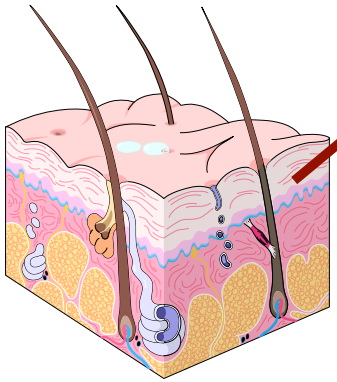

Interneurone inibitorio
GABA
Glicina
Astrociti
TNF-α
Citochine
Chemochine
Microglia
Fibra Aδ/C
Trk A
NGF
BDNF
SP
CGRP
SP
Glu
Glu
5-HT R
Oppioidi R
α2
Fibre inibitorie discendenti
NE
Oppioidi
5-HT
Glu
Glu
Glu
Trk B
KAR
NMDA R
NK1
AMPA R
mGLUR
CGRP R
Oppioidi R
5-HT R
Ca++
Na+
Attivazione PKC
Fibre Aβ
DOLORE CRONICO
Sprouting collaterale - neosinaptogenesi

Likely Mechanism of action of FM pain



Facilitation

- Substance P
  - Decrease SP release in inflammatory states[1]
- Glutamate and EAA
  - Inhibit SP-induced glutamate release[2]



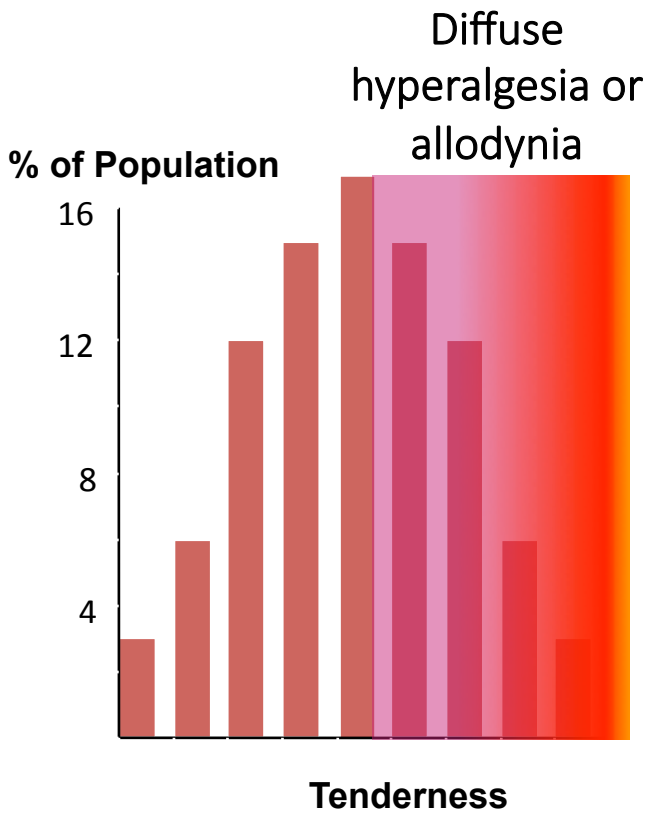
Inhibition

- Descending anti-nociceptive pathways
  - Norepinephrine – serotonin ($5HT1_{a,b}$)
  - Opioids
- GABA
- Cannabinoids
- Adenosine

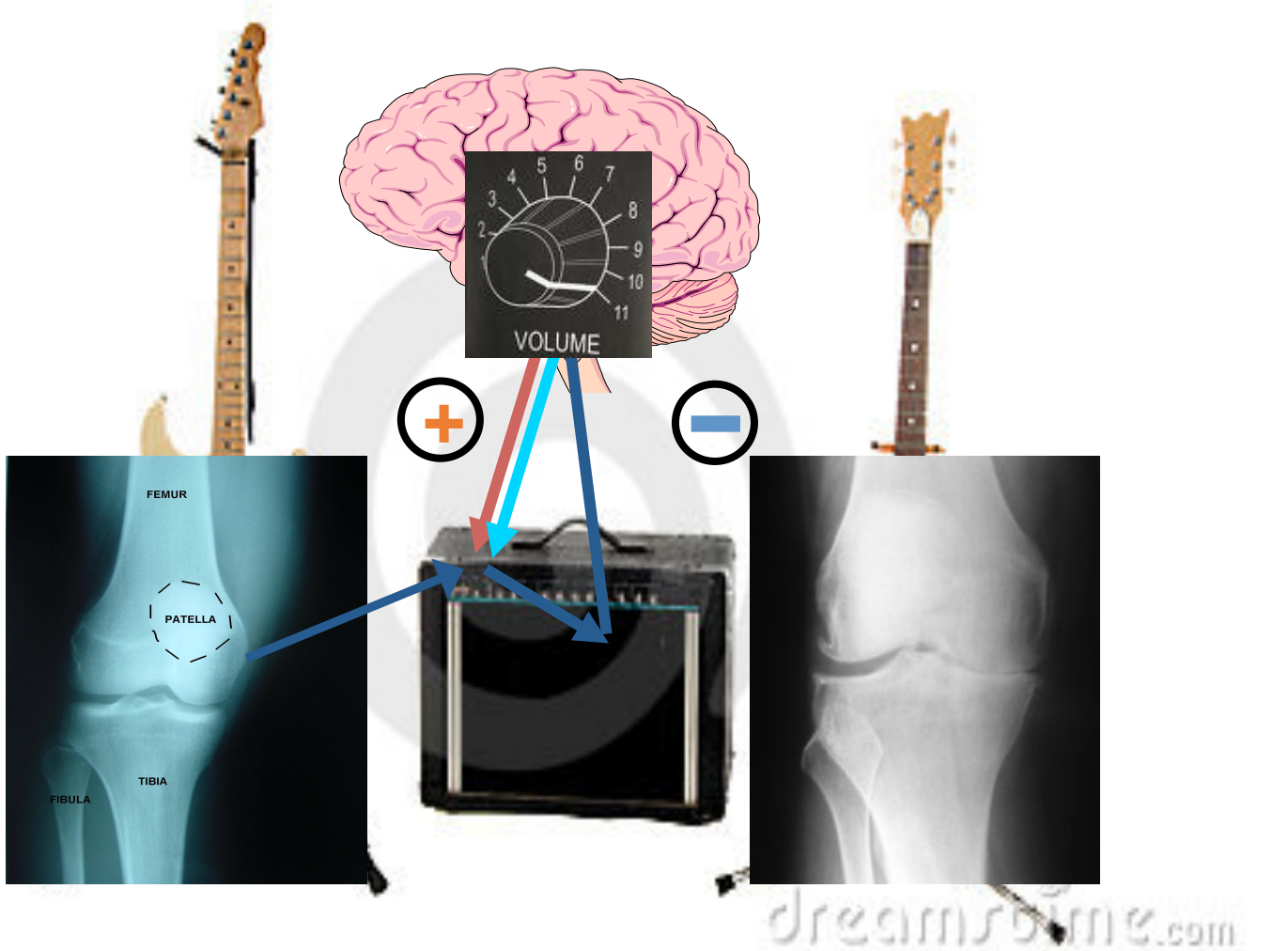
. Fehrenbacher JC, et al. *Pain* 2003;105:133–141.
2. Maneuf YP. *Cell Mol Life Sci* 20031;60:742–750.

Pain and sensory sensitivity in the population

- Like most other physiological processes, we have a "volume control" setting for how our brain and spinal cord processes pain[1]
- This is likely *set* by the genes that we are born with[2-4], and *modified* by neurohormonal factors and neural plasticity
- The higher the volume control setting, the more pain we will experience, irrespective of peripheral nociceptive input



1. Mogil JS. PNAS, 1999;96(14):7744-51. **2.** Amaya et. al. J Neuroscience 2006;26(50): 12852-60. **3.** Tegeder et.al., NatMed. 2006;12(11):1269-77. **4.** Diatchenko et. al. HumMolGenet. 2005;14(1):135-43.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PATELLA
TIBIA
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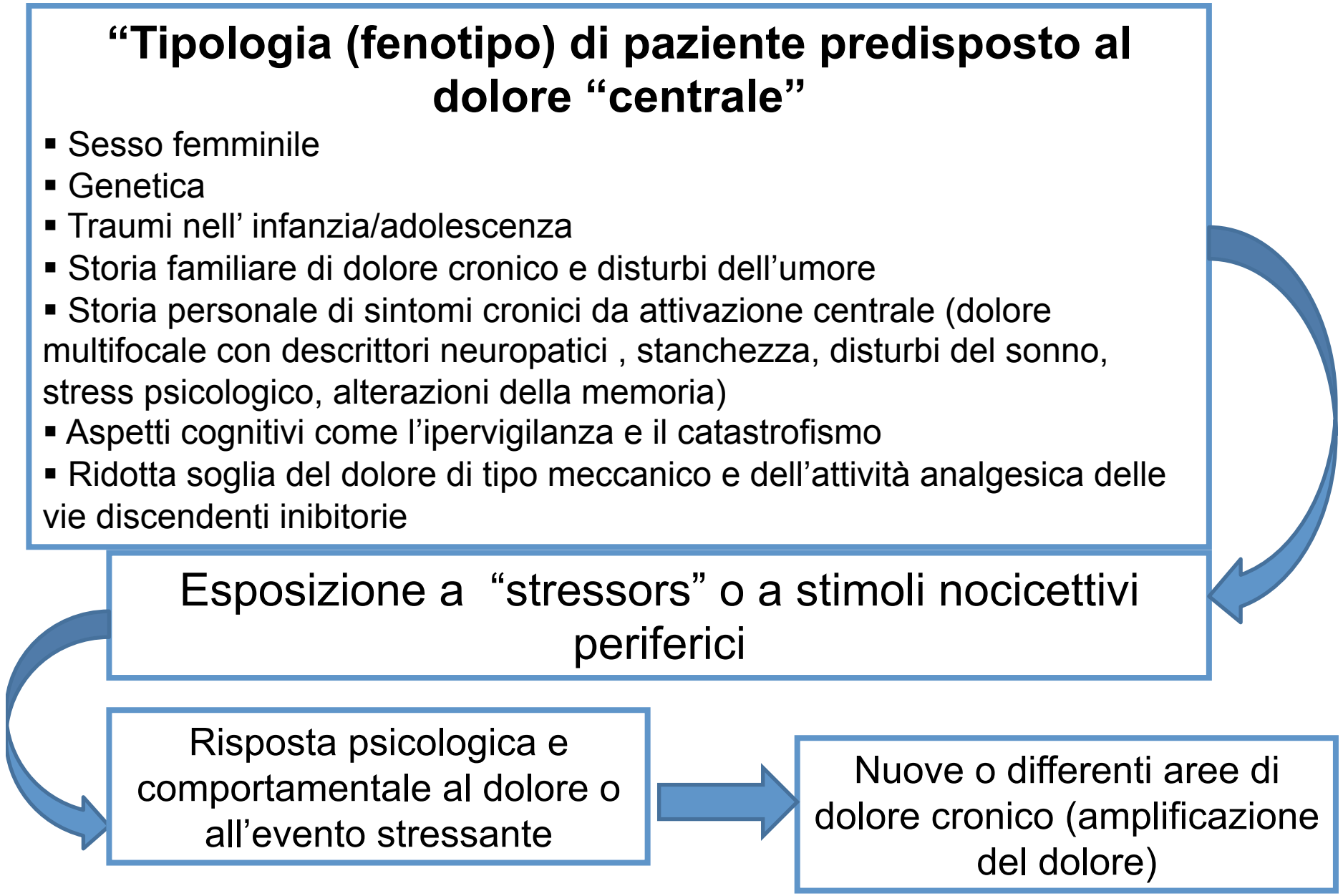
CRONICIZZAZIONE DEL DOLORE

2. **Modello bio-psico-sociale:** interazione tra fattori biologici, psicologici e sociali

Il modello bio-psico-sociale

Considera l'esperienza dolorosa come il risultato dell'interazione tra variabili:

- Biologiche
- Cognitive
- Comportamentali
- Ambientali
- Sociali
- Culturali
- Razziali


"Tipologia (fenotipo) di paziente predisposto al dolore "centrale"
▪ Sesso femminile
▪ Genetica
▪ Traumi nell' infanzia/adolescenza
▪ Storia familiare di dolore cronico e disturbi dell'umore
▪ Storia personale di sintomi cronici da attivazione centrale (dolore multifocale con descrittori neuropatici , stanchezza, disturbi del sonno, stress psicologico, alterazioni della memoria)
▪ Aspetti cognitivi come l'ipervigilanza e il catastrofismo
▪ Ridotta soglia del dolore di tipo meccanico e dell'attività analgesica delle vie discendenti inibitorie
Esposizione a "stressors" o a stimoli nocicettivi periferici
Risposta psicologica e comportamentale al dolore o all'evento stressante
Nuove o differenti aree di dolore cronico (amplificazione del dolore)

Diagnostic and/or classification criteria for fibromyalgia

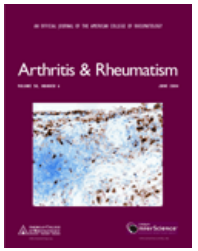
Definizione

- La Fibromialgia (FM) è una condizione clinica comune di **dolore muscoloscheletrico diffuso** nella quale i pazienti presentano tipicamente **allodinia e iperalgesia** in aggiunta a molti sintomi di accompagnamento

- La presenza e la severità della FM, che è spesso basata sulla descrizione dei sintomi riportati dai pazienti, **non può essere determinata da rilievi clinici oggettivi, alterazioni radiografiche o da esami routinariamente utilizzati in laboratorio**

FM: Classification

American College of Rheumatology: 1990



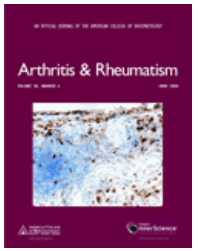
- History (> 3 months) of widespread pain
  - Left and right sided
  - Above and below waist
  - Axial skeletal pain must be present
- Pain (not tenderness) on digital (4 kg) palpation in 11 of 18 tender points
- Both criteria must be satisfied

Specificity 88%
Sensitivity 81%

Wolfe F et Al, Arthritis Rheum 1990, 33:160

FM: Classification

American College of Rheumatology: 1990



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Specificity 88%
Sensitivity 81%

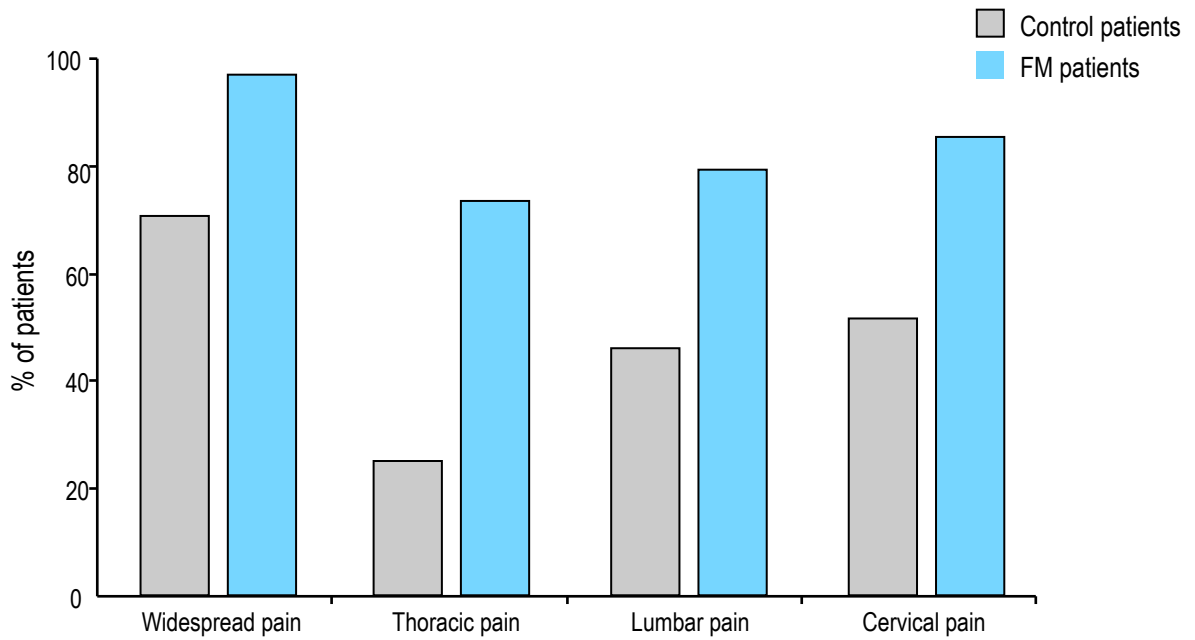
Wolfe F et Al, Arthritis Rheum 1990, 33:160

Associated signs and symptoms (Wolfe 1990)

widespread pain	97.6% of patients
tenderness in > 11/18 tender points	90.1
fatigue	81.4
morning stiffness	77.0
sleep disturbance	74.6
paresthesias	62.8
headache	52.8
anxiety	47.8
dysmenorrhea history	40.6
sicca symptoms	35.8
prior depression	31.5
irritable bowel syndrome	29.6
urinary urgency	26.3
Raynaud's phenomenon	16.7

Wolfe F et Al, Arthritis Rheum 1990, 33:160
The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee.

Widespread Pain Is the Defining Feature of Fibromyalgia

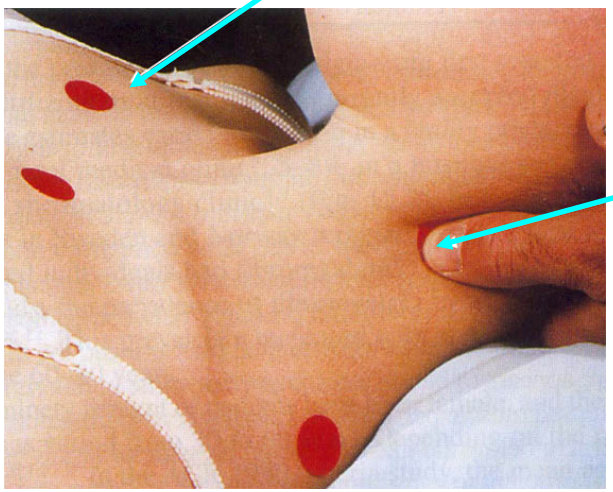


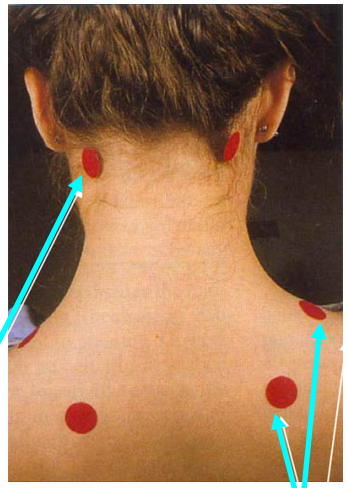
Wolfe et al. *Arthritis Rheum.* 1990; 33:160-172.

Tender Points Map

18 tender points

Second Rib: front chest area) at second costochondral junctions



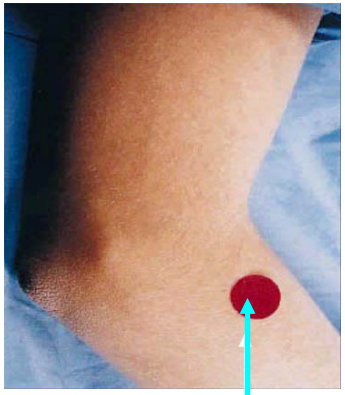


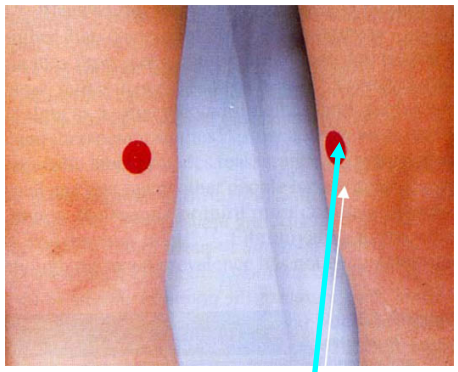
Occiput: back of the neck) at suboccipital muscle insertions

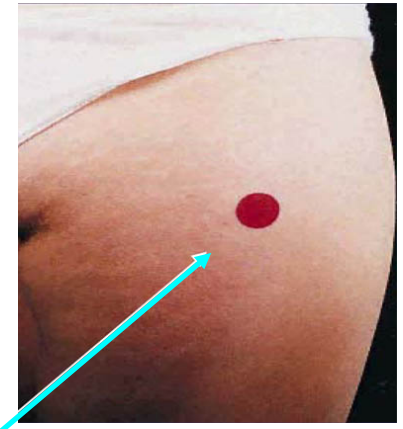
Low Cervical Region: at anterior aspect of the interspaces between the transverse processes

Trapezius Muscle: (back shoulder area) at midpoint of the upper border

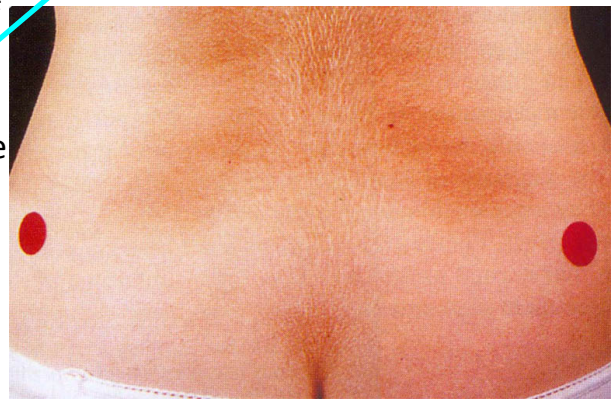
Supraspinatus Muscle: (shoulder blade area) above the medial border of the scapular spine



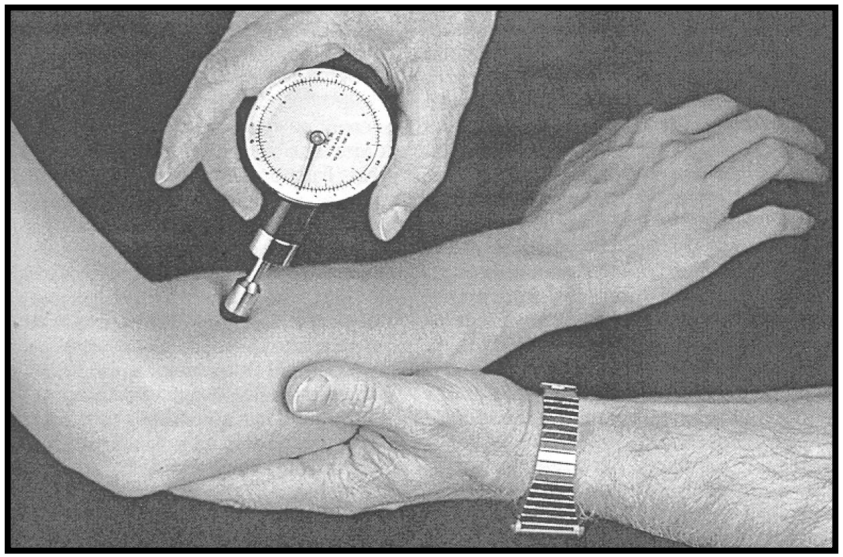




- **Lateral Epicondyle**: (elbow area) 2 cm distal to the lateral epicondyle
- **Gluteal:** (rear end) at upper outer quadrant of the buttocks
- **Greater Trochanter**: (rear hip) posterior to the greater trochanteric prominence**.**
- **Knee**: (knee area) at the medial fat pad proximal to the joint line.



How Evaluate Tender Points



Pressure algometer

Manual algometer

Problems with tender ppints

- Mechanical hyperalgesia is a clinical manifestation of central sensitization and, although an imperfect measure, the manual TP examination has been considered a primary identifier of pain hypersensitivity

S. Lautenbacher, G. B. Rollman, and G. A. McCain, “Multimethod assessment of experimental and clinical pain in patients with fibromyalgia,” Pain, 1994; 59, 45–53.
R. Staud, “Predictors of clinical pain intensity in patients with fibromyalgia syndrome,” Current Pain and Headache Reports, 2005; 9, 316–321

Problems with tender points

- In the development of the 1990 ACR classification criteria for fibromyalgia, TPs were found to be the most powerful discriminator between fibromyalgia and control subjects;
- the best separation occurred at about the **13 TPs for mild tenderness** (the subject state that palpation is painful) and about **6 TPs for moderate or greater tenderness** (the pain complaint is accompanied by facial expression and/or flinch at palpation)

Wolfe F et Al, Arthritis Rheum 1990, 33:160

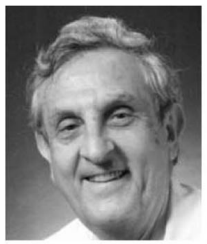
Problems with tender points

- In the clinical context, the 1990-ACR criteria cutoff at 11 TPs, based on a score of mild or greater tenderness, has been criticized for placing a diagnosis of fibromyalgia at the far end of a severity spectrum and for ignoring other key symptoms
- This has led to the suggestion of diagnostic criteria based on pain and typical fibromyalgia symptoms, but omitting the evaluation of mechanical hyperalgesia.

F. Wolfe, D. J. Clauw, M. Fitzcharles et al., "The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity," Arthritis Care and Research, vol. 62, no. 5, pp. 600–610, 2010.

Editorial

The Fibromyalgia Tender Points: Use Them or Lose Them? A Brief Review of the Controversy



MANFRED HARTH, MD, FRCPC,
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Critiques and challenges to the FM concept and the validity of tender points

1. TP are arbitrary and exclusionary
2. TP are subject to bias
3. TP counts do not capture the complexity of FM
4. The relationship of TP to underlying pathology is unclear
5. In practice, the TP count is often not used

Disparity Between Tender Points and Pain Processing

- Disparity between the tender point count and the more sophisticated measures of tenderness likely due to external factors that influence easily biased methods such as the tender point count
- Tender point counts are highly correlated with distress, prompting the suggestion that tender points are a “sedimentation rate for distress”

Wolfe F. The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. Ann Rheum Dis 1997;56:268–71.
Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 2003;30:567–74

1.WPI (widespread pain index): note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain?

Put a check to indicate a painful region. Score will be between 0 and 19

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right		Abdomen
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

2. SS (symptom severity) scale score:
- o Fatigue
- o Walking unrefreshed
- o Cognitive symptoms

For each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
0. no problem
1. slight or mild problems, generally mild or intermittent
2. moderate, considerable problems, often present and/or at a moderate level
3. severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has:*
0. no symptoms
1. few symptoms
2. a moderate number of symptoms
3. a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, walking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

**Somatic symptoms that might be considered:* muscle pain, irritable bowel syndrome, fatigue/ tiredness, thinking or remembering problems, muscle weakness, headache, pain/crambe in the abdomen, numbness/tingling, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, dry eyes, ringing in the ears, heartburn, oral ulcers, loss of/change in taste, seizures, shortness of breath, loss of appetite, rash, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

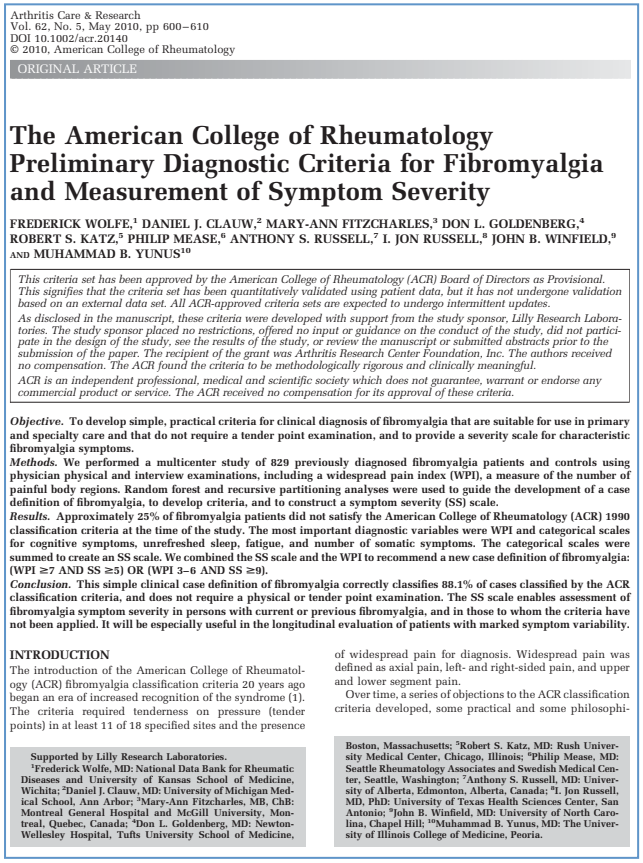
A patient satisfies the diagnostic criteria for fibromyalgia if the following 3 conditions are met:
1. WPI ≥7 and SS scale score ≥5 or WPI 3–6 and SS scale score ≥9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain

2010 ACR preliminary diagnostic criteria

WOLFE F, CLAUW DJ, FITZCHARLES MA . The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Research* 2010; 5: 600-10.

ACR 2010 criteria

- Widespread pain index
  - -Pain in the past week
  - -19 areas
  - -Score = 0-19
- Somatic Symptom Scale
  - -fatigue
  - -waking up un-refreshed
  - -cognitive symptoms
  - -Symptoms generally
  - -Score= 0-12



Arthritis Care & Research
Vol. 62, No. 5, May 2010, pp 600–610
DOI 10.1002/acr.20140

ORIGINAL ARTICLE

The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

FREDERICK WOLFE,[1] DANIEL J. CLAUW,[2] MARY-ANN FITZCHARLES,[3] DON L. GOLDENBERG,[4] ROBERT S. KATZ,[5] PHILIP MEASE,[6] ANTHONY S. RUSSELL,[7] I. JON RUSSELL,[8] JOHN B. WINFIELD,[9] AND MUHAMMAD B. YUNUS[10]

This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria set has been quantitatively validated using patient data, but it has not undergone validation based on an external data set. All ACR-approved criteria sets are expected to undergo intermittent updates.

As disclosed in the manuscript, these criteria were developed with support from the study sponsor, Lilly Research Laboratories. The study sponsor placed no restrictions, offered no input or guidance on the conduct of the study, did not participate in the design of the study, see the results of the study, or review the manuscript or submitted abstracts prior to the submission of the paper. The recipient of the grant was Arthritis Research Center Foundation, Inc. The authors received no compensation. The ACR found the criteria to be methodologically rigorous and clinically meaningful.

ACR is an independent professional, medical and scientific society which does not guarantee, warrant or endorse any commercial product or service. The ACR received no compensation for its approval of these criteria.

Objective. **To develop simple, practical criteria for clinical diagnosis of fibromyalgia that are suitable for use in primary and specialty care and that do not require a tender point examination, and to provide a severity scale for characteristic fibromyalgia symptoms.**

Methods. **We performed a multicenter study of 829 previously diagnosed fibromyalgia patients and controls using physician physical and interview examinations, including a widespread pain index (WPI), a measure of the number of painful body regions. Random forest and recursive partitioning analyses were used to guide the development of a case definition of fibromyalgia, to develop criteria, and to construct a symptom severity (SS) scale.**

Results. **Approximately 25% of fibromyalgia patients did not satisfy the American College of Rheumatology (ACR) 1990 classification criteria at the time of the study. The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. The categorical scales were summed to create an SS scale. We combined the SS scale and the WPI to recommend a new case definition of fibromyalgia: (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9).**

Conclusion. **This simple clinical case definition of fibromyalgia correctly classifies 88.1% of cases classified by the ACR classification criteria, and does not require a physical or tender point examination. The SS scale enables assessment of fibromyalgia symptom severity in persons with current or previous fibromyalgia, and in those to whom the criteria have not been applied. It will be especially useful in the longitudinal evaluation of patients with marked symptom variability.**

INTRODUCTION

The introduction of the American College of Rheumatology (ACR) fibromyalgia classification criteria 20 years ago began an era of increased recognition of the syndrome (1). The criteria required tenderness on pressure (tender points) in at least 11 of 18 specified sites and the presence of widespread pain for diagnosis. Widespread pain was defined as axial pain, left- and right-sided pain, and upper and lower segment pain.

Over time, a series of objections to the ACR classification criteria developed, some practical and some philosophi-

Supported by Lilly Research Laboratories.
[1]Frederick Wolfe, MD: National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine, Wichita; [2]Daniel J. Clauw, MD: University of Michigan Medical School, Ann Arbor; [3]Mary-Ann Fitzcharles, MB, ChB: Montreal General Hospital and McGill University, Montreal, Quebec, Canada; [4]Don L. Goldenberg, MD: Newton-Wellesley Hospital, Tufts University School of Medicine, Boston, Massachusetts; [5]Robert S. Katz, MD: Rush University Medical Center, Chicago, Illinois; [6]Philip Mease, MD: Seattle Rheumatology Associates and Swedish Medical Center, Seattle, Washington; [7]Anthony S. Russell, MD: University of Alberta, Edmonton, Alberta, Canada; [8]I. Jon Russell, MD, PhD: University of Texas Health Sciences Center, San Antonio; [9]John B. Winfield, MD: University of North Carolina, Chapel Hill; [10]Muhammad B. Yunus, MD: The University of Illinois College of Medicine, Peoria.

2010 Fibromyalgia diagnostic criteria

Criteria

A patient satisfies diagnostic criteria for Fibromyalgia if the following 3 conditions are met:

1. Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5
   or WPI 3–6 and SS scale score ≥ 9.
2. Symptoms have been present at a similar level for at least 3 months.
3. The patient does not have a disorder that would otherwise explain the pain.

Arthritis Care & Research
Vol. 62, No. 5, May 2010, pp 600–610

ACR 2011 criteria (2010 modified)

- Widespread pain index
  - -self-report
- Somatic Symptom Scale
  - -fatigue
  - -waking up un-refreshed
  - -cognitive symptoms
- Symptoms generally
  - -headache
  - -pain and cramps in lower abdomen
  - -depression

Fibromyalgia Criteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia

FREDERICK WOLFE, DANIEL J. CLAUW, MARY-ANN FITZCHARLES, DON L. GOLDENBERG, WINFRIED HÄUSER, ROBERT S. KATZ, PHILIP MEASE, ANTHONY S. RUSSELL, I. JON RUSSELL, and JOHN B. WINFIELD

ABSTRACT. ***Objective.*** To develop a fibromyalgia (FM) survey questionnaire for epidemiologic and clinical studies using a modification of the 2010 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia (ACR 2010). We also created a new FM symptom scale to further characterize FM severity.

Methods. The ACR 2010 consists of 2 scales, the Widespread Pain Index (WPI) and the Symptom Severity (SS) scale. We modified these ACR 2010 criteria by eliminating the physician's estimate of the extent of somatic symptoms and substituting the sum of 3 specific self-reported symptoms. We also created a 0–31 FM Symptom scale (FS) by adding the WPI to the modified SS scale. We administered the questionnaire to 729 patients previously diagnosed with FM, 845 with osteoarthritis (OA) or with other noninflammatory rheumatic conditions, 439 with systemic lupus erythematosus (SLE), and 5210 with rheumatoid arthritis (RA).

Results. The modified ACR 2010 criteria were satisfied by 60% with a prior diagnosis of FM, 21.1% with RA, 16.8% with OA, and 36.7% with SLE. The criteria properly identified diagnostic groups based on FM severity variables. An FS score ≥ 13 best separated criteria+ and criteria– patients, classifying 93.0% correctly, with a sensitivity of 96.6% and a specificity of 91.8% in the study population.

Conclusion. A modification to the ACR 2010 criteria will allow their use in epidemiologic and clinical studies without the requirement for an examiner. The criteria are simple to use and administer, but they are not to be used for self-diagnosis. The FS may have wide utility beyond the bounds of FM, including substitution for widespread pain in epidemiological studies. (First Release Feb 1 2011; J Rheumatol 2011;38:1113–22; doi:10.3899/jrheum.100594)

Key Indexing Terms:
FIBROMYALGIA CRITERIA DIAGNOSIS

From the National Data Bank for Rheumatic Diseases, Wichita, Kansas; Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan; Newton-Wellesley Hospital, Tufts University School of Medicine, Boston, Massachusetts; Rush University Medical Center, Chicago, Illinois; Swedish Medical Center and University of Washington, Seattle, Washington; Department of Medicine/Rheumatology, University of Texas Health Sciences Center, San Antonio, Texas; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany; Montreal General Hospital, Division of Rheumatology, McGill University, Montreal, Quebec; and University of Alberta, Edmonton, Alberta, Canada.

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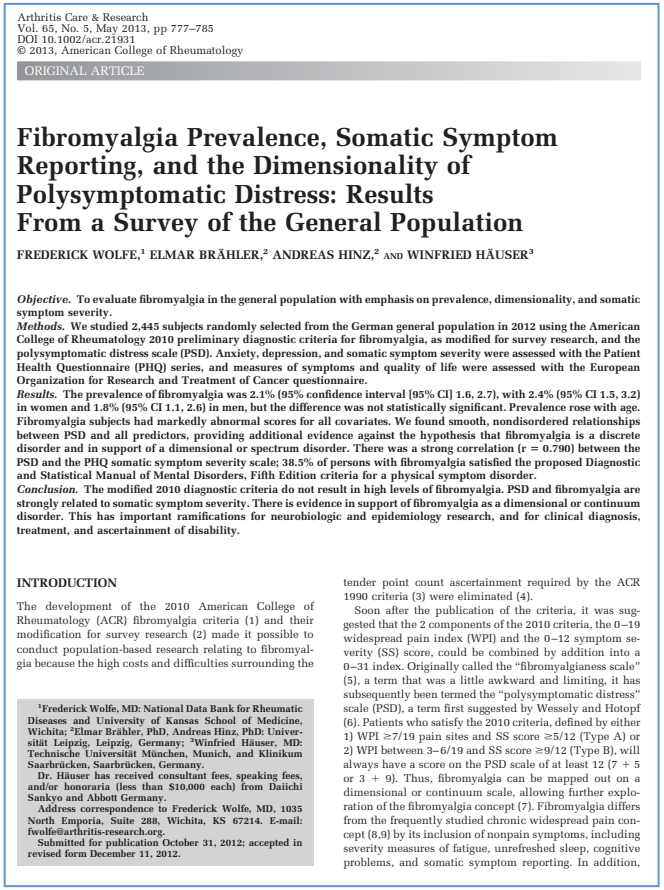
Accepted for publication December 3, 2010.

The publication of American College of Rheumatology (ACR) preliminary diagnostic criteria for fibromyalgia (FM) in 2010 (ACR 2010)[1] eliminated the tender point examination, thus making it possible to study FM in survey and clinical research. The diagnostic criteria for FM are satisfied if the following 3 conditions are met: (1) the Widespread Pain Index (WPI) ≥ 7 and the Symptom Severity Score (SS) ≥ 5, or the WPI is 3–6 and the SS ≥ 9; (2) symptoms have been present at a similar level for at least 3 months; and (3) the patient does not have a disorder that would otherwise explain the pain.

The ACR 2010 study found that about 25% of clinic patients with FM did not satisfy ACR 1990 classification criteria[2]. The study group developed the SS scale so that patients who improve and do not satisfy criteria could be followed for the severity of FM symptoms. This scale could also be used in patients with other rheumatic and nonrheumatic diagnoses to determine the extent to which someone may also have comorbid FM symptoms. In addition, some patients with other rheumatic diseases will also satisfy dichotomous (i.e., yes or no) FM criteria when tested for

ACR 2011 criteria (2010 modified)

- Population survey
  - -Germany N= 2445
  - -Age = 18-91 years
  - -Female = 53.5%
- Prevalence
  - - 2.1% (CI 1.6, 2.7)
  - -Female 2.4 % (CI 1.5, 3.2)
  - - Male 1.8% (CI 1.1 , 2.6)



Arthritis Care & Research
Vol. 65, No. 5, May 2013, pp 777–785
DOI 10.1002/acr.21931

ORIGINAL ARTICLE

Fibromyalgia Prevalence, Somatic Symptom Reporting, and the Dimensionality of Polysymptomatic Distress: Results From a Survey of the General Population

FREDERICK WOLFE,[1] ELMAR BRÄHLER,[2] ANDREAS HINZ,[2] AND WINFRIED HÄUSER[3]

Objective. **To evaluate fibromyalgia in the general population with emphasis on prevalence, dimensionality, and somatic symptom severity.**

Methods. **We studied 2,445 subjects randomly selected from the German general population in 2012 using the American College of Rheumatology 2010 preliminary diagnostic criteria for fibromyalgia, as modified for survey research, and the polysymptomatic distress scale (PSD). Anxiety, depression, and somatic symptom severity were assessed with the Patient Health Questionnaire (PHQ) series, and measures of symptoms and quality of life were assessed with the European Organization for Research and Treatment of Cancer questionnaire.**

Results. **The prevalence of fibromyalgia was 2.1% (95% confidence interval [95% CI] 1.6, 2.7), with 2.4% (95% CI 1.5, 3.2) in women and 1.8% (95% CI 1.1, 2.6) in men, but the difference was not statistically significant. Prevalence rose with age. Fibromyalgia subjects had markedly abnormal scores for all covariates. We found smooth, nondisordered relationships between PSD and all predictors, providing additional evidence against the hypothesis that fibromyalgia is a discrete disorder and in support of a dimensional or spectrum disorder. There was a strong correlation (r = 0.790) between the PSD and the PHQ somatic symptom severity scale; 38.5% of persons with fibromyalgia satisfied the proposed Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for a physical symptom disorder.**

Conclusion. **The modified 2010 diagnostic criteria do not result in high levels of fibromyalgia. PSD and fibromyalgia are strongly related to somatic symptom severity. There is evidence in support of fibromyalgia as a dimensional or continuum disorder. This has important ramifications for neurobiologic and epidemiology research, and for clinical diagnosis, treatment, and ascertainment of disability.**

INTRODUCTION

The development of the 2010 American College of Rheumatology (ACR) fibromyalgia criteria (1) and their modification for survey research (2) made it possible to conduct population-based research relating to fibromyalgia because the high costs and difficulties surrounding the tender point count ascertainment required by the ACR 1990 criteria (3) were eliminated (4).

Soon after the publication of the criteria, it was suggested that the 2 components of the 2010 criteria, the 0–19 widespread pain index (WPI) and the 0–12 symptom severity (SS) score, could be combined by addition into a 0–31 index. Originally called the "fibromyalgianess scale" (5), a term that was a little awkward and limiting, it has subsequently been termed the "polysymptomatic distress" scale (PSD), a term first suggested by Wessely and Hotopf (6). Patients who satisfy the 2010 criteria, defined by either 1) WPI ≥7/19 pain sites and SS score ≥5/12 (Type A) or 2) WPI between 3–6/19 and SS score ≥9/12 (Type B), will always have a score on the PSD scale of at least 12 (7 + 5 or 3 + 9). Thus, fibromyalgia can be mapped out on a dimensional or continuum scale, allowing further exploration of the fibromyalgia concept (7). Fibromyalgia differs from the frequently studied chronic widespread pain concept (8,9) by its inclusion of nonpain symptoms, including severity measures of fatigue, unrefreshed sleep, cognitive problems, and somatic symptom reporting. In addition,

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Dr. Häuser has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Daiichi Sankyo and Abbott Germany.

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Submitted for publication October 31, 2012; accepted in revised form December 11, 2012.

The modified 2010 diagnostic criteria do not result in high levels of fibromyalgia

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 2, February 2015, pp 568–575
DOI 10.1002/art.38905

The Prevalence of Fibromyalgia in the General Population

A Comparison of the American College of Rheumatology 1990, 2010, and Modified 2010 Classification Criteria

Gareth T. Jones,[1] Fabiola Atzeni,[2] Marcus Beasley,[1] Elisa Flüß,[1]
Piercarlo Sarzi-Puttini,[3] and Gary J. Macfarlane[1]

- To determine the prevalence of fibromyalgia in the general population

- Specifically, to compare difference in prevalence using different criteria

  -ACR 1990

  -ACR 2010

  -ACR 2011 (2010 modified)

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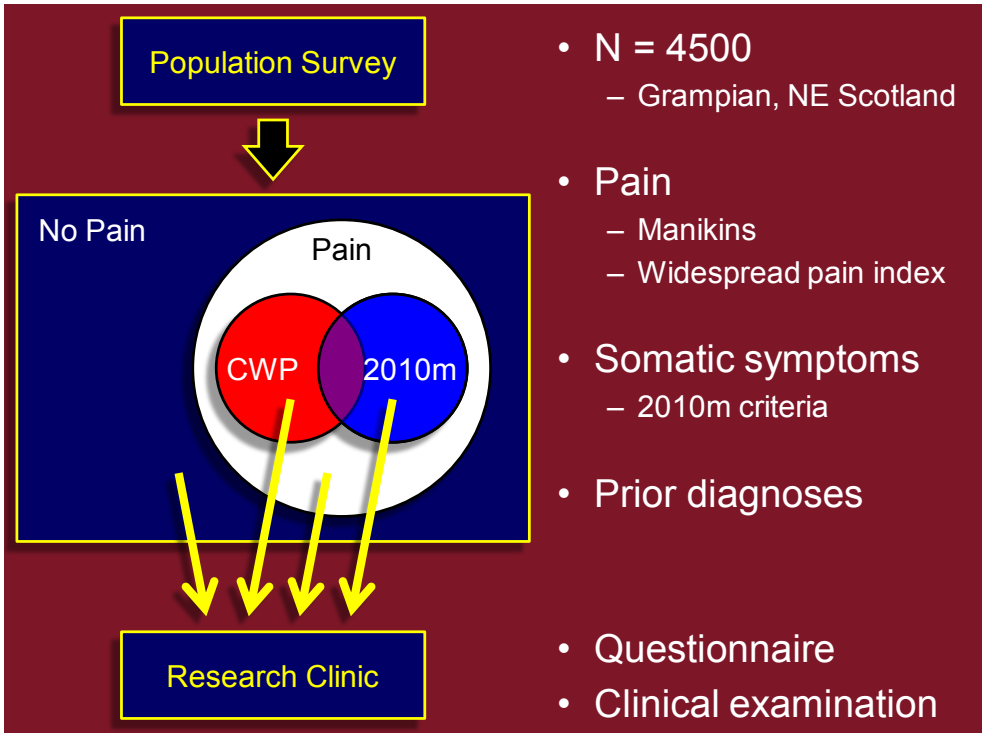
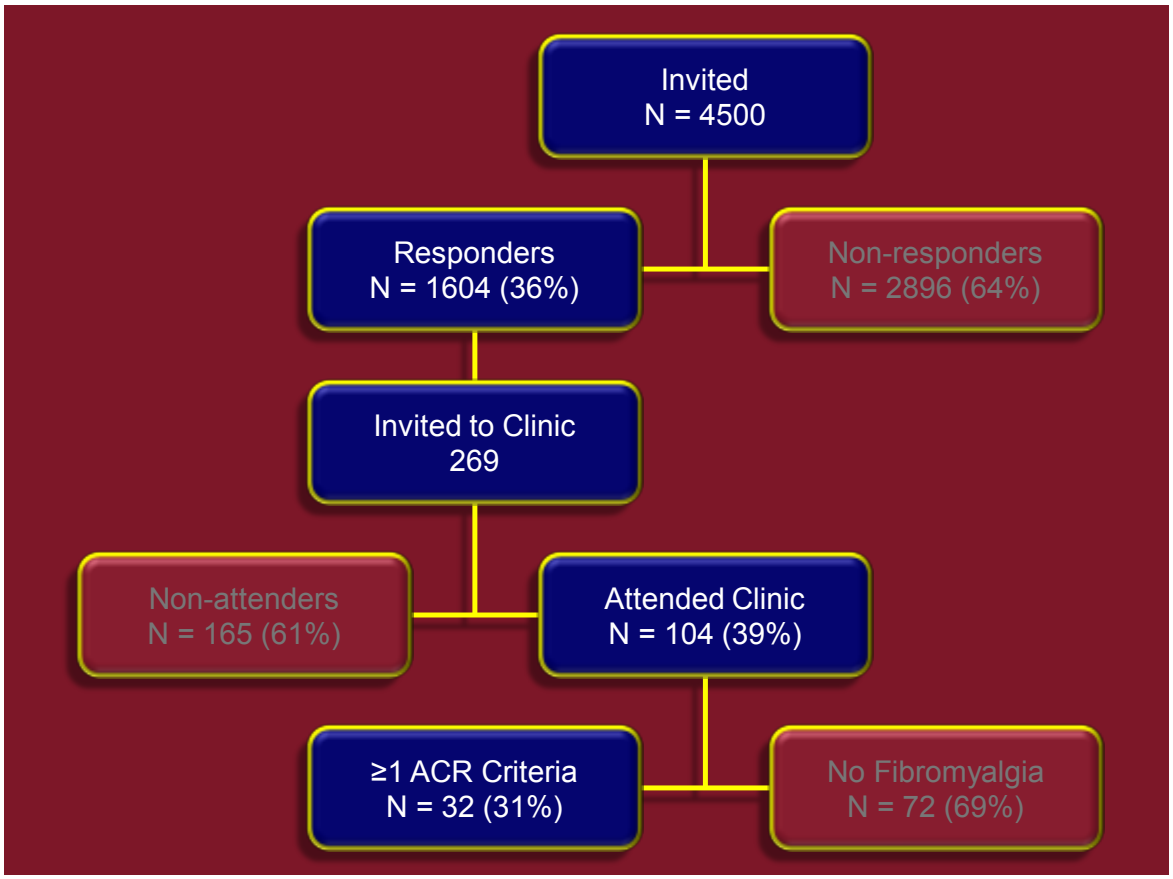


Results


Invited
N = 4500
Responders
N = 1604 (36%)
Non-responders
N = 2896 (64%)
Invited to Clinic
269
Non-attenders
N = 165 (61%)
Attended Clinic
N = 104 (39%)
≥1 ACR Criteria
N = 32 (31%)
No Fibromyalgia
N = 72 (69%)

ARTHRITIS & RHEUMATOLOGY
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The Prevalence of Fibromyalgia in the General Population

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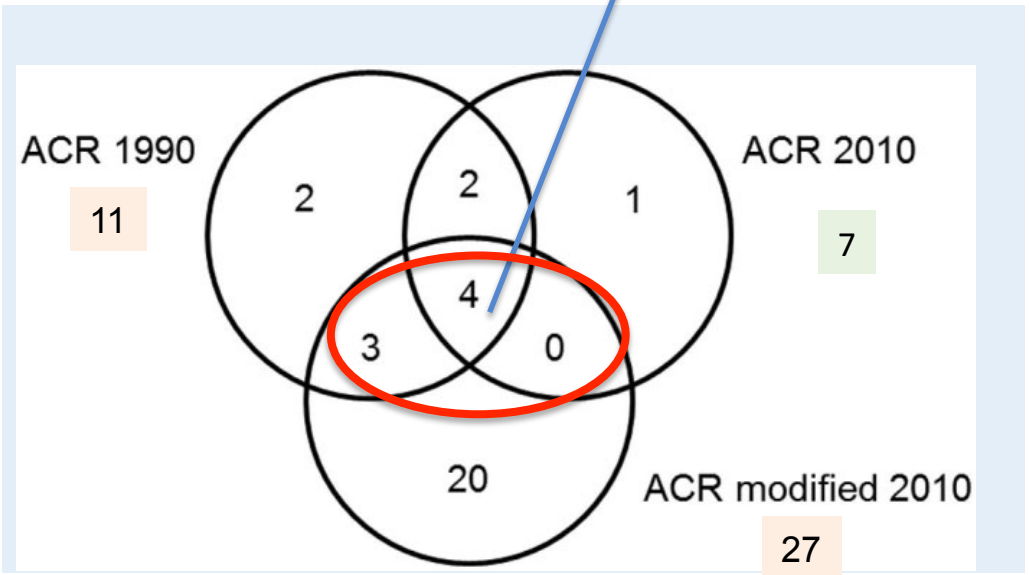
Gareth T. Jones,[1] Fabiola Atzeni,[2] Marcus Beasley,[1] Elisa Flüß,[1]
Piercarlo Sarzi-Puttini,[3] and Gary J. Macfarlane[1]

28%



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The Prevalence of Fibromyalgia in the General Population

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Gareth T. Jones,[1] Fabiola Atzeni,[2] Marcus Beasley,[1] Elisa Flüß,[1] Piercarlo Sarzi-Puttini,[3] and Gary J. Macfarlane[1]

ACR criteria set	Prevalence (95% CI)	Female-to-male ratio	% with rheumatologic diagnoses†
1990 criteria	1.7 (0.7–2.8)	13.7	55
2010 criteria	1.2 (0.3–2.1)	4.8	28
Modified 2010 criteria	5.4 (4.7–6.1)	2.3	45

* ACR = American College of Rheumatology; 95% CI = 95% confidence interval.

The Polysimptomatic Distress Scale (PDS)

- The PDS is obtained by summing the 2 components of the 2010 criteria

  PDS = WPI+ SS

- FM diagnosis will have always a score of at least 12
- Not all subjects with a score ≥ 12 will satisfy FM criteria because there is a small degree of misclassification

The Use of Polysymptomatic Distress Categories in the Evaluation of Fibromyalgia (FM) and FM Severity

Frederick Wolfe, Brian T. Walitt, Johannes J. Rasker, Robert S. Katz, and Winfried Häuser

ABSTRACT. ***Objective.*** The polysymptomatic distress (PSD) scale is derived from variables used in the 2010 American College of Rheumatology (ACR) fibromyalgia (FM) criteria modified for survey and clinical research. The scale is useful in measuring the effect of PSD over the full range of pain-related clinical symptoms, not just in those who are FM criteria-positive. However, no PSD scale categories have been defined to distinguish severity of illness in FM or in those who do not satisfy the FM criteria. We analyzed the scale and multiple covariates to develop clinical categories and to further validate the scale.

Methods. FM was diagnosed according to the research criteria modification of the 2010 ACR FM criteria. We investigated categories in a large database of patients with pain (2732 with rheumatoid arthritis) and developed categories by using germane clinic variables that had been previously studied for severity groupings. By definition, FM cannot be diagnosed unless PSD is at least 12.

Results. Based on population categories, regression analysis, and inspections of curvilinear relationships, we established PSD severity categories of none (0–3), mild (4–7), moderate (8–11), severe (12–19), and very severe (20–31). Categories were statistically distinct, and a generally linear relationship between PSD categories and covariate severity was noted.

Conclusion. PSD categories are clinically relevant and demonstrate FM type symptoms over the full range of clinical illness. Although FM criteria can be clinically useful, there is no clear-cut symptom distinction between FM (+) and FM (–), and PSD categories can aid in more effectively classifying patients. (First Release June 15 2015; J Rheumatol 2015;42:1494–1501; doi:10.3899/jrheum.141519)

Key Indexing Terms:
POLYSYMPTOMATIC DISTRESS FIBROMYALGIA SCALE CATEGORIES

Diagnosis of fibromyalgia (FM) by criteria has depended on identifying a point on a continuum of symptoms where the symptom burden is sufficient. For the 1990 American College of Rheumatology (ACR) criteria[1], that point is ≥ 11 of 18 tender points in patients with widespread pain. The 2010 ACR criteria for FM[2] and the subsequent self-report version of the 2010 criteria (modified 2010) are also based on a symptom severity point[3]. For the 2010 series of criteria, a diagnosis of FM can be made when levels of the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) are sufficiently high (WPI ≥ 7 and SSS ≥ 5 or WPI 3–6 and SSS ≥ 9). The WPI is a 0–19 count of painful nonarticular body regions and the SSS is a 0–12 measure of symptom severity that includes fatigue, sleep, and cognitive problems.

Subsequently, it was found that the underlying (or latent) spectrum of severity that formed the basis for the 2010 criteria could be visualized by adding together elements of the ACR 2010 or modified 2010 criteria to form the polysymptomatic distress (PSD) scale (Figure 1)[4,5]. The scale is obtained by summing the 2 components of the 2010 criteria, the WPI and SSS:

PSD = WPI + SSS

The PSD scale was important because it showed just where the patient's FM-associated symptoms were on the distress continuum while still allowing a dichotomous diagnosis. FM diagnosis by PSD location is estimated. Because of the definitional requirements of the FM criteria that were described above, a positive FM diagnosis will always have a PSD score of at least 12, but not all subjects with a score ≥ 12 will satisfy FM criteria because there is a small degree of misclassification (sensitivity 95%, specificity 93%). This can be seen in Figure 1: the blue circles at a PSD ≥ 12 would be misclassified as patients with FM if PSD alone was used for diagnosis. In Figure 1 (right panel), the lower

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The Polysimptomatic Distress Scale (PDS)

Three issues worth considering for PDS

- the method for determining pain severity,
- the methods used in the derivation of clinically relevant symptoms,
- the disproportionate influence of pain locations relative to symptoms in the final score.

Editorial

A Critical Examination of the Polysymptomatic Distress Scale Construct as a Symptom Severity Questionnaire

A confusion develops between the use of scores to measure severity, and the same scores to establish diagnosis.
Hugh A. Smythe
J Rheumatol 2011;38:975-8

The assessment of disease severity is an essential undertaking related to morbidity and mortality. Ideally such assessment involves the use of objective markers, such as the level of hemoglobin in anemia or distribution of the number of erosions in rheumatoid arthritis. In many diseases within the sphere of rheumatology, objective markers have yet to be discovered. This situation has led to a profusion of questionnaires aimed at measuring disease severity. Such questionnaires need to be carefully designed to address the disorder under scrutiny and comprehensively validated to ensure their scientific reliability.

The main symptom in most rheumatological disorders is pain. There are currently no generally available objective measures of pain, and its assessment invariably relies upon questionnaires, such as the Brief Pain Inventory[1], or scales such as the visual analog scale[2,3]. Further, the evaluation of pain is complicated by its multidimensionality; most patients with chronic pain are fatigued, commonly depressed, often functionally impaired, and existentially distressed. The development of questionnaires has become a specialty in its own right, with its own arcane vocabulary, statistical complexities, and even its own journals. Achieving the right balance of generality and specificity without loss of content or efficiency is a challenging undertaking.

In this issue of *The Journal*, Wolfe and colleagues present the Polysymptomatic Distress Scale (PSD) as a useful general severity measure and advocate its ease of interpretation by assigning 5 severity categories (none, mild, moderate, severe, and very severe)[4]. The PSD is derived from Dr. Wolfe's 2010 diagnostic criteria for fibromyalgia (FM)[5]. It combines 2 scales used for diagnosis: the Widespread Pain Index (WPI; 0–19) and the Symptom Severity Scale (SSS; 0–12) for a combined PSD total of 0–31[6]. The WPI consists of 19 nonarticular regions assessed for their presence/absence of pain. The SSS contains 6 symptoms: fatigue, sleep, cognition, headache, abdominal pain/cramping, and depression. "Polysymptomatic Distress" is the newest term for the scales previously named FM Symptom and "Fibromyalgianess", although there has been no change in content. The authors commend the PSD as a multipurpose instrument: (a) a measure of FM severity, (b) a "universal quantity" for assessing symptom severity for all disorders, (c) an "approximate diagnosis" of FM, and (d) an instrument for clinical and research purposes. To quote:

> We suggest that the distribution of PSD represents an aspect of the human condition, i.e., some patients report more pain and distress and some less, and PSD can be seen as a broad continuous distribution.... We also note that using the continuous PSD scale rather than classifying patients into FM or widespread pain groups makes it easier to understand the relationship between variables and the degree of the patient's problem, and patients on both sides of the FM or widespread pain dichotomy are often more similar than different[7].

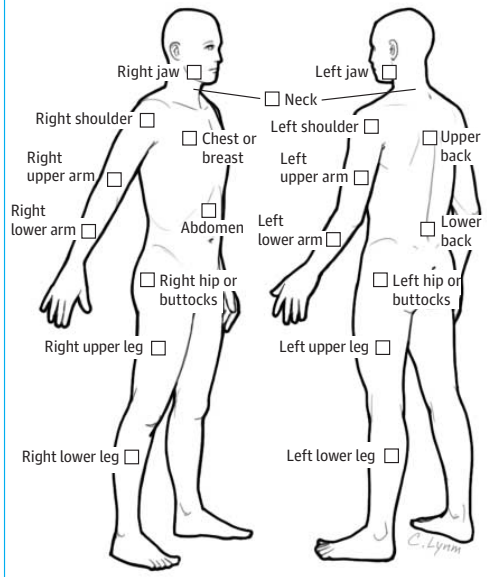
The development of a scientifically valid, widely accepted questionnaire, presents many difficult choices that influence its ultimate acceptance and validity. There are 3 issues that are worth considering when using the PSD: the method for determining pain severity, the methods used in the derivation of clinically relevant symptoms, and the disproportionate influence of pain locations relative to symptoms in the final score.

Pain locations as a measure of pain severity. The PSD relies on the 19-point WPI component as its primary assessment of pain. However, the WPI is inherently underrepresentative of pain regions; in its development only nonarticular regions

Patient Self-report Survey for the Assessment of Fibromyalgia Based on Criteria in the 2011 Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia

Widespread pain
(1 point per check box. Score range : 0-19 points)

(1) Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.



Symptom severity
(score range: 0-12 points)

(2) For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.
- **No problem**
- **Slight or mild problem**: generally mild or intermittent
- **Moderate problem**: considerable problems; often present and/or at a moderate level
- **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

(3) During the **past 6 months** have you had any of the following symptoms?

	Points	0	1
A. Pain or cramps in lower abdomen		☐ No	☐ Yes
B. Depression		☐ No	☐ Yes
C. Headache		☐ No	☐ Yes

Additional criteria (no score)

(4) Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at **least 3 months**?
☐ No ☐ Yes

(5) Do you have a disorder that would otherwise explain the pain?
☐ No ☐ Yes

ACR indicates American College of Rheumatology. Scoring information is shown in black. The possible score ranges from 0 to 31 points; **a score ≥12 points is consistent with a diagnosis of fibromyalgia**.

Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia

FREDERICK WOLFE,[1] MARY-ANN FITZCHARLES,[2] DON L. GOLDENBERG,[3] WINFRIED HÄUSER,[4] ROBERT L. KATZ,[5] PHILIP J. MEASE,[6] ANTHONY S. RUSSELL,[7] I. JON RUSSELL,[8] AND BRIAN WALITT[9]

Previously unreported rheumatology practice data from 514 patients and 30 physicians in the ACR 2010 study.

Evaluation

- the widespread pain index,
- polysymptomatic distress (PSD) scale,
- tender point count (TPC),
- fibromyalgia diagnosis using 2010 and 2011 rules.

Arthritis Care Res (Hoboken). 2016 May;68(5):652-9.

Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia

FREDERICK WOLFE,[1] MARY-ANN FITZCHARLES,[2] DON L. GOLDENBERG,[3] WINFRIED HÄUSER,[4] ROBERT L. KATZ,[5] PHILIP J. MEASE,[6] ANTHONY S. RUSSELL,[7] I. JON RUSSELL,[8] AND BRIAN WALITT[9]

Previously unreported rheumatology practice data from 514 patients and 30 physicians in the ACR 2010 study.

Results

- MD and PT diagnostic agreement was substantial (83.4%, k = 0.67).
- PSD scores differed slightly (12.3 MD, 12.8 PT; P = 0.213).
- The TPC was strongly associated with both the MD (r 5 0.779) and PT PSD scales (r = 0.702).

Arthritis Care Res (Hoboken). 2016 May;68(5):652-9.

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- The 2010 American College of Rheumatology (ACR) physician-based and the 2011 patient-based fibromyalgia criteria yield consistent results overall in a group of rheumatology patients. But there are **many widely discordant physician/patient pairs.**
- **The 2011 criteria are much better for research** because of multiple examiners (the patients) and the ease of assessment.
- There is acceptable agreement in diagnosis and the polysymptomatic distress scale for research, but insufficient agreement for clinical decisions and diagnosis.
- We recommend **adjudication of symptom data by patients and physicians together** to resolve discordance, as recommended by the 2010 ACR criteria.

Arthritis Care Res (Hoboken). 2016 May;68(5):652-9.

2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria

Frederick Wolfe, MD[a,b,*], Daniel J. Clauw, MD[c], Mary-Ann Fitzcharles, MD[d], Don L. Goldenberg, MD[e,f], Winfried Häuser, MD[g,h], Robert L. Katz, MD[i], Philip J. Mease, MD[j,k], Anthony S. Russell, MD[l], Irwin Jon Russell, MD, PhD[m], Brian Walitt, MD, MPH[n]

Fibromyalgia (2016 revison criteria) may now be diagnosed in adults when all of the following criteria are met:

(1) **Generalized pain, defined as pain in at least 4 of 5 regions, is present**.

(2) Symptoms have been present at a similar level for at least 3 months.

(3) Widespread pain index (WPI) > or equal to 7 and symptom severity scale (SSS) score > or equal to 5 or WPI of 4–6 and SSS score > 9.

(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria

Frederick Wolfe, MD[a,b,*], Daniel J. Clauw, MD[c], Mary-Ann Fitzcharles, MD[d], Don L. Goldenberg, MD[e,f], Winfried Häuser, MD[g,h], Robert L. Katz, MD[i], Philip J. Mease, MD[j,k], Anthony S. Russell, MD[l], Irwin Jon Russell, MD, PhD[m], Brian Walitt, MD, MPH[n]

Criteria

A patient satisfies modified 2016 fibromyalgia criteria if the following 3 conditions are met:

(1) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9.

(2) Generalized pain, defined as pain in at least 4 of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.

(3) Symptoms have been generally present for at least 3 months.

(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

Ascertainment

(1) WPI: note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19

Left upper region (Region 1)	*Right upper region (Region 2)*	*Axial region (Region 5)*
Jaw, left[a]	Jaw, right[a]	Neck
Shoulder girdle, left	Shoulder girdle, right	Upper back
Upper arm, left	Upper arm, right	Lower back
Lower arm, left	Lower arm, right	Chest[a]
		Abdomen[a]
Left lower region (region 3)	*Right lower region (Region 4)*	
Hip (buttock, trochanter), left	Hip (buttock, trochanter), right	
Upper leg, left	Upper leg, right	
Lower leg, left	Lower leg, right	

(2) Symptom severity scale (SSS) score

Fatigue

Waking unrefreshed

Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

0 = No problem

1 = Slight or mild problems, generally mild or intermittent

2 = Moderate, considerable problems, often present and/or at a moderate level

3 = Severe: pervasive, continuous, life-disturbing problems

The symptom severity scale (SSS) score: is the sum of the severity scores of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0–9) plus the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:

(1) Headaches (0–1)

(2) Pain or cramps in lower abdomen (0–1)

(3) And depression (0–1)

The final symptom severity score is between 0 and 12

The fibromyalgia severity (FS) scale is the sum of the WPI and SSS

The FS scale is also known as the polysymptomatic distress (PSD) scale.

[a] Not included in generalized pain definition.

- **An Internet website** has been used to collect data.
- Fibromyalgia Impact Questionnaire Revised version, self-administered Fibromyalgia Activity Score, and Self-Administered Pain Scale were used as questionnaires.
- **Hierarchical agglomerative clustering was applied** to the data obtained in order to identify symptoms and functional-based subgroups.

Journal of Pain Research

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ORIGINAL RESEARCH

Identifying the symptom and functional domains in patients with fibromyalgia: results of a cross-sectional Internet-based survey in Italy

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Flavio Mozzani[2]
Antonella Draghessi[1]
Fabiola Atzeni[3]
Rosita Catellani[2]
Alessandro Ciapetti[4]
Marco Di Carlo[1]
Piercarlo Sarzi-Puttini[5]

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Objective: The aims of this cross-sectional study were to investigate the usefulness of using an Internet survey of patients with fibromyalgia in order to obtain information concerning symptoms and functionality and identify clusters of clinical features that can distinguish patient subsets.
Methods: An Internet website has been used to collect data. Fibromyalgia Impact Questionnaire Revised version, self-administered Fibromyalgia Activity Score, and Self-Administered Pain Scale were used as questionnaires. Hierarchical agglomerative clustering was applied to the data obtained in order to identify symptoms and functional-based subgroups.
Results: Three hundred and fifty-three patients completed the study (85.3% women). The highest scored items were those related to sleep quality, fatigue/energy, pain, stiffness, degree of tenderness, balance problems, and environmental sensitivity. A high proportion of patients reported pain in the neck (81.4%), upper back (70.1%), and lower back (83.2%). A three-cluster solution best fitted the data. The variables were significantly different ($P<0.0001$) among the three clusters: cluster 1 (117 patients) reflected the lowest average scores across all symptoms, cluster 3 (116 patients) the highest scores, and cluster 2 (120 patients) captured moderate symptom levels, with low depression and anxiety.
Conclusion: Three subgroups of fibromyalgia samples in a large cohort of patients have been identified by using an Internet survey. This approach could provide rationale to support the study of individualized clinical evaluation and may be used to identify optimal treatment strategies.
Keywords: fibromyalgia, Internet, FIQR, FAS, cluster analysis, SAPS, pain

Introduction

Fibromyalgia (FM) is a chronic heterogeneous syndrome that affects ~2%–3% of the general population.[1–3] Its primary symptom is chronic, widespread pain associated with generalized tenderness on light palpation. Many patients report a multitude of additional complaints and symptoms,[4] including fatigue, exhaustibility and stiffness, and impaired concentration and memory (a complaint that is increasingly recognized as an independent symptom, namely, "fibrofog" or "dyscognition", according to medical literature).[5] The combinations and severity of symptoms may vary from patient to patient, and this makes it difficult to understand the disease and the development of appropriate treatment strategies.[6] However, stratifying patients by cluster analysis into more homogeneous subgroups on the basis of their patient-relevant clinical features may help to overcome these limitations.[7–14] Cluster analysis allows to identify clinical features and quantifies the importance of each cluster.[15,16]

A comprehensive assessment of main symptoms and the evaluation of the impact on the multidimensional aspects of function should be a routine part of patient care

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Identifying the symptom and functional domains in patients with fibromyalgia: results of a cross-sectional Internet-based survey in Italy

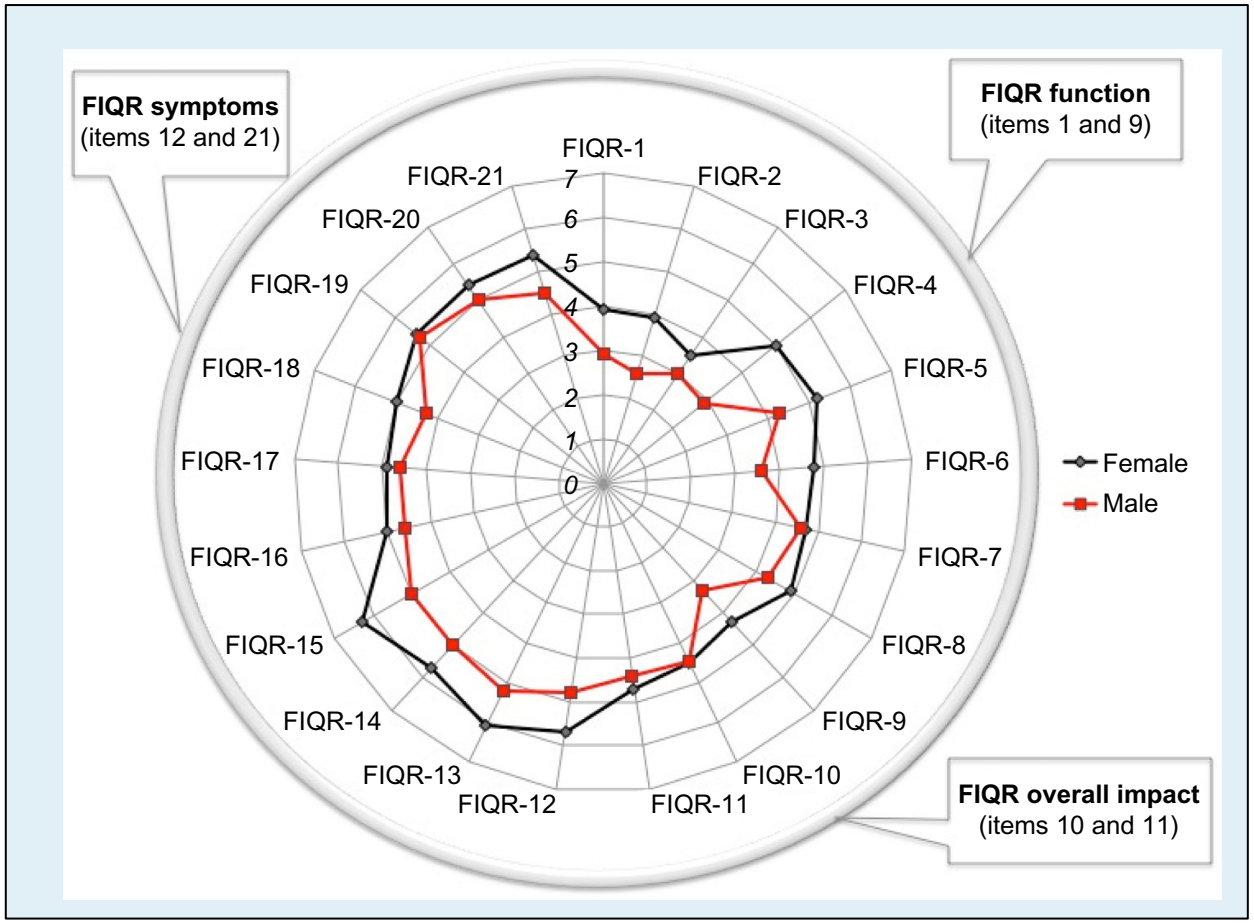
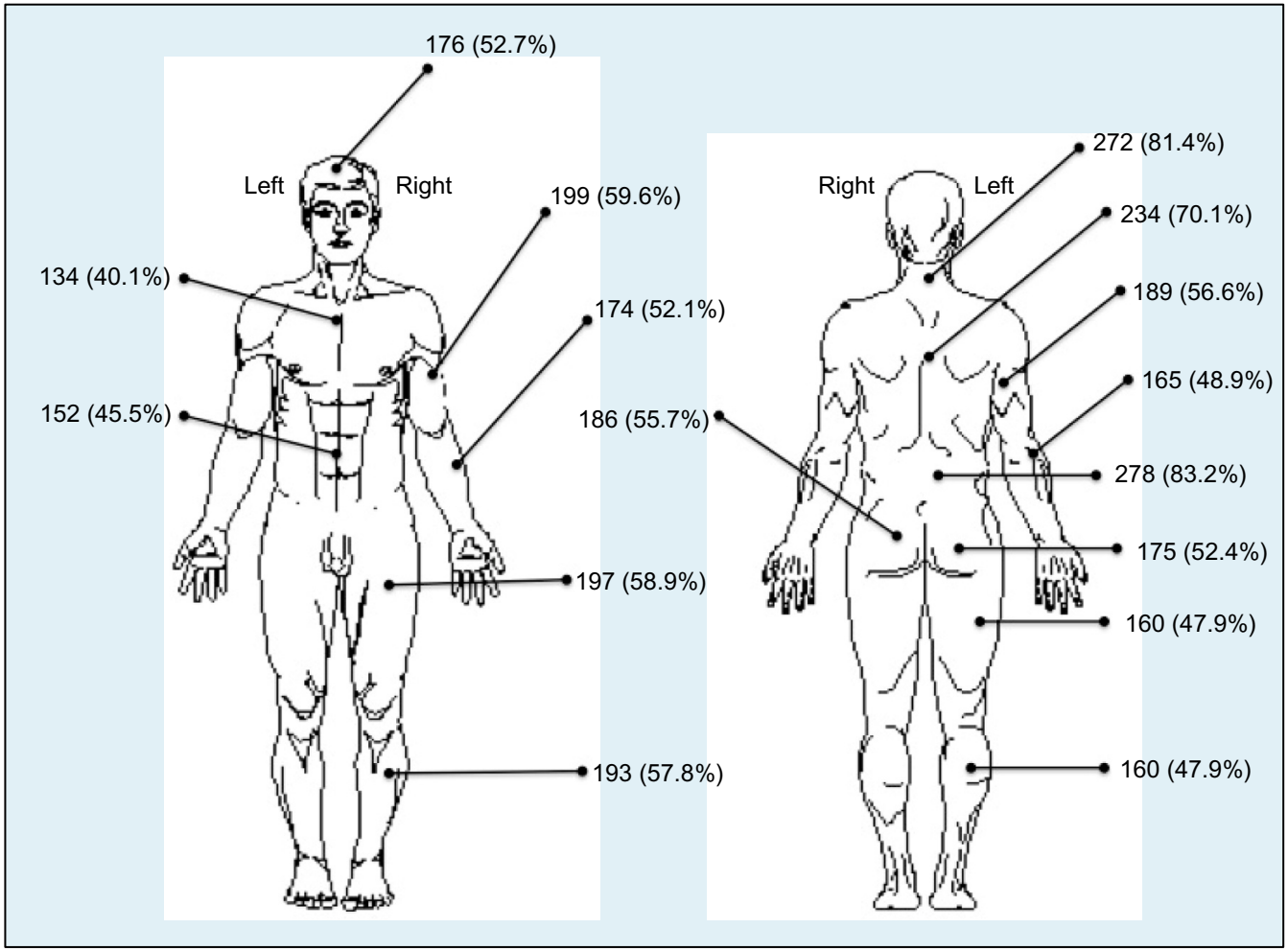


Figure 1 Spydergrams of the FIQR domains.
Notes: The domain scores are plotted from 0 (best, at the center) to 10 (worst, at the outside).
Abbreviation: FIQR, Fibromyalgia Impact Questionnaire Revised version.

Identifying the symptom and functional domains in patients with fibromyalgia: results of a cross-sectional Internet-based survey in Italy



Pain by location expressed in terms of percentage (%) as revealed by the Self-Administered Pain Scale. **Note:** Data are presented as n (%).

Identifying the symptom and functional domains in patients with fibromyalgia: results of a cross-sectional Internet-based survey in Italy

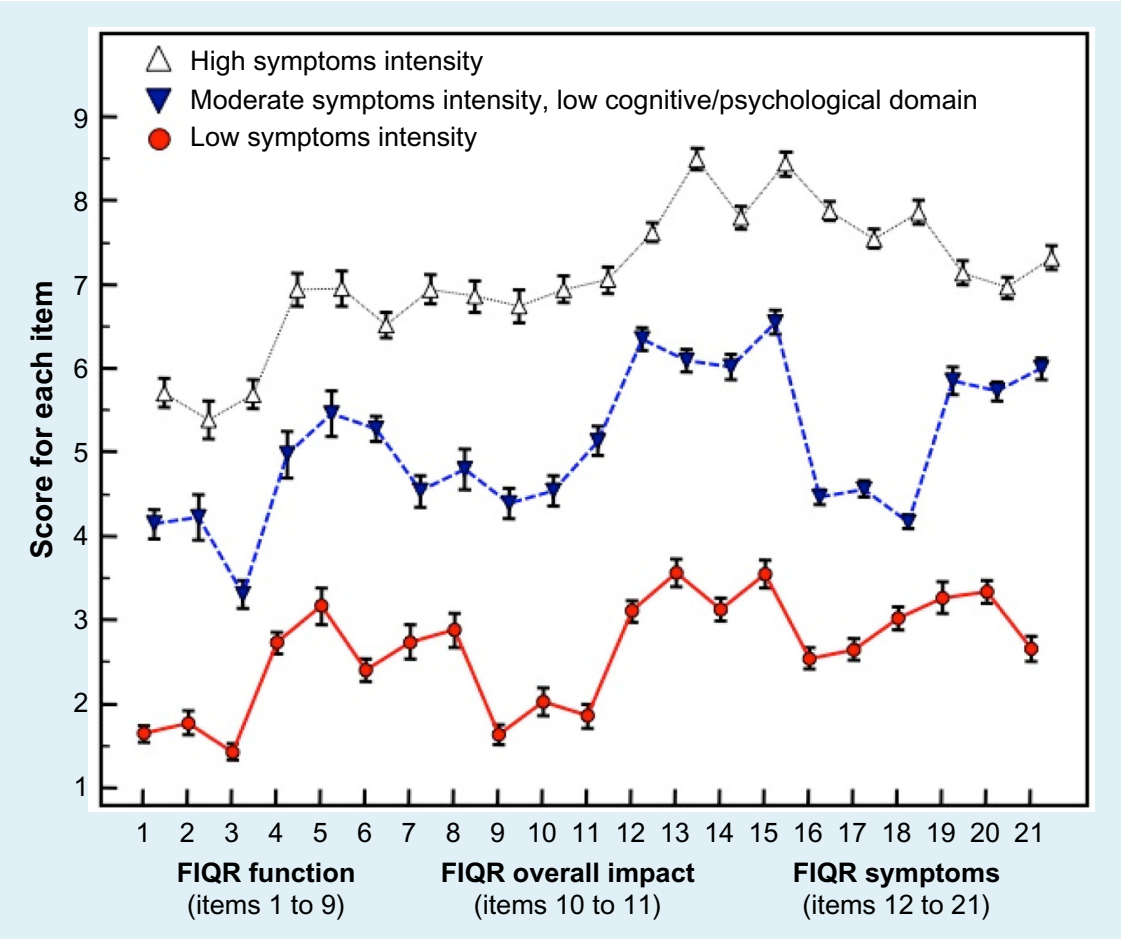


Figure 3 Cluster pro les.
Notes: Cluster 1 (n=117, red line) showed generally low symptom intensity; cluster 2 (n=120, blue line) was characterized by moderate symptoms and low cognitive/ psychological domain scores; cluster 3 (n=116, gray line) showed the least control over pain, considerable tenderness, high symptom levels, and considerable cognitive/ psychological problems.
Abbreviation: FIQR, Fibromyalgia Impact Questionnaire Revised version.

Identification of a MicroRNA Signature for the Diagnosis of Fibromyalgia

Germán Cerdá-Olmedo[1,2☯], Armando Vicente Mena-Durán[1☯], Vicente Monsalve[1], Elisa Oltra[1,3]*

Genome-wide expression profiling of miRNAs was assessed in Peripheral Blood Mononuclear Cells (PBMCs) of FM patients (N=11) and population-age-matched controls (N=10) using human v16-miRbase 3D-Gene microarrays (Toray Industries, Japan). Selected miRNAs from the screen were further validated by RT-qPCR.

Microarray Average values after global normalization.

miRNA ID	Control Average	FM Average	Ratio C/FM Average
hsa-miR-223-3p	66736.98	10577.74	6.31
hsa-miR-451a	4830.07	358.62	13.47
hsa-miR-338-3p	374.20	32.22	11.62
hsa-miR-143-3p	506.26	45.42	11.15
hsa-miR-145-5p	546.05	52.58	10.39

PLoS ONE 2015 ; 10(3): e0121903.

Identification of a MicroRNA Signature for the Diagnosis of Fibromyalgia

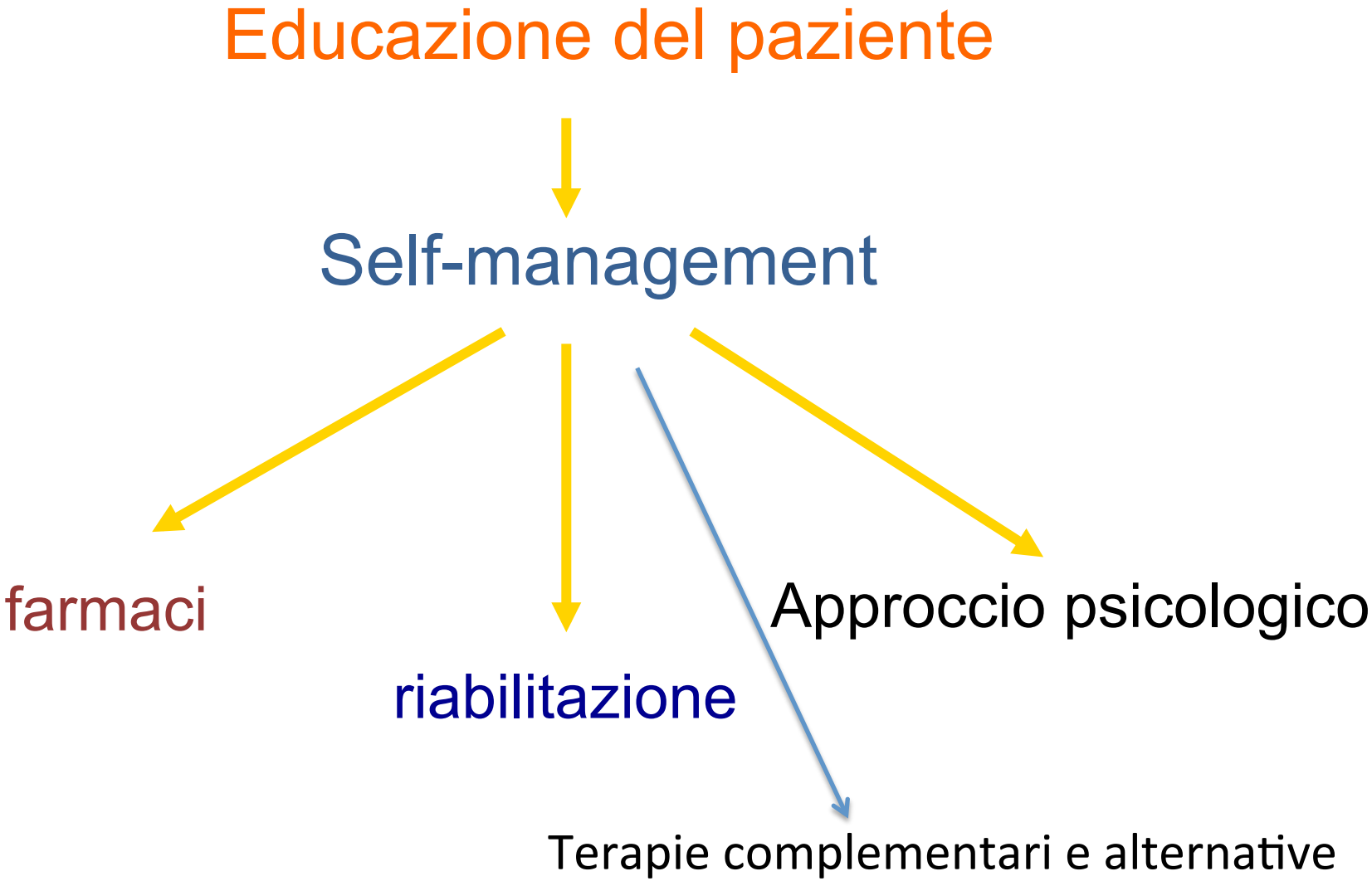
Germán Cerdá-Olmedo[1,2☯], Armando Vicente Mena-Durán[1☯], Vicente Monsalve[1], Elisa Oltra[1,3]*

Globally, **20% of the miRNAs analyzed** (233/1212) showed downregulation of at least 2-fold in patients. This might indicate a general de-regulation of the miRNA synthetic pathway in FM. No significant correlations between miRNA inhibition and FM cardinal symptoms could be identified

A signature of five strikingly downregulated miRNAs (hsa-miR223-3p, hsa- miR451a, hsa-miR338-3p, hsa-miR143-3p and hsa-miR145-5p) may be used as **biomarkers of FM**

PLoS ONE 2015 ; 10(3): e0121903.

Approccio multidisciplinare



Trattamento multidisciplinare della FM nella pratica clinica

Step 1

Educazione del paziente

- Descrivere la condizionee
- Discutere e valutare le possibili modalità terapeutiche

Step 2

Trattamento farmacologico

- monoterapia
- Terapia di combinazione(step-up, step-down)

Step 3

Trattamento non farmacologico

- Esercizio
- Stretching
- Condizionamento aerobico
- Terapia cognitivo-comportamentale
- Psicoterapia

Step 4

Modalità aggiuntive (solitamente scelte dal paziente)

- agopuntuta
- Medicina complementare o alternativa

Sarzi-Puttini P, Buskila D, Atzeni F et al Semin Arthritis Rheum 2008

Trattamento della Fibromialgia: Strategia terapeutica raccomandata

Una terapia multidisciplinare individualizzata ai sintomi e alla tipologia del paziente è raccomandata

Una combinazione di terapie farmacologiche e non farmacologiche può dare risultati nella maggior parte dei pazienti

Nonfarmacologica

- **Esercizio aerobico**
- **Terapia cognitivo comportamentale**
- **Educazione del paziente**
- **Rinforzo muscolare**
- **Agopuntura**
- **Biofeedback**
- **Balneoterapia**
- **Ipnositerapia**

Farmacologica

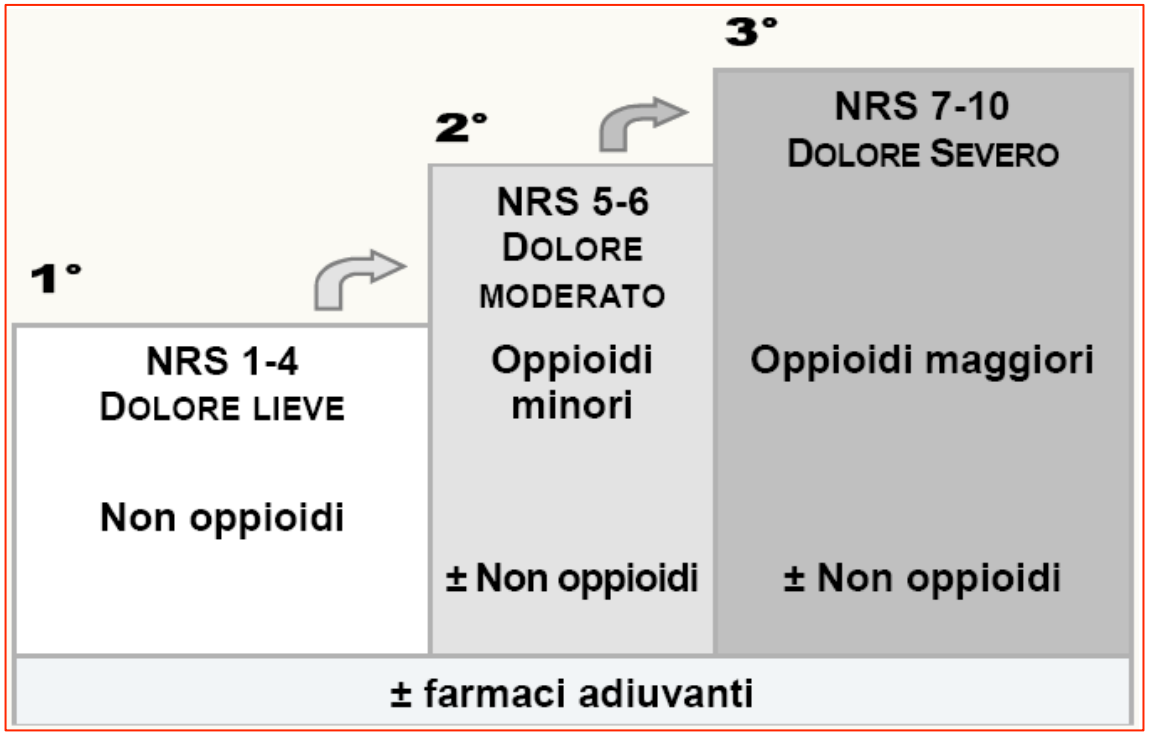
- **Analgesici**
- **Analgesici antiepilettici**
- **Antidepressivi**
- **Opioidi**

Mease. *J Rheumatol.* 2005;32(suppl 75):6-21. Carville et al. *Ann Rheum Dis*. 2008;67(4):536-41. Goldenberg et al. *JAMA*. 2004;292:2388-2395. Clauw & Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701. Arnold et al. *Arthritis Rheum.* 2007;56:1336-1344.

Self-management

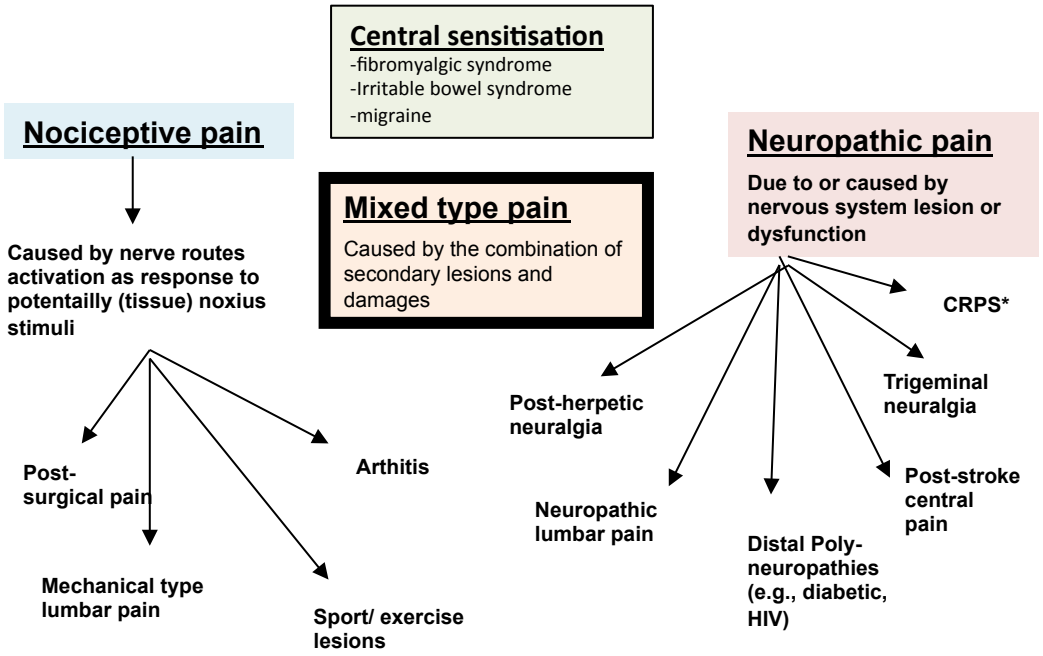
- Il paziente deve diventare un esperto della sua malattia
- Deve decidere come impostare la terapia
- Deve gestire i cambiamenti
- Deve decidere se il dolore sarà per sempre un compagno della sua esistenza oppure no

Scala OMS



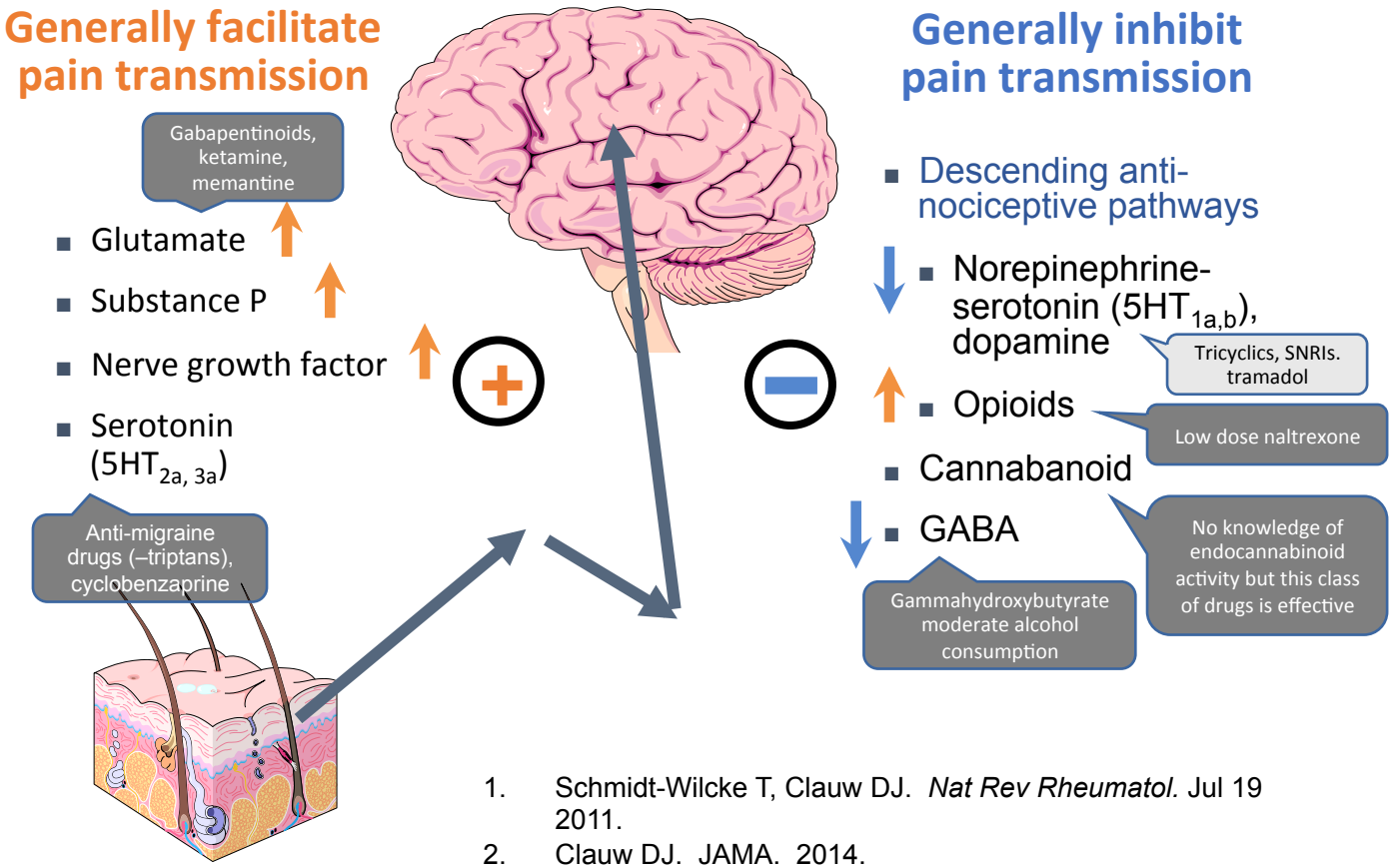
Scala dell'Organizzazione mondiale della sanità (WHO, 1996) modificata.

PAIN: NOCICEPTIVE vs NEUROPHATIC vs CENTRAL SENSITISATION



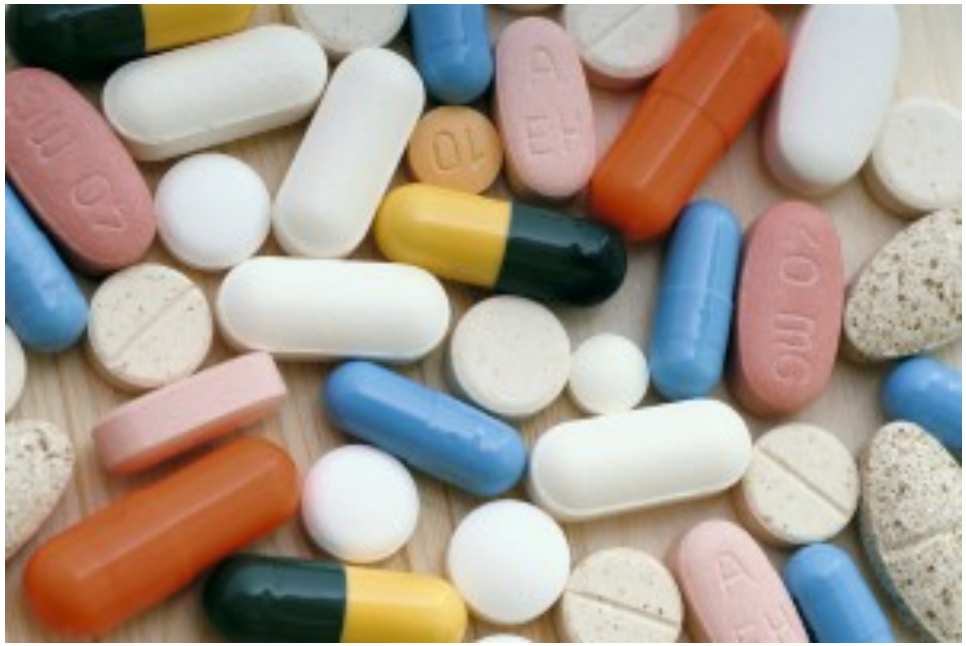
* Complex regional pain syndrome

CNS Neurotransmitters Influencing Pain
Arrows indicate direction in Fibromyalgia



1. Schmidt-Wilcke T, Clauw DJ. *Nat Rev Rheumatol.* Jul 19 2011.
2. Clauw DJ. JAMA. 2014.

I farmaci sono amici del genere umano



I principali farmaci utilizzati nel trattamento della fibromialgia

Farmaco	Classificazione	Dosaggio iniziale (mg)	Dosaggio di mantenimento (mg)	Approvato FDA per la FM
Amitriptilina	antidepressivo	5-10	30-60	no
Ciclobenzaprina	miorilassante	10	40-50	no
Pregabalin	anticonvulsivante	25-75	150-600	si
Gabapentina	anticonvulsivante	100-300	900-2400	no
Duloxetina	antidepressivo	30	60-120	si
Milnacipran	antidepressivo	12.5	50-100	si
Tramadolo	oppiaceo debole	25-50	150	no
Paracetamolo	analgesico	500-1000	3000	no
Tizanidina	miorilassante	4	8-36	no
Alprazolam	ansiolitici	0.25-0.5	0-5-2.0	no
Zolpidem	Ipnotico non benzodiazepinico	2,5-5	5-10	no
Venlafaxina	antidepressivo	37.5	75-150	no
Paroxetina	antidepressivo	10	20-40	no
Fluoxetina	antidepressivo	10	20	no
Mirtazipina	antidepressivo	15	15-30	no

La finestra terapeutica

Efficacia clinica

Effetti collaterali

Può essere molto stretta

Trattamento farmacologico e fibromialgia

Quali sono le problematiche degli studi farmacologici nei pazienti fibromialgici ?

Placebo and nocebo responses in randomised controlled trials of drugs applying for approval for fibromyalgia syndrome treatment: systematic review and meta-analysis

W. Häuser[1,2], P. Sarzi-Puttini[3], T.R. Tölle[4], F. Wolfe[5]

La risposta placebo è definita come la riduzione di un sintomo come risultato di fattori correlati alla percezione del paziente dell'intervento placebo

Clin Exp Rheumatol 2012; 30 (Suppl. 74): S78-S87.

Placebo and nocebo responses in randomised controlled trials of drugs applying for approval for fibromyalgia syndrome treatment: systematic review and meta-analysis

W. Häuser[1,2], P. Sarzi-Puttini[3], T.R. Tölle[4], F. Wolfe[5]

18 studi con 3546 pazienti in placebo sono stati analizzati.

La stima complessiva di una riduzione del dolore del 50% nel gruppo placebo era del 18.6% (95% CI 17.4 to 19.9%) dei pazienti

Clin Exp Rheumatol 2012; 30 (Suppl. 74): S78-S87.

European Journal of Neurology 2012, **19:** 672–680 doi:10.1111/j.1468-1331.2011.03528.x

REVIEW ARTICLE

Nocebo in fibromyalgia: meta-analysis of placebo-controlled clinical trials and implications for practice

D. D. Mitsikostas[a], N. G. Chalarakis[a], L. I. Mantonakis[a], E.-M. Delicha[a,b] and P. P. Sfikakis[b]

[a]*Department of Neurology, Naval Hospital, Athens; and* [b]*First Department of Propaedeutic and Internal Medicine, Laiko General Hospital, Athens University, Athens, Greece*

L' effetto Nocebo si riferisce a eventi avversi (effetti collaterali) generati da aspettative negative del paziente il quale ritiene che il trattamento farmacologico causerà probabilmente effetti tossici invece di un miglioramento clinico.

Questo effetto nocebo può essere misurato negli studi clinici randomizzati e controllati.

Percentuale di interruzione a causa di intolleranza nei pazienti trattati con placebo (effetto nocebo) negli studi clinici randomizzati e controllati di sclerosi multipla, cefalea e fibromialgia

Quadro clinico	Interruzione placebo (%)	Intervallo di confidenza
Sclerosi multipla	2.1	1.6-2.67
Cefalea	4.75	3.28-6.45
Fibromialgia	9.5	8.8-10.9

Conclusioni su come utilizzare i farmaci

- Utilizzare pochi farmaci e diventare esperti nel loro utilizzo
- Il paziente fibromialgico deve imparare a gestire i dosaggi dei farmaci e a modificarli lentamente
- Molti dei nostri pazienti prendono 3-4 farmaci contemporaneamente e questo aumenta il rischio di effetti colllaterali

What is new on fibromyalgia

- Terminology and diagnostic criteria
- Pathogenesis
- Clinical picture
- Genetics and Markers of disease
- Pharmacological treatment
- Non-pharmacological treatment
- New guidelines and/or reccomandations

Past Fibromyalgia (FM) Guidelines

Association	Objectives	Methods	Results
APS (American Pain Society)	To provide evidence-based guidelines for diagnosis and manangement of FM syndrome in children and adults and to improve quality of care	Review of clinical trials and meta-analyses Rating scheme ranked evidence Guidelines reached by consensus of interdisciplinary panel of 13 experts	Guidelines for diagnosis based on American College of Rheumatology criteria and other symptomatic assessments Guidelines for specific pharmacologic and nonpharmacologic interventions
EULAR (European League Against Rheumatism)	To develope evidence-based recommendations for the mangement of FM syndrome	Systematic review of pharmacologic and nonpharmacologic intervention studies Rating scheme ranked evidence Recommendations reached by consensus of task force of 19 international European experts	2 General recommendations for recognition / diagnosis and multidisciplinary approach to management 4 Recommendations for nonpharmacologic management 4 Recommandations for pharmacologic management

Burckhardt CS et al American Pain Society,2005, Goldenberg DL et al JAMA, 2004, Carvile SF et al, Ann Rheum Dis 2008, Mease PJ et al, J Rheumatol 2005, Mease P et al J Rheumatol 2007

Comparison of APS and EULAR Guidelines for Fibromyalgia - FM Management

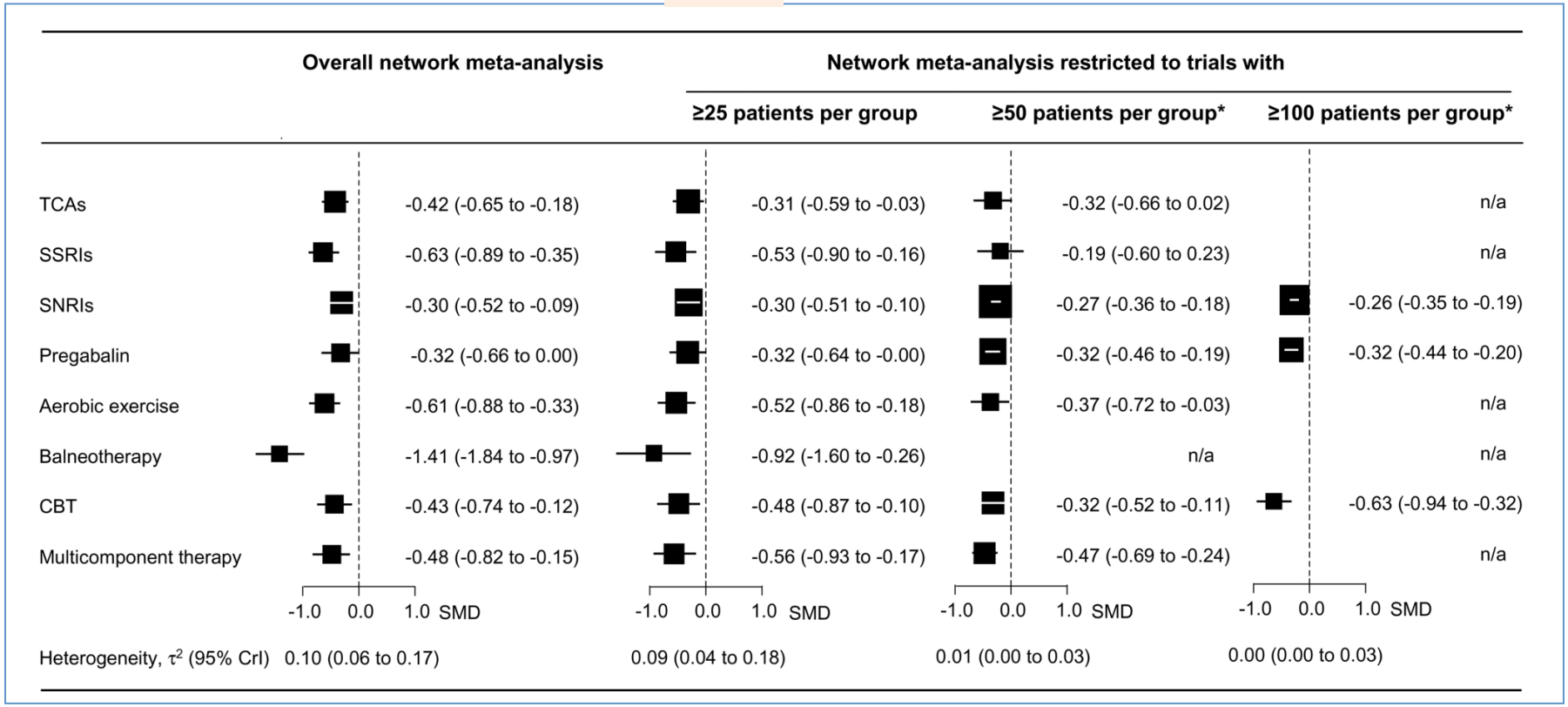
	Nonpharmacologic Therapy	Pharmacologic Therapy	Limitations of study Analysis
APS (American Pain Society)	Strong evidence: Patient education CBT Aerobic exercise Multidisciplinary therapy Moderate evidence: Strength training Acupuncture Hypnotherapy Biofeedback Balneotherapy	**Strong evidence**: **Amitriptyline 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

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]

Pain



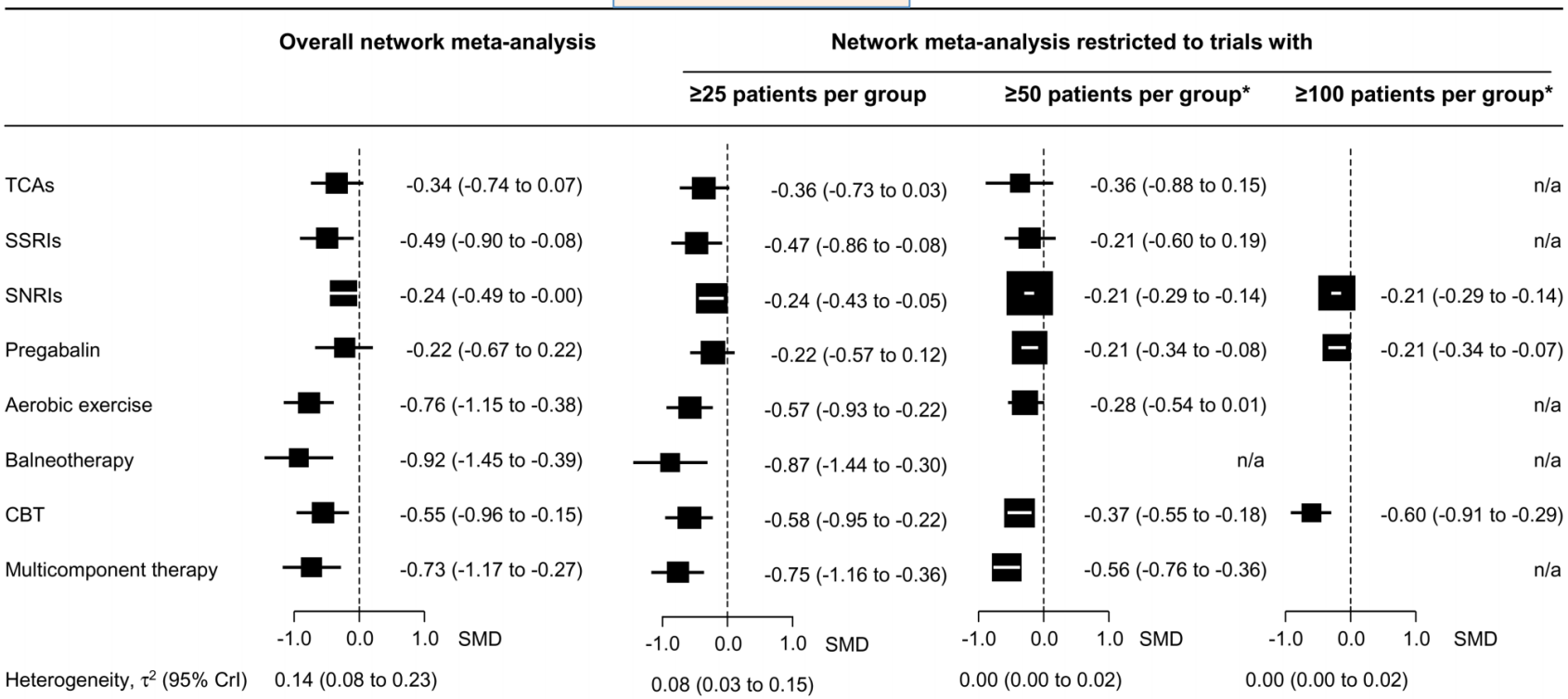
Estimates of standardised mean differences (SMDs) with 95% credibility intervals (95% CrI) in pain for therapeutic interventions compared with placebo from overall network meta-analyses and network meta-analyses restricted to trials with ≥25, ≥50 and ≥100 patients per group and corresponding between-trial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

Ann Rheum Dis 2013;72:955–962

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]

Quality of life



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

2016 EULAR revised recommendations for the management of fibromyalgia

EULAR FM recommendations

- The original EULAR recommendations for management of FM used evidence up to 2005.

- There were few studies and mainly of poor quality: most recommendations were based on "expert opinion".

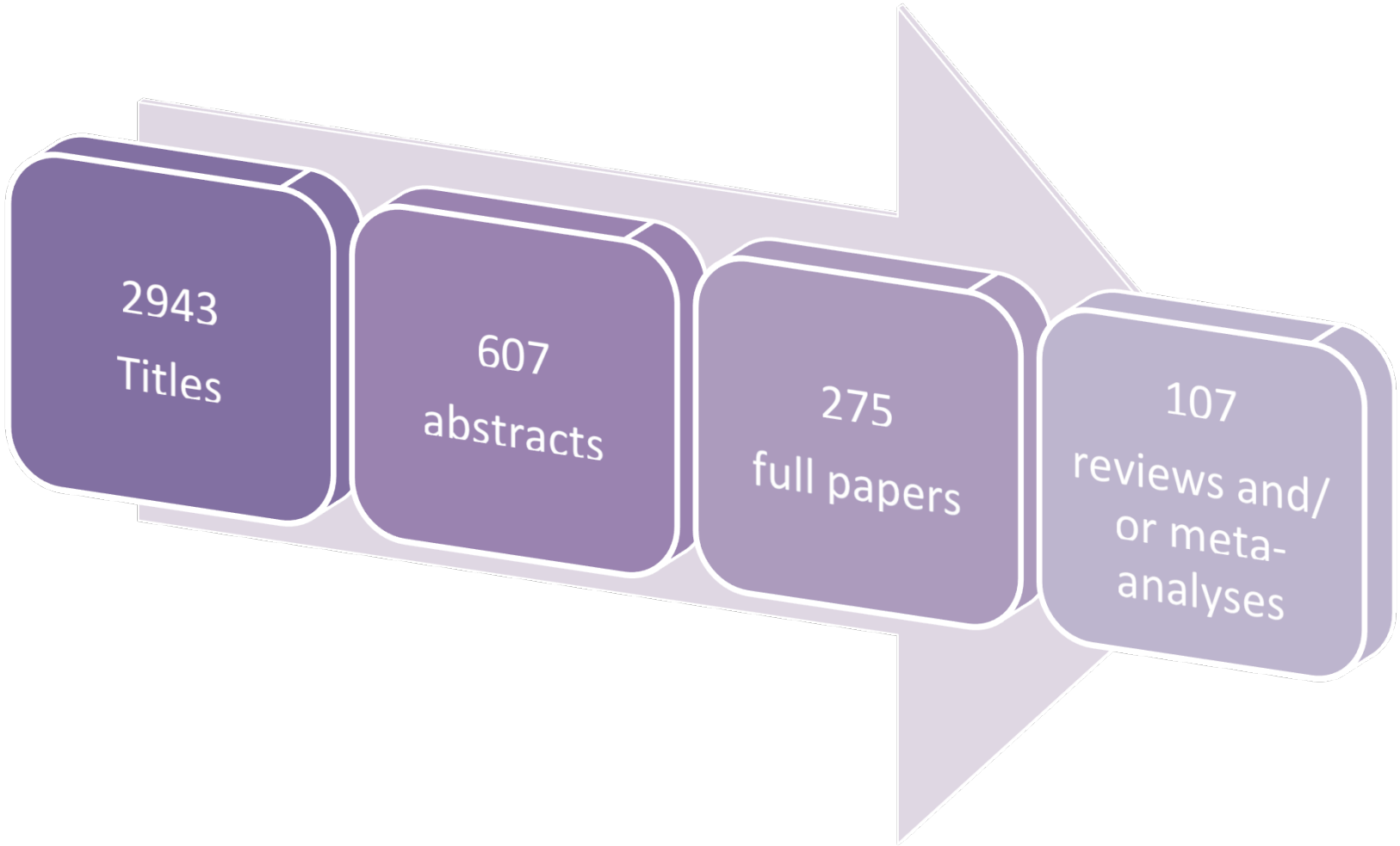
- It had been recommended that they be updated after four years, but it is only now, a decade later we update them with a view to making them more evidence based.

Carville et al, Rheumatology, 2008

Assessing Evidence

- We focussed on systematic reviews (+/- meta-analysis) and undertook quality assessment.
- Key outcomes: pain, fatigue, sleep, daily functioning.
- Key aspects influencing assessment: number of trials, number of patients, outcomes assessed, quality of reviews/trials, effect size, adverse events, cost.

Identifying eligible reviews



Overarching principles of management 1

- Optimal management requires prompt diagnosis.
- Full understanding of fibromyalgia requires comprehensive assessment of pain, function, and psychosocial context.
- It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features.
- In general, the management of FM should take the form of a graduated approach

Overarching principles of management 2

- Management should aim at improving health-related quality of life balancing benefit and risk of treatment which often requires a multidisciplinary approach with a combination of non-/ pharmacological treatment modalities.

- These should be tailored according to: pain intensity, function, associated features (e.g. depression), fatigue, sleep disturbance, patient comorbidities; by shared decision making with the patient.

- Initial management should focus on non-pharmacological therapies

Specific recommendations 1

Recommendation	Level of evidence	Grade	Agreement
Non-Pharmacological Management			
Aerobic and strengthening exercise	**Meta-analysis**	**Strong for**	**100%**
Cognitive Behavioural Therapies	**Meta-analysis**	**Weak for**	**100%**
Multicomponent therapies	**Meta-analysis**	**Weak for**	**93%**
Defined physical therapies: acupuncture or hydrotherapy	**Meta-analysis**	**Weak for**	**93%**
Meditative movement therapies (qigong, yoga, tai chi) and Mindfulness Based Stress Reduction	**Meta-analysis**	**Weak for**	**71-73%**

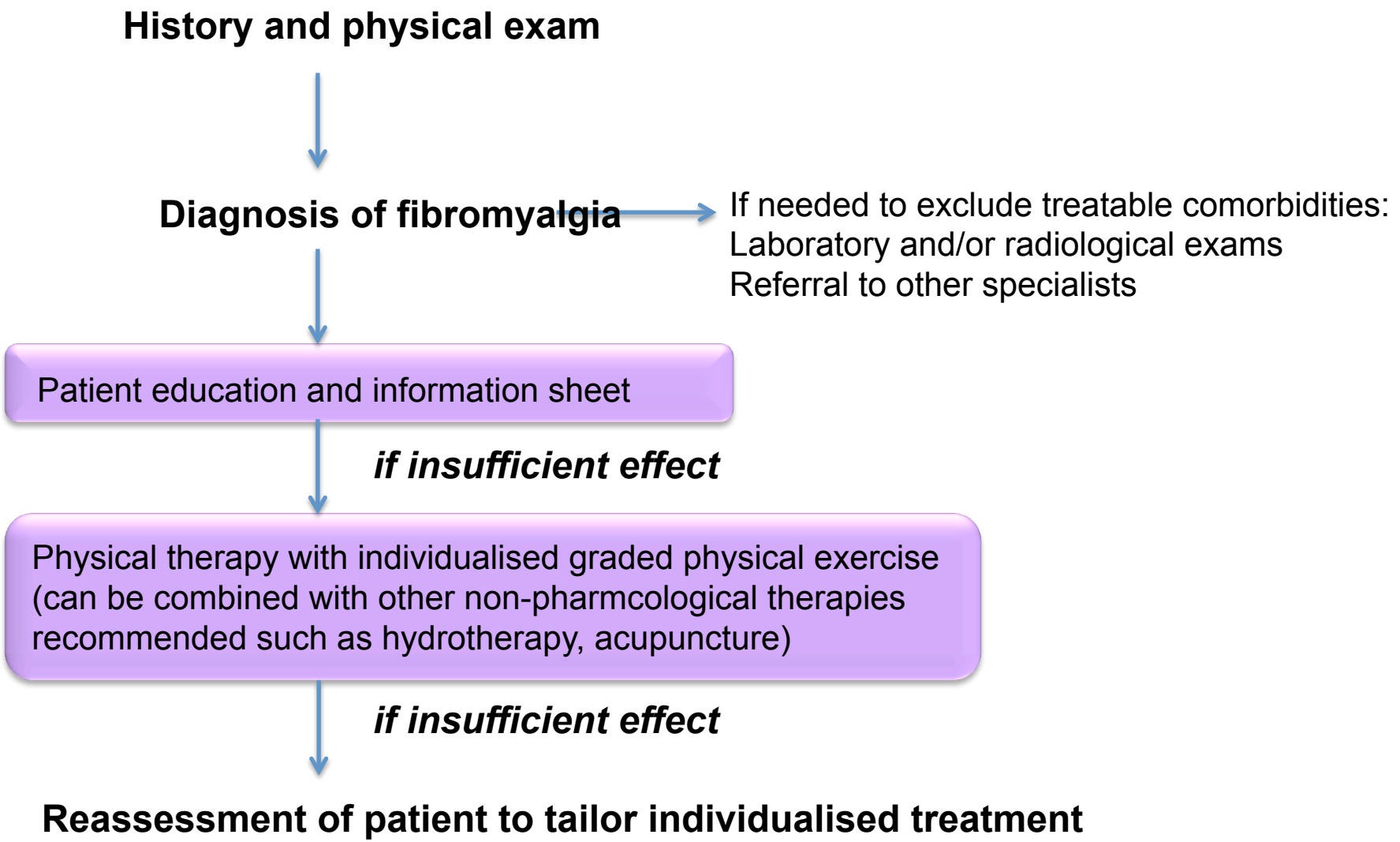
Agreement: % of working group scoring ≥ 7 on 0-10 VAS of how much they agreed with recommendation

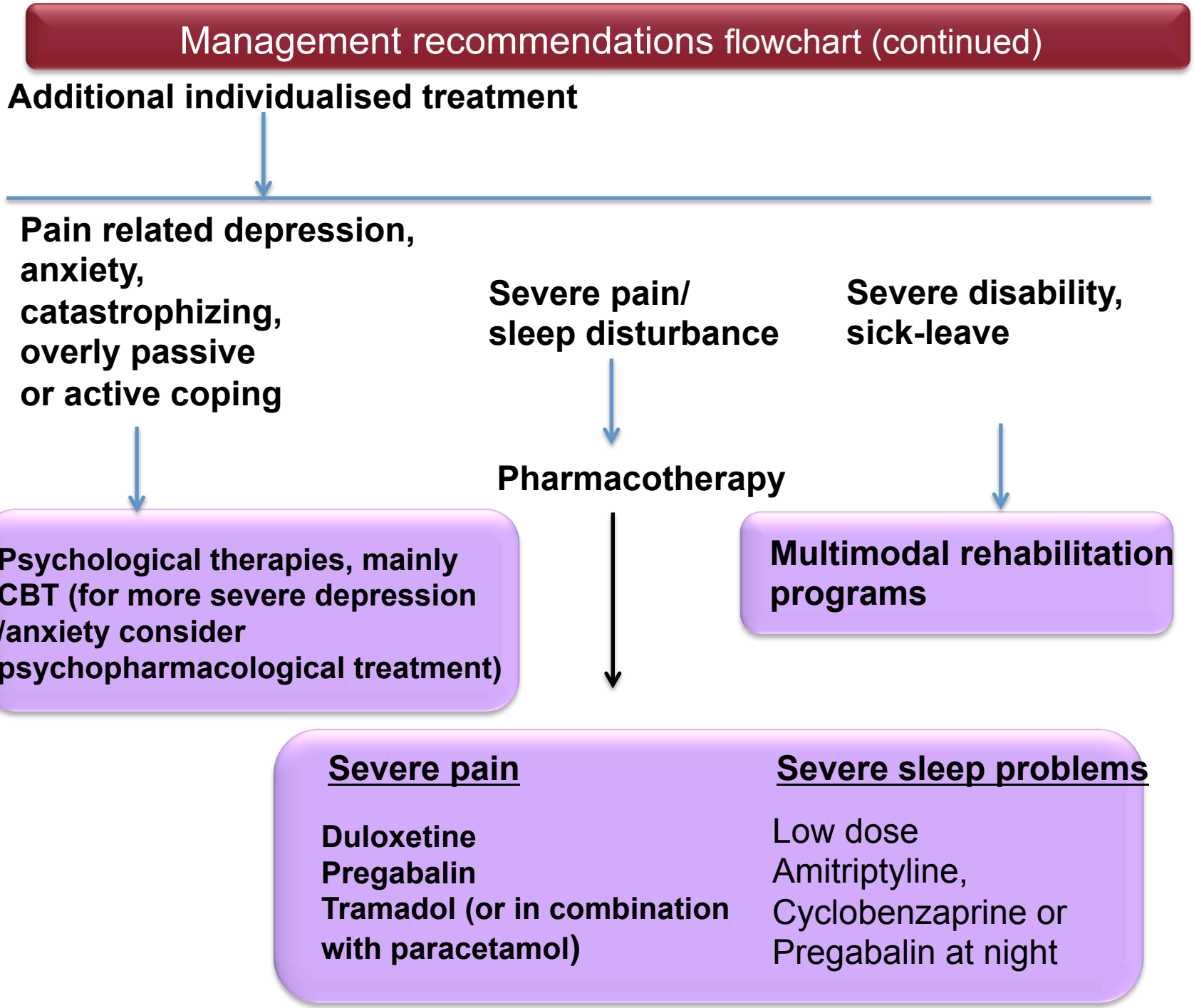
Specific recommendations 2

Recommendation	Level of evidence	Grade	Agreement
Pharmacological Management			
Amitriptyline (at low dose)	**Meta-analysis**	**Weak for**	**100%**
Duloxetine or Milnacipran	**Meta-analysis**	**Weak for**	**100%**
Tramadol	**Review**	**Weak for**	**100%**
Pregabalin	**Meta-analysis**	**Weak for**	**94%**
Cyclobenzaprine	**Meta-analysis**	**Weak for**	**75%**

Agreement: % of working group scoring ≥ 7 on 0-10 VAS of how much they agreed with recommendation

Management recommendations flowchart

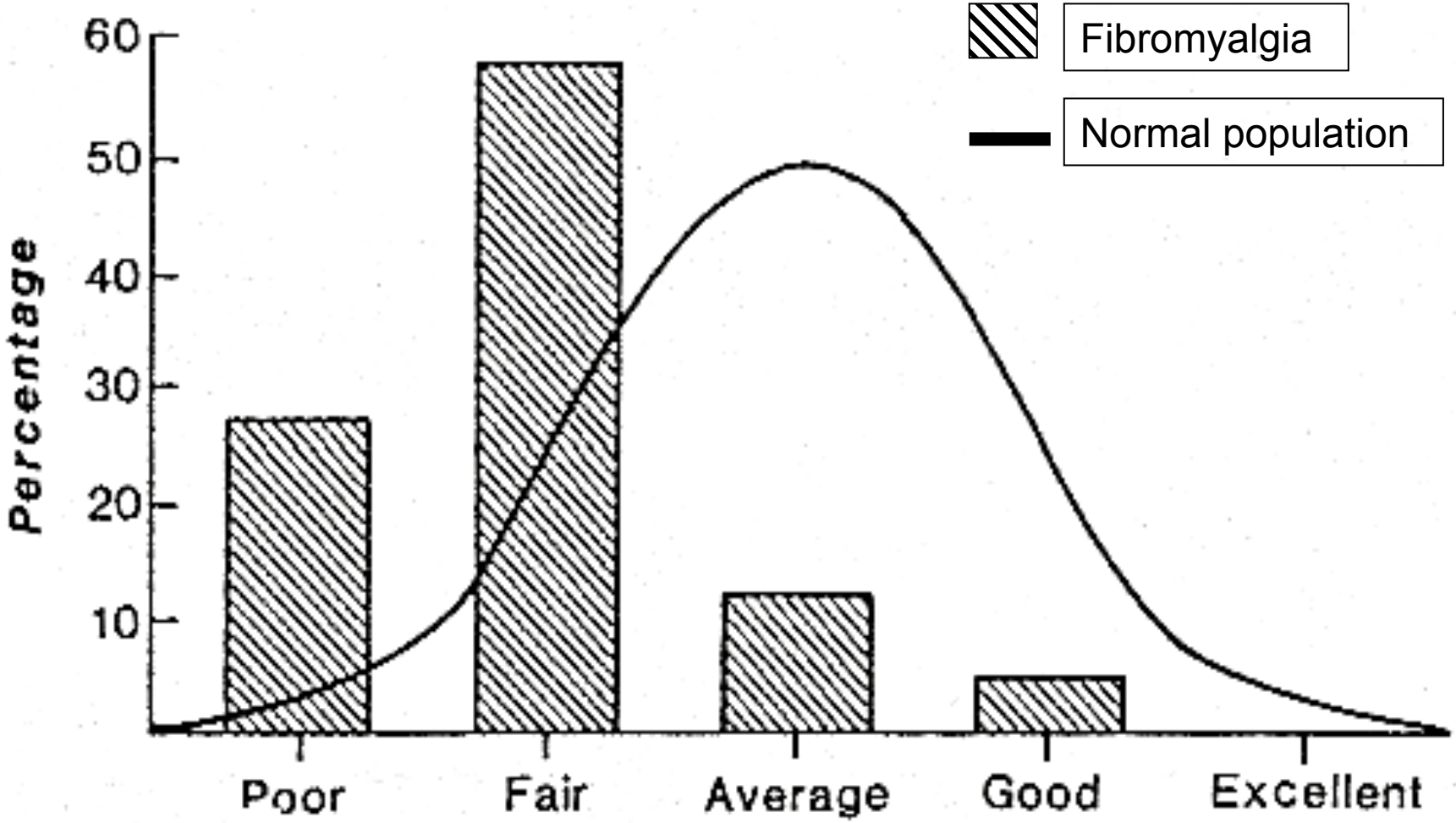



Management recommendations flowchart (continued)
Additional individualised treatment
Pain related depression, anxiety, catastrophizing, overly passive or active coping
Severe pain/ sleep disturbance
Severe disability, sick-leave
Pharmacotherapy
Psychological therapies, mainly CBT (for more severe depression /anxiety consider psychopharmacological treatment)
Multimodal rehabilitation programs
Severe pain
Duloxetine
Pregabalin
Tramadol (or in combination with paracetamol)
Severe sleep problems
Low dose Amitriptyline, Cyclobenzaprine or Pregabalin at night

Research priorities

- **Which type of exercise is most effective: strength and/or aerobic training?**
- **Is a combined pharma and non-pharma approach, more effective than single modality management?**
- **Are there characteristics of patients which predict response to specific therapies?**
- **How should FM be managed when it occurs as a co-morbidity to inflammatory arthritis?**
- **What aspects of healthcare system design optimise outcome for patients?**

La forma fisica nei pazienti fibromialgici



Bennett RM. J Rheumatol 1989; 16:185-91.

Differenti Strategie di terapia psicologica del dolore

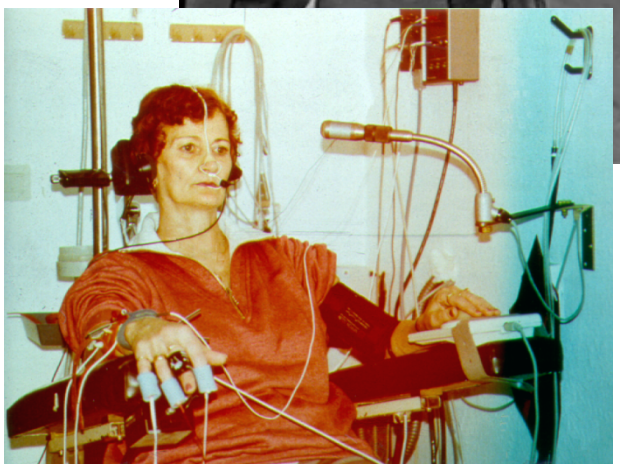
- Terapia Cognitivo-Comportamentale

  Focus sulle attitudini al dolore e allo stress

- Terapia operante sul dolore

  Focus operativo sul dolore con lo scopo di sviluppare comportamenti di salute nonostante il dolore cronico

- Biofeedback - Rilassamento



Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials

MARY-ANN FITZCHARLES,[1] PETER A. STE-MARIE,[1] WINFRIED HÄUSER,[2] DANIEL J. CLAUW,[3] SHAHIN JAMAL,[4] JACOB KARSH,[5] TARA LANDRY,[6] SHARON LECLERCQ,[7] JASON J. MCDOUGALL,[8] YORAM SHIR,[1] KAM SHOJANIA,[9] AND ZACH WALSH[4]

Current preparations are available as 4 products:

- the **herbal product** administered by a weight measurement in grams,

3 pharmacologic preparations, including 2 synthetic oral agents,

- **dronabinol,** a stereoisomer of D9- THC,
- **nabilone**, a synthetic analog of D9-THC,
- an oromucosal spray of cannabis extract, **nabiximol**, a combination of D9-THC and CBD as well as trace amounts of minor phytocannabinoids

Arthritis Care Res (Hoboken). 2016 May;68(5):681-8

Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials

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Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9:164–73.

The treatment group showed statistically improved pain and FIQ score at 4 weeks.

The 16% reduction in FIQ total score does, exceed the reported minimum important difference for a change of 14% in the FIQ total score

There were no serious adverse events reported for the study.

Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia and Analgesia 2010;110:604–1

Both agents showed a positive effect on sleep.

There were no significant differences between treatments for effect on pain or quality of life.

Adverse events of dizziness, drowsiness, nausea, and dry mouth were more frequently reported in the nabilone treatment group. There were no serious adverse events.

Arthritis Care Res (Hoboken). 2016 May;68(5):681-8

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

Kevin F. Boehnke,* Evangelos Litinas,† and Daniel J. Clauw‡,§

Sensitivity Analysis of Outcomes of Interest

Outcome of Interest	*Entire Set of Questionnaires (N = 244)*	*Questionnaires That Were ≥60% Completed (N = 192)*	*Questionnaires That Were ≥80% Completed (N = 186)*	*Questionnaires That Were Fully Completed (N = 185)**
FM score	9.23 (5.52)	9.28 (5.54)	9.15 (5.40)	9.16 (5.42)
Opioid use change	−63% (46%)	−63% (47%)	−64% (44%)	−64% (45%)
Degree to which side effects of medication affect daily function (before using medical cannabis); scale from 1 to 10	6.44 (2.91)	6.42 (2.91)	6.46 (2.89)	6.51 (2.88)
Degree to which side effects of medication affect daily function (after using medical cannabis); scale from 1 to 10	2.77 (2.35)	2.78 (2.36)	2.78 (2.38)	2.79 (2.39)
Number of medication classes used (before cannabis use)	2.35 (1.43)	2.34 (1.44)	2.36 (1.44)	2.38 (1.44)
Number of medication classes used (after cannabis use)	1.82 (.94)	1.84 (.95)	1.83 (.95)	1.81 (.95)
Quality of life change	45% (28%)	45% (28%)	45% (29%)	45% (29%)

NOTE. All quantities reported as mean (SD).
*Only fully completed questionnaires were used for final analyses.

J Pain. 2016 Jun;17(6):739-44.

Novel pharmaceutical options for treating fibromyalgia

Maria Chiara Gerardi[a], Alberto Batticciotto[a], Rossella Talotta[a], Manuela Di Franco[b], Fabiola Atzeni[a] and Piercarlo Sarzi-Puttini[a]

[a]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy; [b]Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy

Investigational drug trials

Trial (status)	Drug	Duration	Primary outcome measures	Secondary outcome measures
Phase II (completed) NCT01693692	TD-9855 (group 1) *versus* TD-9855 (group 2) *versus* placebo	6 weeks	Percentage change in mean pain score	FIQ; PGIC
Phase III (recruiting) NCT02187471 NCT02187159 NCT02146430	Mirogabalin(DS-5565) 15 mg/day and mirogabalin (DS55-65) 15 mg twice a day *versus* placebo Pregabalin 150 mg twice a day as active comparator	13 weeks	DS-5565 *versus* placebo: Change in weekly ADPS	DS-5565 *versus* pregabalin: change in ADPS; DS-5565 *versus* placebo: proportion of responders; change in PGIC, FIQ, MFI-20, HADS, SF-36, EQ-5D, ADSIS, BPI-SF; Safety
Phase IIb (completed) NCT01903265	CYCLOBENZAPRINE sublingual 2.8 mg (TNX-102) *versus* placebo	12 weeks	Change from baseline in patient-perceived pain	PGIC; FIQ; patient pain improvement response rate; SF-36 physical component score; safety
Phase III (recruiting) NCT02436096	CYCLOBENZAPRINE sublingual 2.8 mg (TNX-102) *versus* placebo	12 weeks	Proportion of patients with $a \geq 30\%$ improvement from baseline in perceived pain	PGIC; Proportion of patients with a PGIC of 'very much improved' or 'much improved'; FIQ; PROMIS; PROMIS score for sleep disturbance; assessment of sleep quality; PROMIS score for fatigue; average pain severity score; safety
Phase II (recruiting) NCT00366535	NEUROTROPIN for 12 weeks then placebo for 12 weeks *versus* placebo for 12 weeks and then active medication for 12 weeks	25 weeks	Relief of pain and improvement in functional capacity	Pain thresholds at specific tender points

ADPS, average daily pain score; ADSIS, average daily sleep interference score; BPI-SF, Brief Pain Inventory Short Form; EQ-5D, EuroQoL Instrument 5 Domains; FIQ, Fibromyalgia Impact Questionnaire; MFI-20, HADS, Hospital Anxiety and Depression Scale; Multidimensional Fatigue Inventory; PGIC, Patient's Global Impression of Change; PROMIS, Patient Reported Outcomes Measurement System; SF-36, Short Form 36 questionnaire.

Quali incertezze oggi

- La terminologia fibromialgia è corretta o riflette un'ipotesi diagnostica troppo orientata al dolore cronico muscoloscheletrico?
- E' possibile definire dei biomarcatori di malattia?
- Sarà possibile disporre di farmaci che agiscano in maniera specifica sui meccanismi di centralizzazione del dolore?
- E' possibile che il nostro SSN riconosca a tutti gli effetti la fibromialgia e ne garantisca le cure appropriate?