La Fibromialgia definizione, clinica e terapia

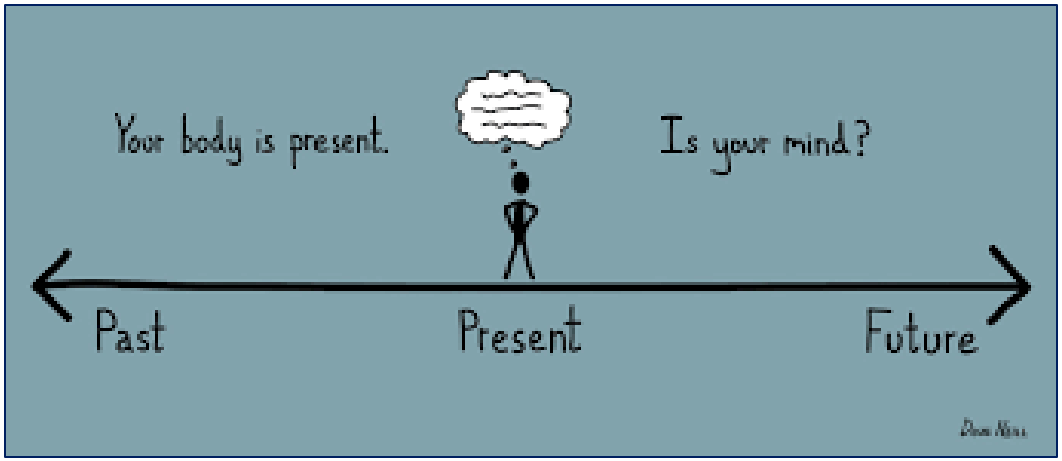
Stefano Stisi

Responsabile

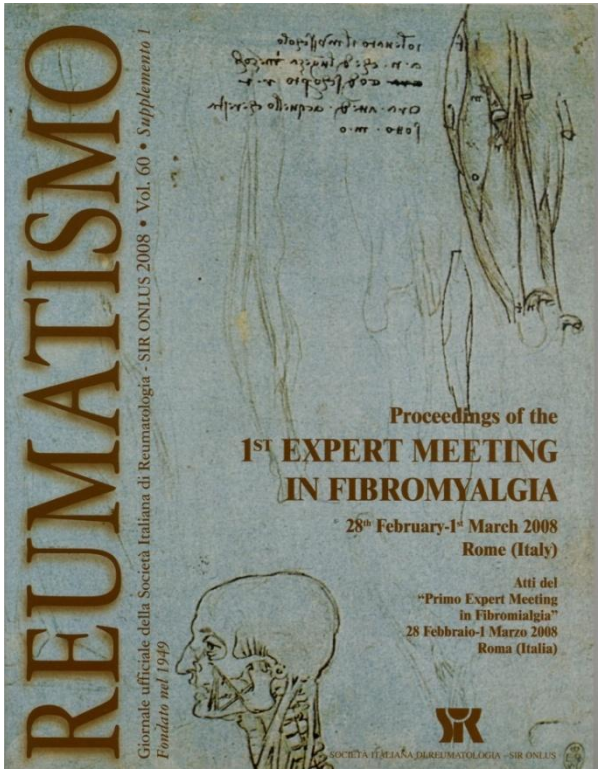
SD e reparto di Reumatologia

AO "G.Rummo Benevento

Fibromialgia cross-road tra psiche e corpo.



"Fibromyalgia is a central sensitisation syndrome characterised by dysfunctions in the neurocircuits involving the perception, transmission and processing of nociceptive afferents, with the prevalent manifestation of pain at the level of the musculoskeletal system. In addition to pain, there may be a multitude of accompanying symptoms (asthenia, sleep disturbances, abdominal pains…) that are common to other central sensitisation syndromes.
Particular genetic characteristics and a reduced individual capacity to tolerate "stressors" predispose individuals to the onset of the disease".



M. Cazzola, P. Sarzi Puttini, S. Stisi, M. Di Franco, L. Bazzichi, R. Carignola, R.H. Gracely, F. Salaffi, F. Marinangeli, R. Torta, M.A. Giamberardino, D. Buskila, M. Spath, G. Biasi, G. Cassisi, R. Casale, L. Altomonte, G. Arioli, A. Alciati, A. Marsico, F. Ceccherelli, G. Leardini, R. Gorla, F. Atzeni (Italian Fibromyalgia Network)

Fibromyalgia syndrome: definition and diagnostic aspects

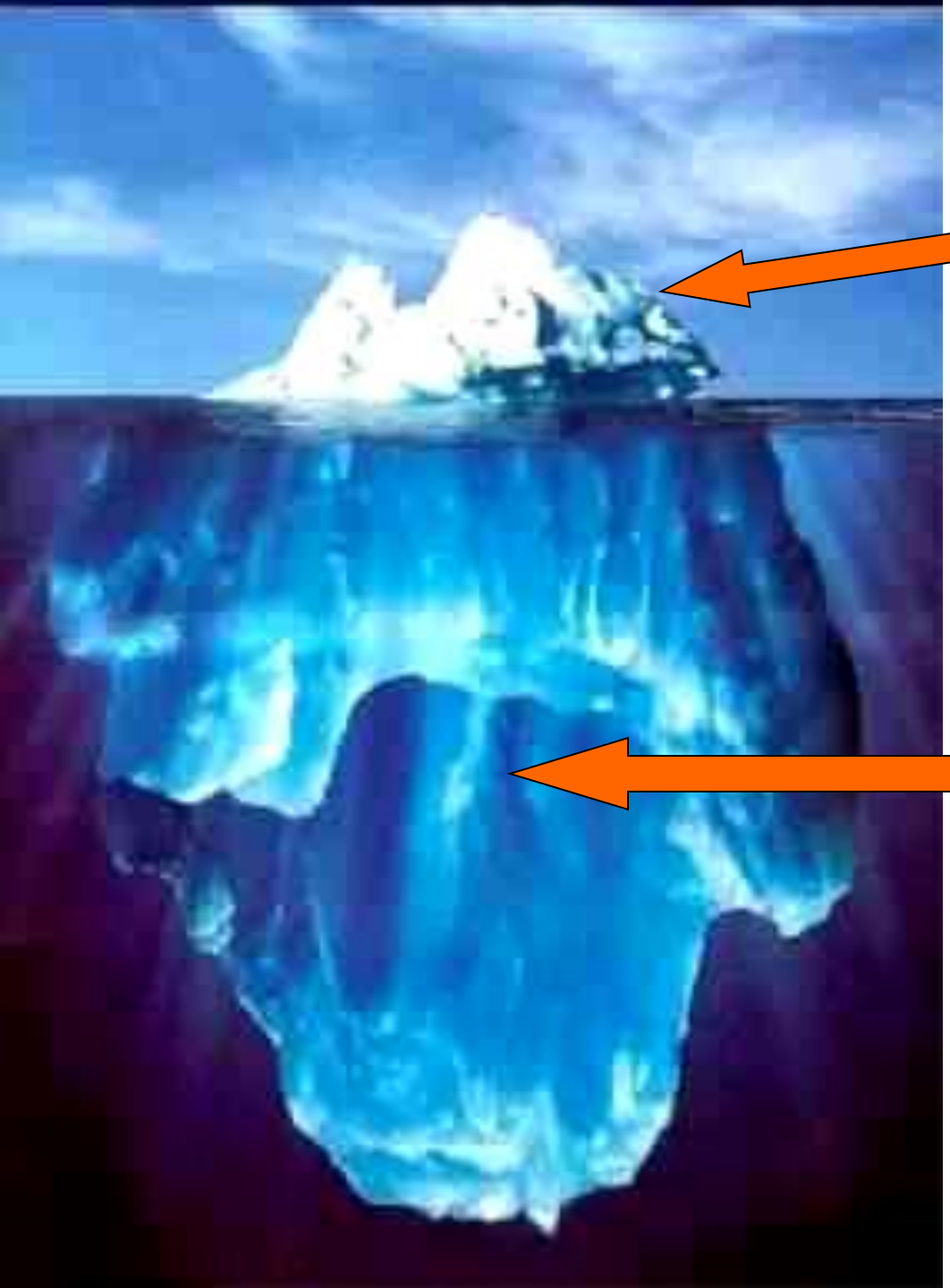
Reumatismo, 2008; 60: Supplemento 1: 3-14

CWP

Chronic Widespread Pain

FM

Fibromyalgia



FIBROMYALGIC SYNDROME

è una patologia estrema e peculiare nel contesto di una condizione dolorosa

CHRONIC WIDESPREAD PAIN

Il dolore cronico diffuso è la "*conditio sine qua non*" di una diagnosi di FM.

Clin Rheumatol (2015) 34:1473–1479
DOI 10.1007/s10067-015-2975-1

ORIGINAL ARTICLE

Is it necessary to strictly diagnose fibromyalgia syndrome in patients with chronic widespread pain?

Arzu Yagiz On[1] · Dilek Aykanat[1] · Funda Calis Atamaz[1] · Can Eyigor[2] · Hayriye Kocanogullari[3] · Fahrettin Oksel[3]

Received: 5 December 2014 / Revised: 12 May 2015 / Accepted: 13 May 2015 / Published online: 26 May 2015

Abstract The applicability of the American College of Rheumatology (ACR) 1990 and 2010 criteria for the diagnosis of fibromyalgia syndrome (FMS) was determined in 284 patients with chronic widespread pain (CWP) including those with regional and systemic painful disorders. On the basis of initial evaluation, patients were classified into three groups. Group 1, those without any comorbid disease (N=105), group 2, those having regional non-inflammatory painful disorders (N=104), and group 3, those with a diagnosis of an inflammatory rheumatic disease (N=75). Overall, 65 % of the patients fulfilled the 1990 criteria, while 94 % of them fulfilled the 2010 criteria. Almost all of the patients (97 %) with CWP did meet at least one of the criteria set, regardless of whether they have accompanying painful disorders. Widespread pain index (WPI), symptom severity scale (SS), and fibromyalgia impact questionnaire (FIQ) scores were found to be significantly higher in the patients who satisfied the 1990 criteria than those who did not (P<0.001). Tender point counts were found to be significantly correlated with WPI, SS, FIQ, and Beck depression inventory (BDI) scores (P<0.001). The findings of the study support the suggestion that FMS is just a continuum of CWP, rather than a distinct diagnostic entity. As treatment of FMS is usually identical with that of CWP, strict diagnosis of FMS will provide little or no significance from the viewpoint of clinical practice. We suggest that future research should be directed toward classification of CWP to provide guidance to clinicians in selecting effective therapies.

Keywords Fibromyalgia · Pain · Rheumatoid arthritis · Soft tissue rheumatism

✉ Funda Calis Atamaz
atamaz_02@yahoo.com

[1] Department of Physical Medicine and Rehabilitation, Ege University Medical Faculty, Izmir, Turkey

[2] Department of Anesthesiology, Pain Clinic, Ege University Medical Faculty, Izmir, Turkey

[3] Department of Internal Medicine, Division of Rheumatology, Ege University Medical Faculty, Izmir, Turkey

Introduction

Fibromyalgia syndrome (FMS) is a chronic widespread pain (CWP) syndrome, which is associated with a series of somatic and cognitive symptoms such as fatigue, sleep disturbance, anxiety, and depression. CWP is the hallmark of FMS, being the entry point of clinical pathways suggested for FMS [1]. Although CWP has been recognized for centuries, various terms have been used to strictly define chronic pain syndromes, including FMS. However, because of the lack of a specific clinical sign or an objective diagnostic indicator, it has been a challenging disorder to diagnose, and the concept of FMS as a distinct entity has been questioned by many authors.

The American College of Rheumatology (ACR) 1990 classification criteria (1990 criteria) has been the sole diagnostic criteria for FMS until recently [2]. A patient with CWP must have a positive clinical examination for tender point (TP) counts to meet the 1990 ACR criteria for FMS. Although these criteria have made the FMS a discrete disease, use of TPs has drawn a number of criticisms regarding their validity, specifity, and usability in diagnosing FMS [3]. Population-based studies demonstrated linear associations between features of psychological distress and the TP count in patients meeting the 1990 ACR criteria, suggesting that FMS may be the extreme end of a continuum of pain and rather than a discrete entity [4, 5]. More recent studies have shown that the relationship between FMS and distress is not solely due

Abstract

- The applicability of the American College of Rheumatology (ACR) 1990 and 2010 criteria for the diagnosis of fibromyalgia syndrome (FMS) was determined in 284 patients with chronic widespread pain (CWP) including those with regional and systemic painful disorders.
- On the basis of initial evaluation, patients were classified into three groups. Group 1, those without any comorbid disease (N=105), group 2, those having regional non-inflammatory painful disorders (N=104), and group 3, those with a diagnosis of an inflammatory rheumatic disease (N=75). Overall, 65 % of the patients fulfilled the 1990 criteria, while 94 % of them fulfilled the 2010 criteria.
- Almost all of the patients (97 %) with CWP did meet at least one of the criteria set, regardless of whether they have accompanying painful disorders. Widespread pain index (WPI), symptom severity scale (SS), and fibromyalgia impact questionnaire (FIQ) scores were found to be significantly higher in the patients who satisfied the 1990 criteria than those who did not ($P<0.001$). Tender point counts were found to be significantly correlated with WPI, SS, FIQ, and Beck depression inventory (BDI) scores ($P<0.001$).
- The **findings of the study support the suggestion that FMS is just a continuum of CWP, rather than a distinct diagnostic entity**. As treatment of FMS is usually identical with that of CWP, strict diagnosis of FMS will provide little or no significance from the viewpoint of clinical practice. We suggest that future research should be directed toward classification of CWP to provide guidance to clinicians in selecting effective therapies.

Clin Rheumatol (2015) 34:1323–1325
DOI 10.1007/s10067-015-2982-2

EDITORIAL

Does it mean anything to diagnose fibromyalgia (FM) in somebody with chronic widespread pain?

Luis Jose Catoggio[1]

Received: 12 May 2015 /Revised: 13 May 2015 /Accepted: 18 May 2015 /Published online: 29 May 2015

The paper in this volume by On et al. [1] raises the issue of whether there is a purpose in diagnosing fibromyalgia (FM) in patients with chronic widespread pain (CWP). They propose that, being FM at the more severe end of the spectrum of CWP, treatment is similar and whether to diagnose FM or not does not make a difference. Furthermore, since the update of FM criteria in 2010 which excludes the tender points, diagnosis has become more widespread and perhaps less specific. Diagnosis of FM with 2010 criteria includes many patients that would not fulfill 1990 criteria and excludes the concept of secondary fibromyalgia since patients with other conditions able to cause pain are excluded. Both the criteria, particularly the story behind both of them, have been well described by one of the main authors involved, Dr. Fred Wolfe [2, 3].

What a conundrum!

As a practicing rheumatologist who sees over one hundred patients a month in outpatient clinics, of which about a quarter are FM [4], I find diagnosing the condition useful. Furthermore, I also find it useful to differentiate between "primary" and "secondary" FM, considering the prevalence of FM in the musculoskeletal diseases (inflammatory or not) we treat. "Secondary", not in considering the inflammatory disease as a cause but to recognize that pain may be different and both conditions have to be approached in perhaps different ways.

This is an Editorial for http://dx.doi.org/10.1007/s10067-015-2975-1

✉ Luis Jose Catoggio
luis.catoggio@hospitalitaliano.org.ar

[1] Rheumatology Section, Hospital Italiano de Buenos Aires, Gascon 450, 1181 Buenos Aires, Argentina

But do clinicians, neurologists, rheumatologists, and psychiatrists who see the same patients with "presumed" FM or other conditions within the spectrum of chronic widespread pain call them differently and treat them in a similar way? Or are they really different situations? In which case, why should it be a similar treatment? Or, finally, should the treatments be different?

About three decades ago, I was told that fibromyalgia was what rheumatologists in the first half of the last century called fibrositis, and others "psychogenic rheumatism" [5]. Considering the links with anxiety, sleep disturbances, etc., the latter name has been useful to many of us in our approach to these patients. However, one thing about the links is the relationship between "psychological" factors and fibromyalgia and another is to regard them as causative agents of the condition [5].

When reading earlier literature, it is clear that fibrositis ended up being a misnomer, since the initial evidence of inflammation was not confirmed [6], and this is what most today call fibromyalgia. However, some authors in the late forties tried to differentiate between fibrositis and psychogenic rheumatism [5]. A lot of this information came from soldiers, both in the UK and the USA returning from the Second World War, with traumas arising from this event [5]. Yet both these terms, and many others, have been used since the late 1800s to date as "equivalents" or variants of what we now call fibromyalgia as very elegantly reviewed by Inanici and Yunus in 2004 [6].

The term psychogenic, as meaning causative, has been an issue and recently addressed in another review [7] which augurs the demise of the term psychogenic rheumatism. However, as clearly stated in Inanici and Yunus' review [6], "this organic versus psychogenic polemic continues to persist today". Indeed, as late as 1978, Reynolds both described a series of patients with what he called psychogenic rheumatism [8] but also complained almost a decade later about the

Catoggio's conclusions

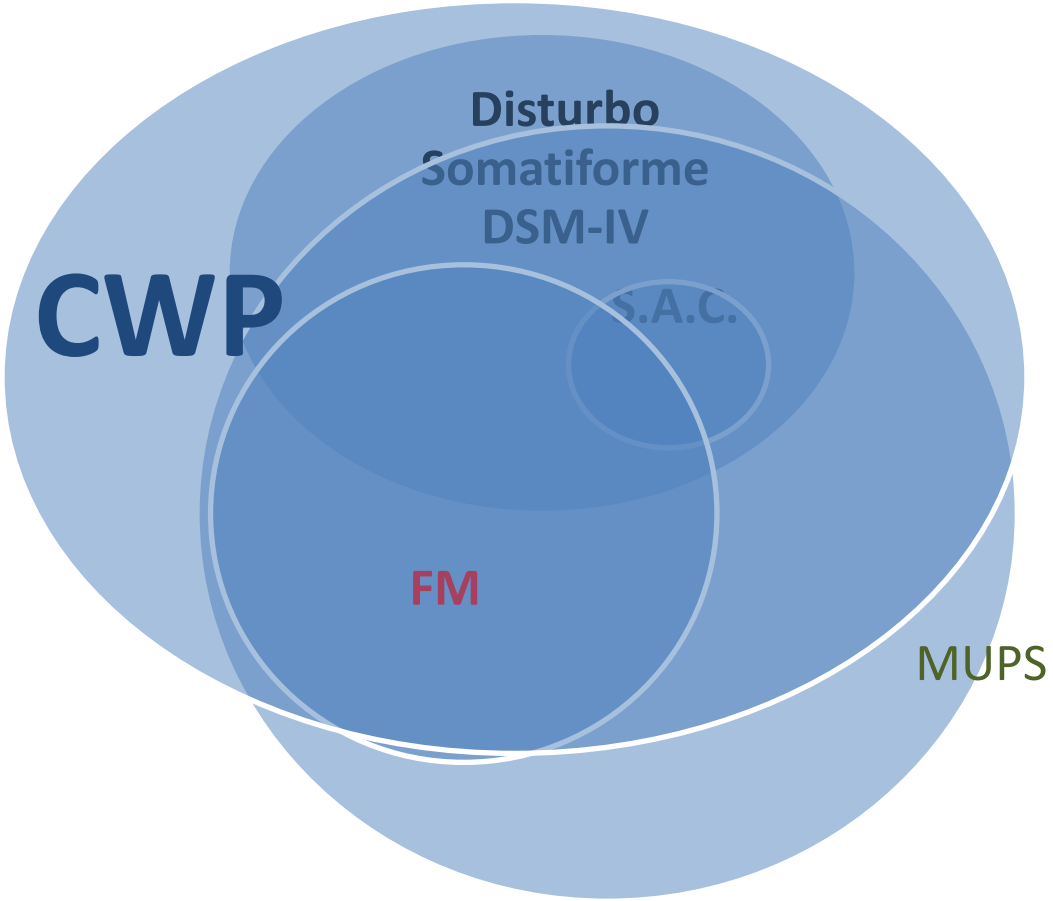
Is it useful to diagnose FM in the context of chronic widespread pain or does it not make a difference?

- Undoubtedly, my opinion will be that of a rheumatologist. And, after having reviewed these papers discussed above, **I still find it useful**.
- And I find it useful to distinguish primary FM from that associated with other musculoskeletal diseases.

Catoggio's conclusions

- However, it would be useful for primary care providers (clinicians, family, doctors, etc.), rheumatologists, neurologists, psychiatrists, etc. to get together and put into perspective the issues and possible definitions, overlaps, limits of CWP, FM, MUPS, and somatoform disorders.

Overlap painfull Syndromes

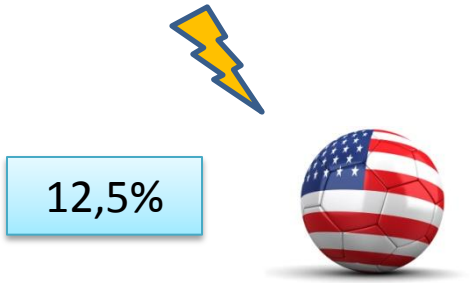


Caratterizzano la fibromialgia…

- Larga prevalenza epidemiologica;
- Sesso femminile;
- Genetica;
- Comportamento sedentario, di allerta-paura;
- Comorbilità psichica, sindromi disfunzionali, disturbi del sonno, interpretazione catastrofica del dolore (catastrophizing pain).

Prevalenza del CWP

T. Schochat, H. Raspe. ***Elements of fibromyalgia in an open population***.
Rheumatology 2003;42:829–835



Croft P. ***The epidemiology of widespread pain***.
J Musculoskeletal Pain 2002; 10: 191–199.

Prevalenza della FM

3,3%

White KP, Speechley M, Hart M, Ostbye T. ***The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario***. *J Rheumatol.* 1999;26:1570–1576.

2,2%

Salaffi F. et aa. ***Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study.*** Clin Exp Rheumatol. 2005 Nov-Dec;23(6):819-28

1,4%

Bannwarth B et al. ***Fibromyalgia syndrome in the general population of France: A prevalence study.*** Joint Bone Spine. 2008 Sep 24

2,4%

Mas J. et al ***Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain.*** Clin Exp Rheumatol. 2008 Jul-Aug;26(4):519-26

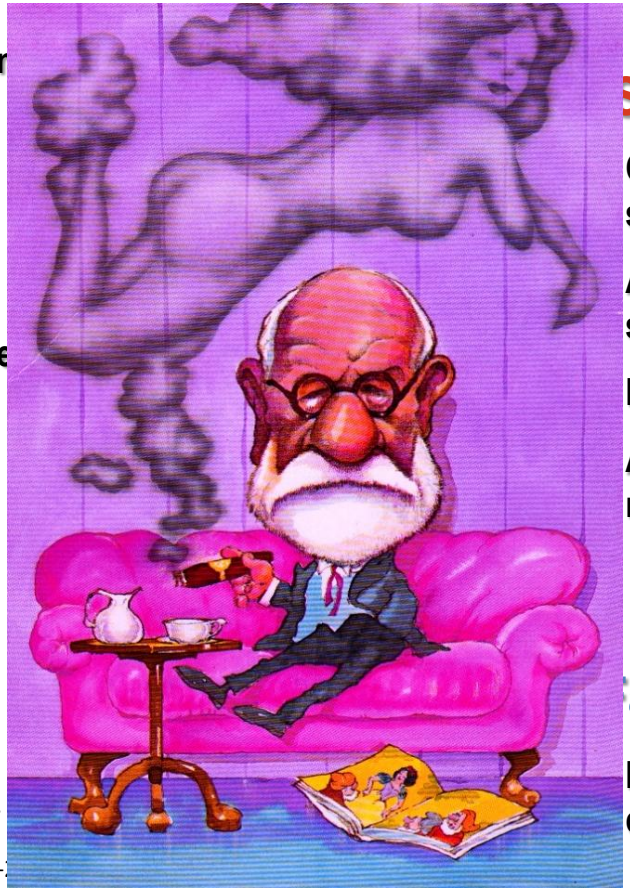
Core Clinical Features of Fibromyalgia

Dysfunctional Syndromes

- Irritable bowel syndrome, temporo-mar
  disorder, restless legs syndrome, etc

Widespread Pain

- Chronic, widespread pain is the defining feature of FM
- Patient descriptors of pain include: aching, exhausting, nagging, and hurting
- Presence of tender points



Sleep Disturbances

Characterized by nonrestorative sleep and increased awakenings

Abnormalities in the continuity of sleep and sleep architecture

Reduced slow-wave sleep

Abnormal alpha wave intrusion in non-REM sleep

atigue/Stiffness

Morning stiffness and fatigue are common characteristics of FM

Wolfe F et al. *Arthritis Rheum*. 1995;38:19-28.
Leavitt F et al. *Arthritis Rheum*. 1986;29:775-781.
Wolfe F et al. *Arthritis Rheum*. 1990;33:160-172.
Roizenblatt S et al. *Arthritis Rheum*. 2001;44:222-
Harding SM. *Am J Med Sci*. 1998;315:367-376.
Henriksson KG. *J Rehabil Med*. 2003;(suppl 41):89-94.

Psychiatric Disorders in Patients With Fibromyalgia

A Multicenter Investigation

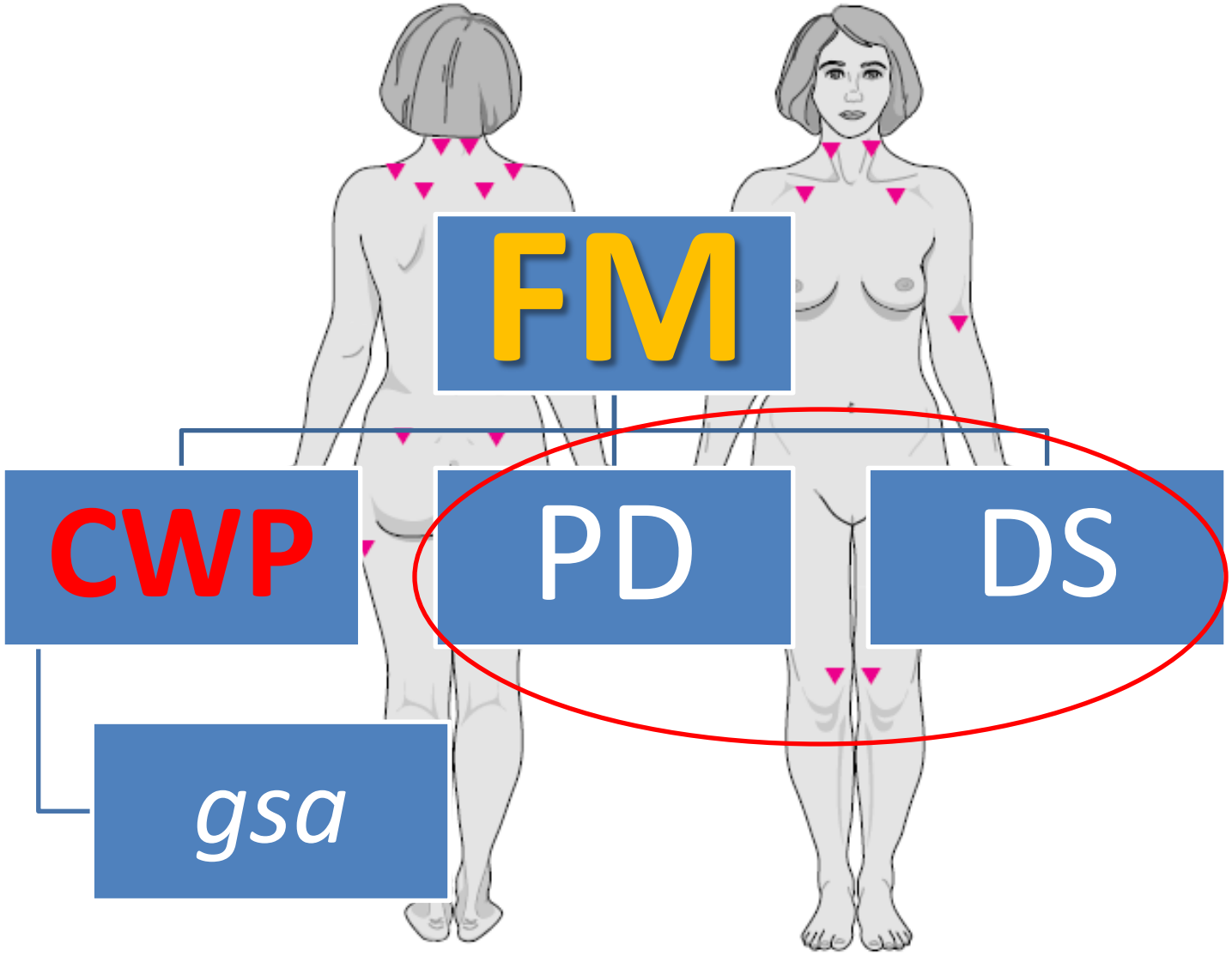
STEVEN A. EPSTEIN, M.D., GARY KAY, PH.D.
DANIEL CLAUW, M.D., ROBERT HEATON, PH.D.
DANIEL KLEIN, PH.D., LAUREN KRUPP, M.D.
JULIE KUCK, PH.D., VINITA LESLIE
DAVID MASUR, PH.D., MARK WAGNER, PH.D.
RANDY WAID, PH.D., SIDNEY ZISOOK, M.D.

The authors conducted an investigation in four tertiary-care centers to determine if psychiatric comorbidity and psychological variables were predictive of functional impairment in patients with fibromyalgia syndrome (FMS). Seventy-three individuals were administered the Structured Clinical Interview for DSM-III-R, the Rand 36-item Health Survey (SF-36), and multiple self-report measures. The patients with FMS were found to have a high lifetime and current prevalence of major depression and panic disorder. The most common disorders were major depression (lifetime [L] = 68%, current [C] = 22%); dysthymia (10% [C only]); panic disorder (L = 16%, C = 7%); and simple phobia (L = 16%, C = 12%). The self-report scales revealed significant elevations in depression, anxiety, neuroticism, and hypochondriasis. Functional impairment on all measures of the SF-36 was severe (e.g., physical functioning = 45.5 and role limitations due to physical problems = 20.0). Stepwise multiple-regression analysis revealed that current anxiety was the only variable that predicted a significant proportion of the variance (29%) in SF-36 physical functioning. Thus, in this multicenter study, the persons with FMS exhibited marked functional impairment, high levels of some lifetime and current psychiatric disorders, and significant current psychological distress. Current anxiety level appears to be an important correlate of functional impairment in individuals with FMS.

(Psychosomatics 1999; 40:57–63)

TABLE 4. Most prevalent psychiatric disorders compared with data on women from the National Comorbidity Survey (NCS)

	%			
Disorder	Fibromyalgia Syndrome (Lifetime)	Fibromyalgia Syndrome (Current)	NCS Current	NCS 12-Month Prevalence
Major depression	69	23	21	13
Panic disorder	17	9	5	3
Simple phobia	17	13	16	13
Social phobia	7	9	16	9
Any mood disorder	69	29	24	14
Any anxiety disorder	35	27	31	23
Any psychiatric disorder	81	48	47	31


FM
CWP
PD
DS
gsa

Arthritis Rheumatol. 2015 Nov;67(11):3047-57. doi: 10.1002/art.39252.

Differences in Sedentary Time and Physical Activity Between Female Patients With Fibromyalgia and Healthy Controls: The al-Ándalus Project.

Segura-Jiménez V[1], Álvarez-Gallardo IC[1], Estévez-López F[2], Soriano-Maldonado A[1], Delgado-Fernández M[1], Ortega FB[1], Aparicio VA[3], Carbonell-Baeza A[4], Mota J[5], Silva P[5], Ruiz JR[1].

Author information

Abstract

OBJECTIVE: To characterize the levels of objectively measured time spent in sedentary activities (sedentary time) and physical activities in female patients with fibromyalgia and compare them with the levels in age-matched healthy control women.

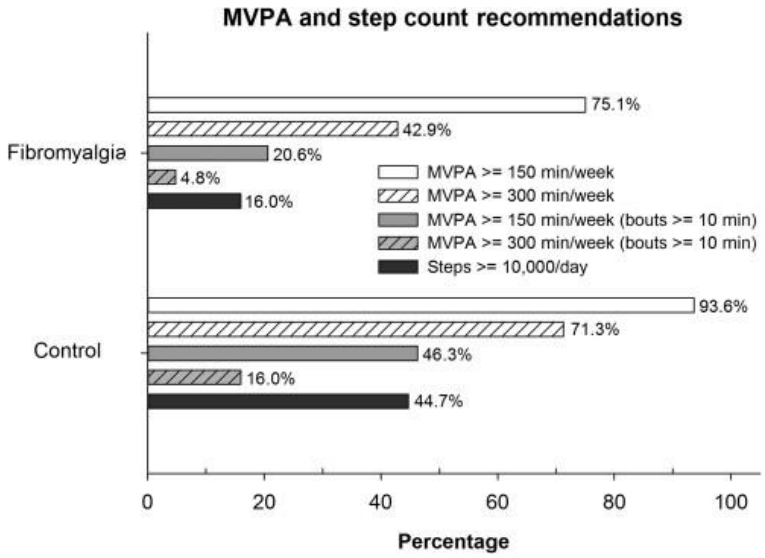
METHODS: The study comprised 413 female patients with fibromyalgia (mean±SD age 51.9±7.4 years) and 188 female control subjects (age 50.9±7.5 years). Sedentary time, the amount of time spent engaged in physical activity, and step counts were measured using triaxial accelerometry. The amounts of time (minutes/day) during which the participants were engaged in sedentary behaviors as well as in physical activity of different intensities (light, moderate, and moderate-to-vigorous) and the step counts were calculated.

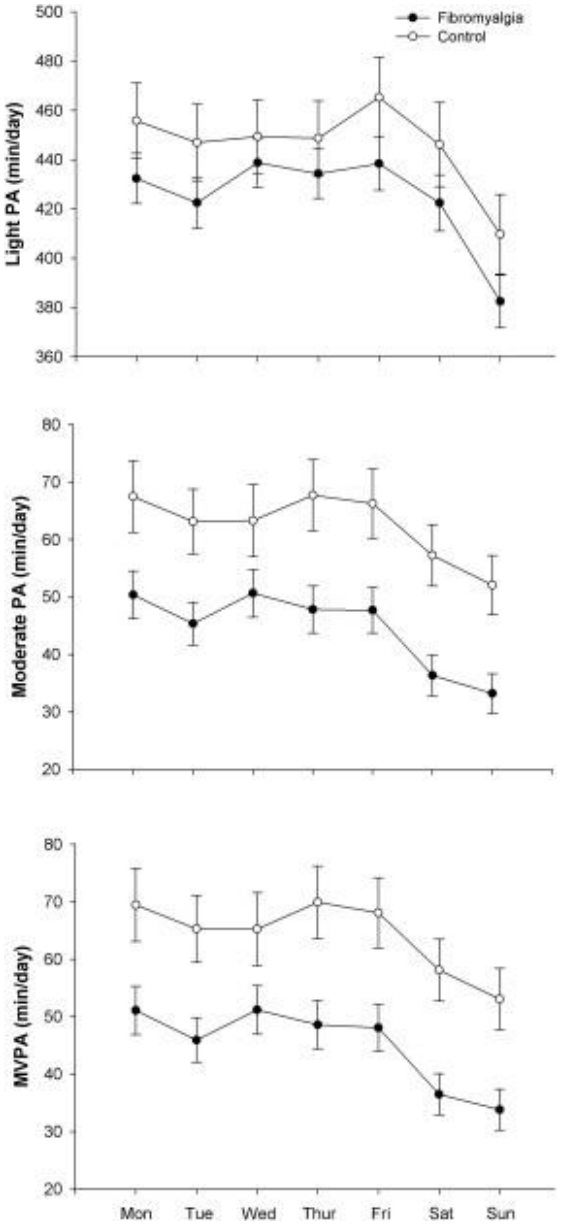
RESULTS: The amount of time spent in sedentary behavior was longer in patients with fibromyalgia compared with controls (estimated mean±SEM difference 39±8 minutes/day; $P < 0.001$). The patients with fibromyalgia spent less time than controls engaged in light physical activity (mean±SEM difference -21±7 minutes/day; $P = 0.005$), moderate physical activity (mean±SEM difference -17±3 minutes/day; $P < 0.001$), and moderate-to-vigorous physical activity (mean±SEM difference -19±3 minutes/day; $P < 0.001$). The patients with fibromyalgia took fewer steps/day compared with the control subjects (mean±SEM difference -1,881±262 steps/day; $P < 0.001$). Only 20.6% of the patients with fibromyalgia and 46.3% of the control subjects fulfilled the recommendation for 150 minutes/week of moderate-to-vigorous physical activity in bouts of at least 10 minutes/bout ($\chi(2) = 41.8$, $P < 0.001$). Similarly, only 16.0% of the patients fulfilled the recommendation for ≥10,000 steps/day compared with 44.7% of the control subjects ($\chi(2) = 56.8$, $P < 0.001$). Both the patients and the control subjects were more active (physical activity of all intensities and numbers of steps) on weekdays than on weekend days (all $P \leq 0.001$).

CONCLUSION: Female patients with fibromyalgia spent more time in sedentary behaviors and were less physically active than age-matched controls. The low proportions of female patients with fibromyalgia and control subjects who met the physical activity and step count recommendations is worrisome.

Sedentarietà e FM

- Female patients with fibromyalgia spent more time in sedentary behaviors and were less physically active than age-matched controls.

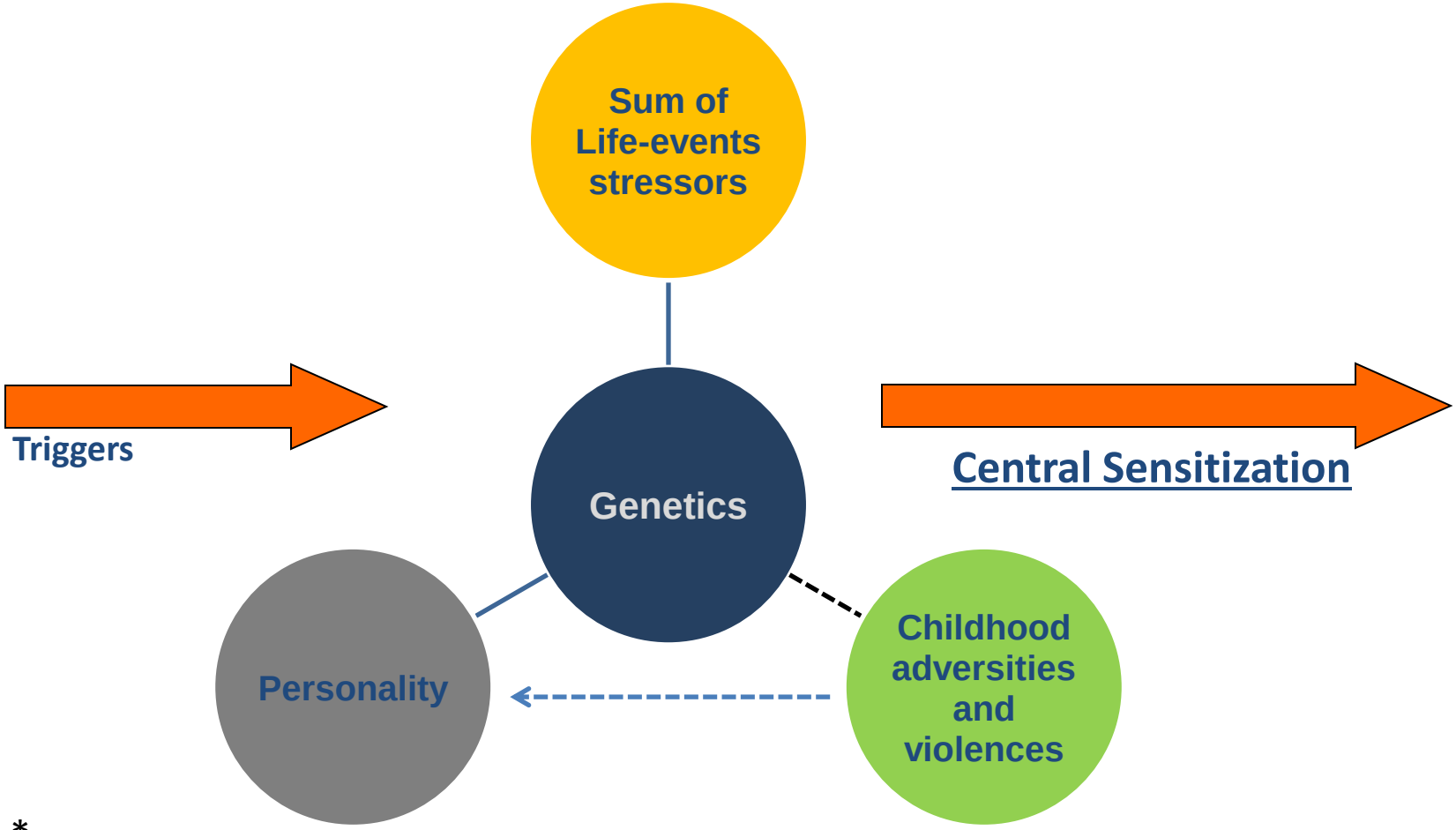




S. Stisi1, M. Cazzola2, D. Buskila3, M. Spath4, M.A.Giamberardino5, P. Sarzi-Puttini6, G. Arioli7, A. Alciati8, G. Leardini9, R. Gorla10, A. Marsico11, F. Ceccherelli12, L. Bazzichi13, R. Carignola14, R.H. Gracely15, F. Salaffi16, F. Marinangeli17, R. Torta18, M. Di Franco19, G. Biasi20, G. Cassisi21, R. Casale22, L. Altomonte23, F. Atzeni6 (Italian Fibromyalgia Network)

Etiopathogenetic mechanisms of fibromyalgia syndrome

Reumatismo, 2008; 60: Supplemento 1: 25-35



* Modificato da: ***Van Houdenhovea B, Egle U.T.*** **- Fibromyalgia: a stress disorder? - Psychother Psychosom 2004;73:267–275**


Genetics

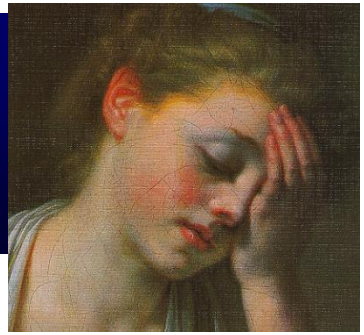
Buskila D, Neumann L, Hazanov I.

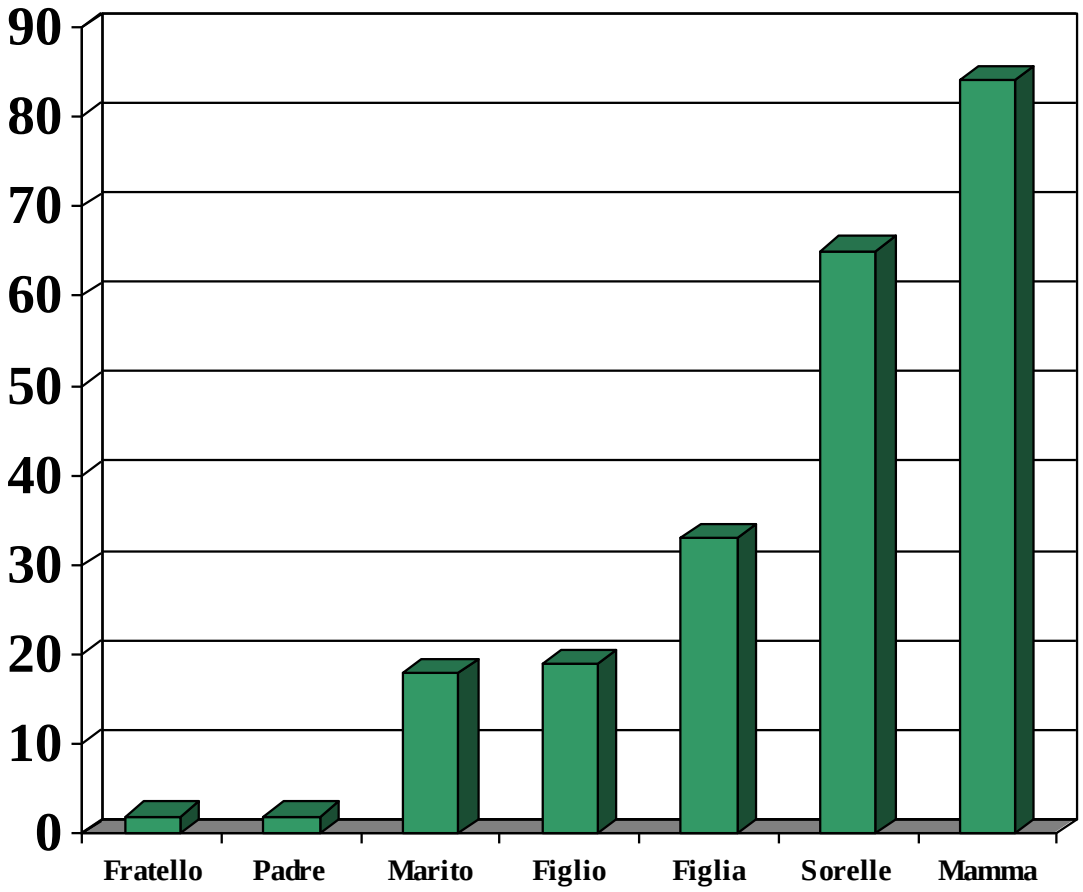
***Familial aggregation in the Fibromyalgia Syndrome*.**

Semin Arthritis Rheum 26: 605-611, 1996

- The authors studied the familial occurrence of fibromyalgia (FMS) to determine a possible role of genetic and familial factors in this syndrome. Fifty-eight offspring aged 5 to 46 years (35 males and 23 females) from 20 complete nuclear families ascertained through affected mothers with FMS were clinically evaluated for FMS according to the ACR 1990 diagnostic criteria. FMS symptoms, quality of life, physical functioning, and dolorimetry thresholds were assessed in all subjects. Sixteen offspring (**28%**) were found to have FMS. The M/F ratio among the affected was 0.8 compared with 1.5 in the whole study group. Offspring with and without FMS did not differ on anxiety, depression, global well-being, quality of life, and physical functioning. A high prevalence of FMS was observed among offspring of FMS mothers. Because psychological and familial factors were not different in children with and without FMS, the high familial occurrence of this syndrome may be attributable to genetic factors.

Aggregazione famigliare





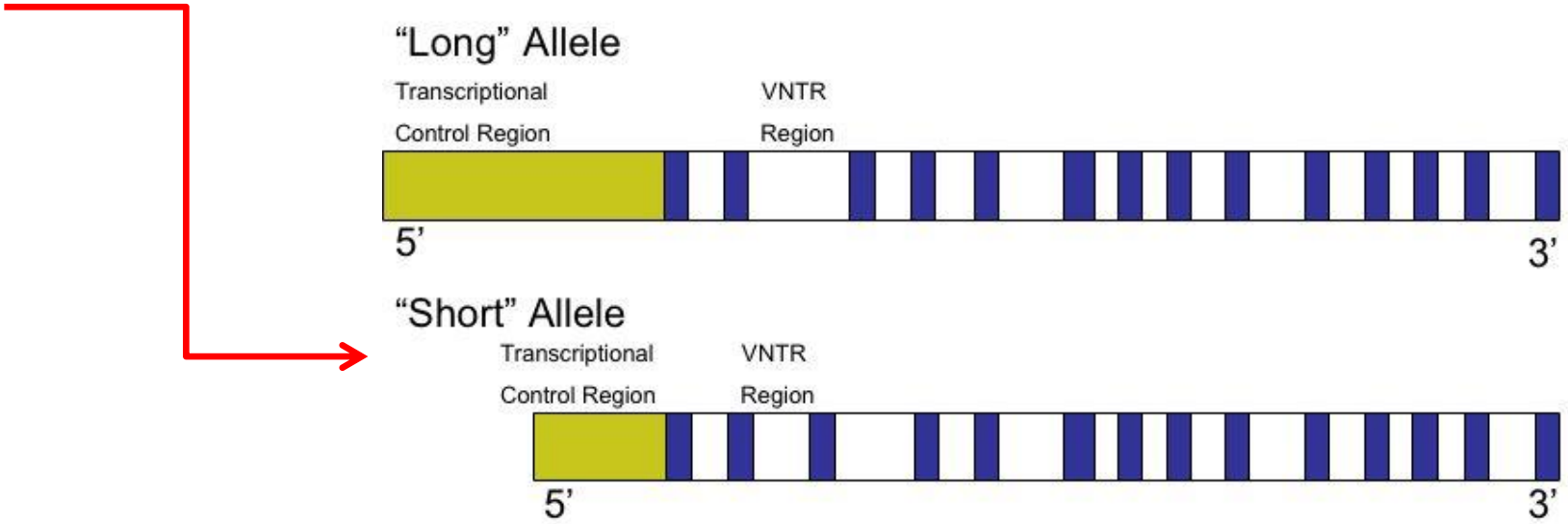
Buskila, 1996

Buskila, Reumatismo 2008

- The clear familial aggregation in FMS and related conditions **may represent either genetic or environmental influence, or most likely a combination of both**.
- At present no evidence has emerged to suggest a monogenic mode of transmission and a **multifactorial mode of transmission** is generally presumed.
- Research done in recent years has demonstrated a role for **polymorphisms of genes** in the serotoninergic, dopaminergic and catecholaminergic systems in the etiology of FMS.

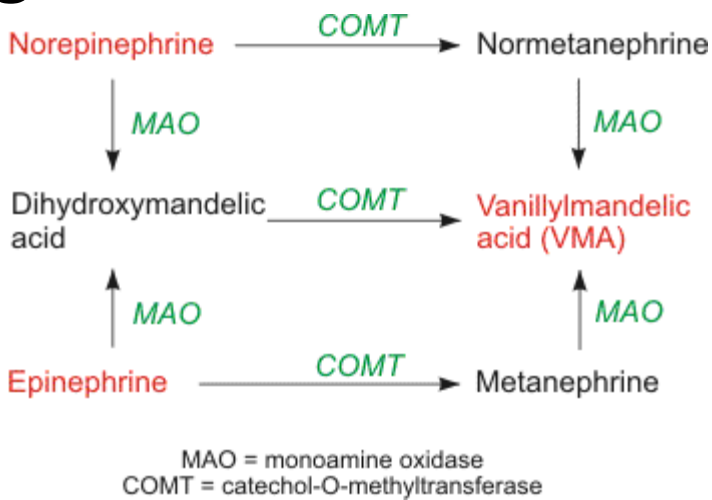
5-HTT

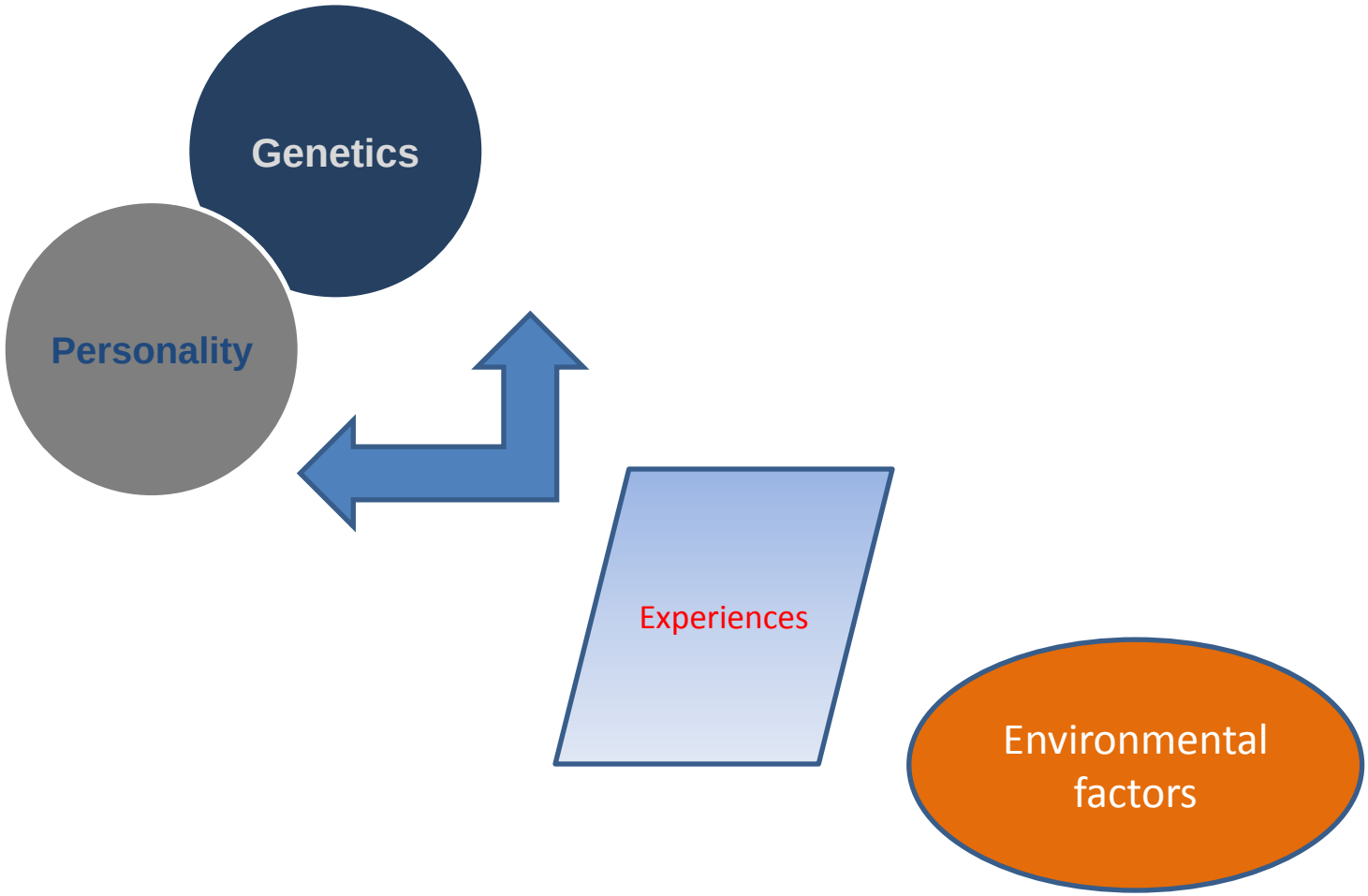
- Offenbaecher and colleagues (10) analyzed the genotypes of the promoter region of the serotonin transporter gene (5-HTT) in 62 patients with FMS and 110 healthy controls. A significantly higher frequency of the S/S genotype of the serotonin transporter promoter region was found in FMS patients (31%) compared with healthy controls (16%). The **S/S subgroup exhibited higher mean levels of depression and psychological distress**. It was suggested that the results support the notion of altered serotonin metabolism in at least a subgroup of patients with FMS.



COMT

- Individuals homozygous for the **Met 158 allele** of the catechol – O methyltransferase (COMT) polymorphism (Val 158 Met) show diminished regional mu-opioid system responses to pain compared with heterozygotes. These effects were accompanied by **higher sensory and affective ratings of pain and a more negative internal affective state**.




Genetics
Personality
Experiences
Environmental factors

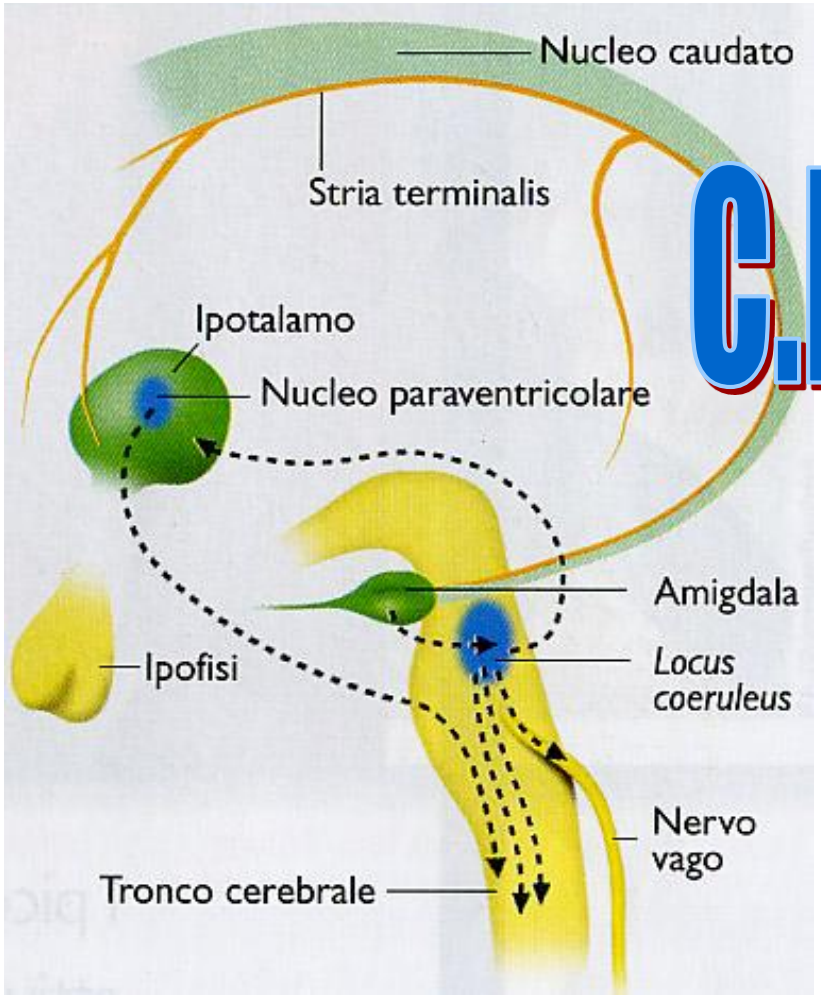

Personality

Catastrophizing

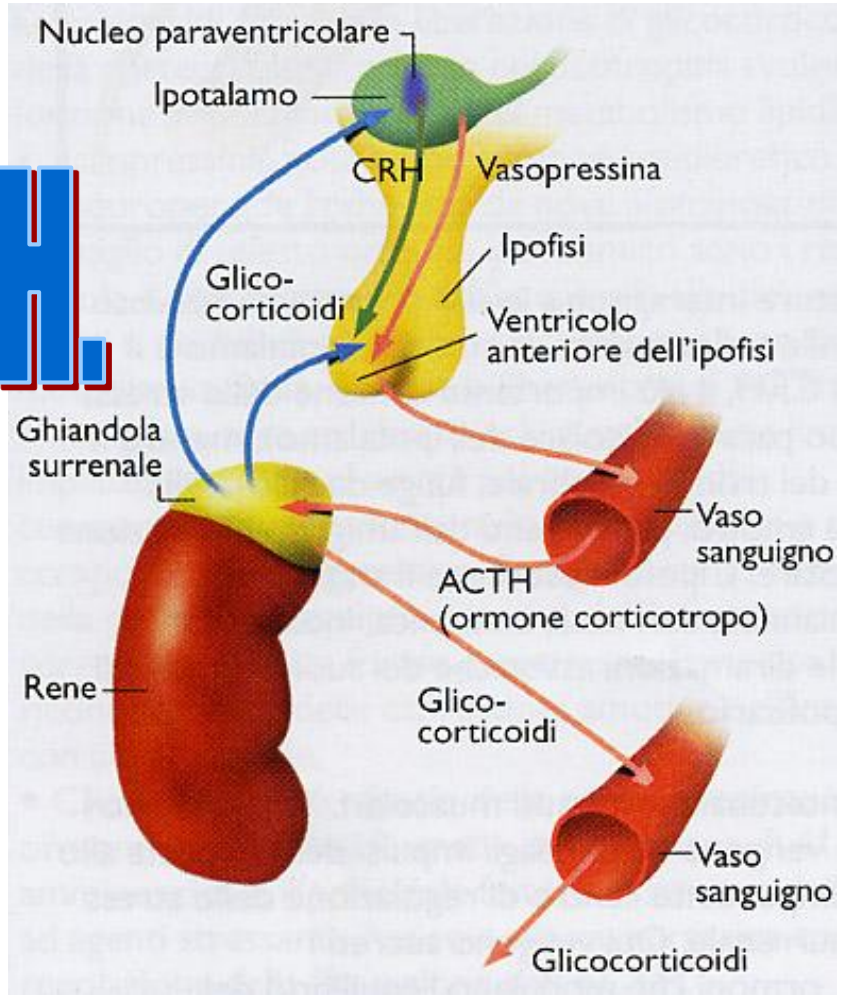
- A previous study suggested that pain catastrophizing is significantly associated with increased activity in some brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), and emotional aspects of pain (claustrum, closely connected to amygdala).
- These results suggest that **catastrophizing influences pain perception by altering attention and anticipation, and heightening emotional responses to pain**.

Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 2004; 127: 835-43.

Stress response system



C.R.H.



LC-NE axis

HPA axis

LAVORO ORIGINALE

Influenza dello stress nella fibromialgia

Distress influence in fibromyalgia

S. Stisi, C. Venditti, I. Sarracco
Reparto di Reumatologia, Azienda Ospedaliera di rilievo nazionale "G.Rummo", Benevento

SUMMARY

Objective: *Fibromyalgia syndrome (FM) is a controversial chronic painful syndrome. Although the aetiology is unknown, FM is frequently correlated with stressors events. Recent studies highlighted the frequent comorbidity with anxiety and depression and a close relationship between stress and pain.*

Methods: *We evaluated the relevance of stressors events in 23 patients with FM (mean age: 45.7±7.4 SD), compared with 18 healthy controls (mean age: 41.7±6.4 SD) and 17 patients with dysfunctional syndrome (mean age 40.8±6.1). We performed the italian validated rapid assessment of the stress test (VRS) for the assessment of stress. Furthermore, we evaluated the psychological history for a semi-quantitative assessment (IVAS) of the 49 stress-generating events listed in 1994's DSM-IV.*

Results: *The group of "healthy" subjects showed stress values at VRS test (mean: 7.00±4.65 SD) significantly lower (p=0.0001) than the patients with "dysfunctional syndrome" (mean 14.82±7.69 SD) and those with FM (mean 20.04±9.90 SD). The IVAS test, showed higher values in FM subgroup than healthy (p=0.0001) and dysfunctional syndromes (p=0,007). Also, the patients with FM showed a greater gravity to attribute to single stressors events (p=0.02).*

Conclusions: *Our results emphasize the importance of the perceived stress among the patients with FM, and support the hypothesis that FM could be due to a psycho-neuro-endocrinal response to several stressors events in patients with genetical hyperresponsiveness to stress.*

Reumatismo, 2008; 60(4):274-281

INTRODUZIONE

La sindrome fibromialgica primaria (SFp) è una controversa sindrome dolorosa cronica, a eziologia sconosciuta, frequentemente correlabile alle reazioni di adattamento allo stress, caratterizzata da un dolore muscolo-scheletrico diffuso e dalla presenza di punti algogeni *(tender-points)*, evocabili alla pressione in corrispondenza di specifiche sedi tendinee e muscolari, e da una varietà di sintomi clinici d'accompagnamento. La sua diagnosi è essenzialmente clinica e si basa sui criteri dell'American College of Rheumatology (ACR) del 1990 che prevedono la presenza da almeno tre mesi, di un dolore muscolo-scheletrico diffuso e dalla presenza di dolorabilità dei tender-points in numero (almeno 11/18) e modalità sufficienti (1). Alla sintomatologia dolorosa con allodinia e iperalgesia, si associano altri disturbi, quale astenia, alterazioni del sonno, rigidità mattutina, e/o altre sindromi disfunzionali quali dismenorrea, colon irritabile, cefalea tensiva, dispepsia funzionale gastrica, disordine temporo-mandibolare (2).

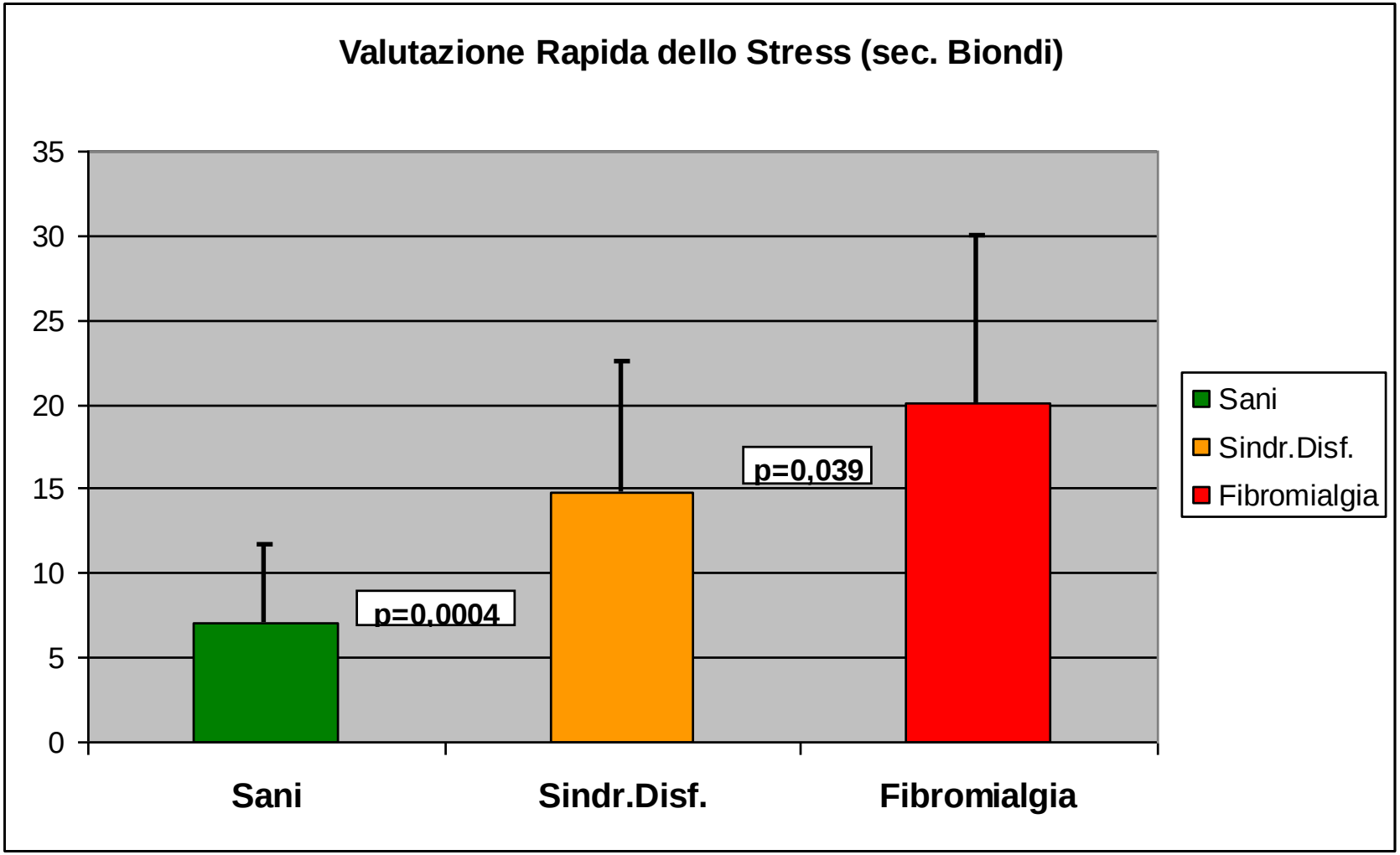
La SFp interessa maggiormente il sesso femminile, con una prevalenza nella popolazione generale che è valutata tra lo 0,3 e il 3,3% (3).

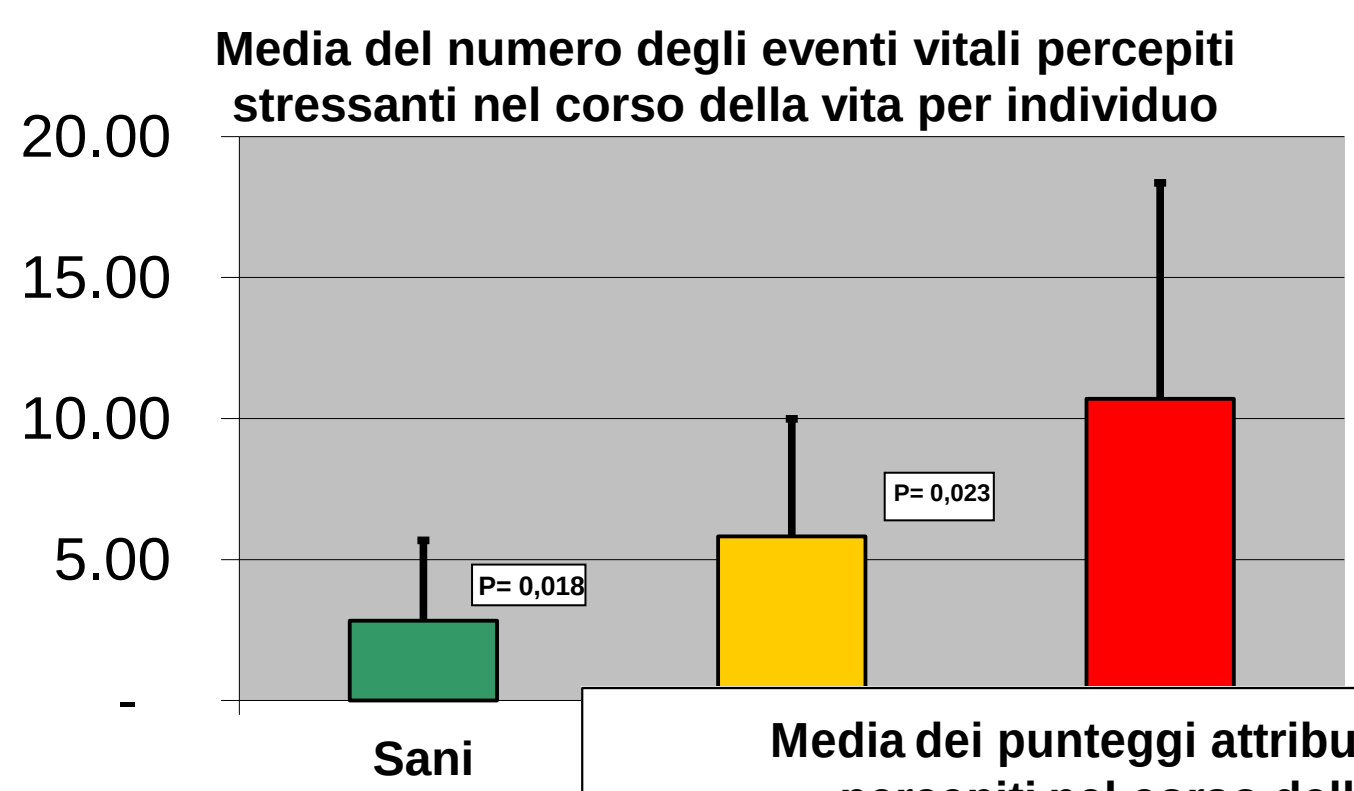
Dal punto di vista patogenetico, mentre una causa muscolare non sembra essere determinante, sempre più evidenze correlano la sintomatologia fibromialgica a un disturbo della percezione dolorosa del sistema nervoso centrale (4, 5).

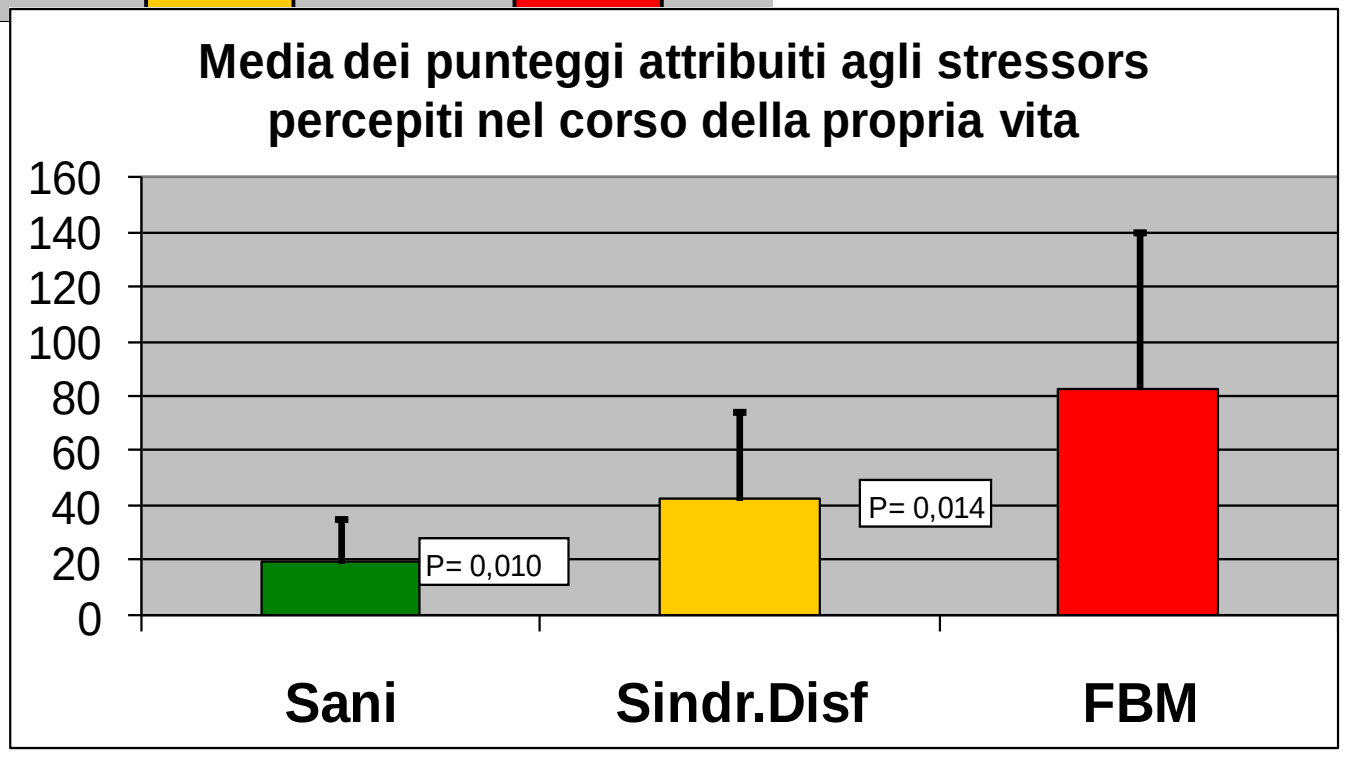
Svariati studi psicologici sul malato fibromialgico hanno evidenziato la frequente comorbidità con ansia e depressione, senza mai chiarire però, se tali patologie ne fossero la causa o il risultato (6, 7). Recentemente sono stati evidenziati gli stretti rapporti di causa-effetto tra lo stress e il dolore (8). Per eventi stressanti s'intendono tutti gli stimoli che comportano la necessità di riadattamento dell'individuo e che provocano un cambiamento dell'o-

Indirizzo per la corrispondenza:
Dott. Stefano Stisi
Reparto di Reumatologia
A.O. "Gaetano Rummo"
Via dell'Angelo, 1 - 82100 Benevento
e-mail: stefano.stisi@ao-rummo.it

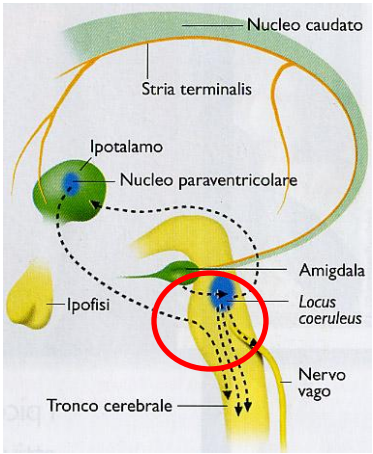
FM and stress




Media del numero degli eventi vitali percepiti stressanti nel corso della vita per individuo
20.00
15.00
10.00
5.00
-
P= 0,018
P= 0,023
Sani


Media dei punteggi attribuiti agli stressors percepiti nel corso della propria vita
160
140
120
100
80
60
40
20
0
P= 0,010
P= 0,014
Sani
Sindr.Disf
FBM

Fear and pain



J Cogn Neurosci. 2004 Sep;16(7):1289-301.

Context-dependent deactivation of the amygdala during pain.

Petrovic P, Carlsson K, Petersson KM, Hansson P, Ingvar M.

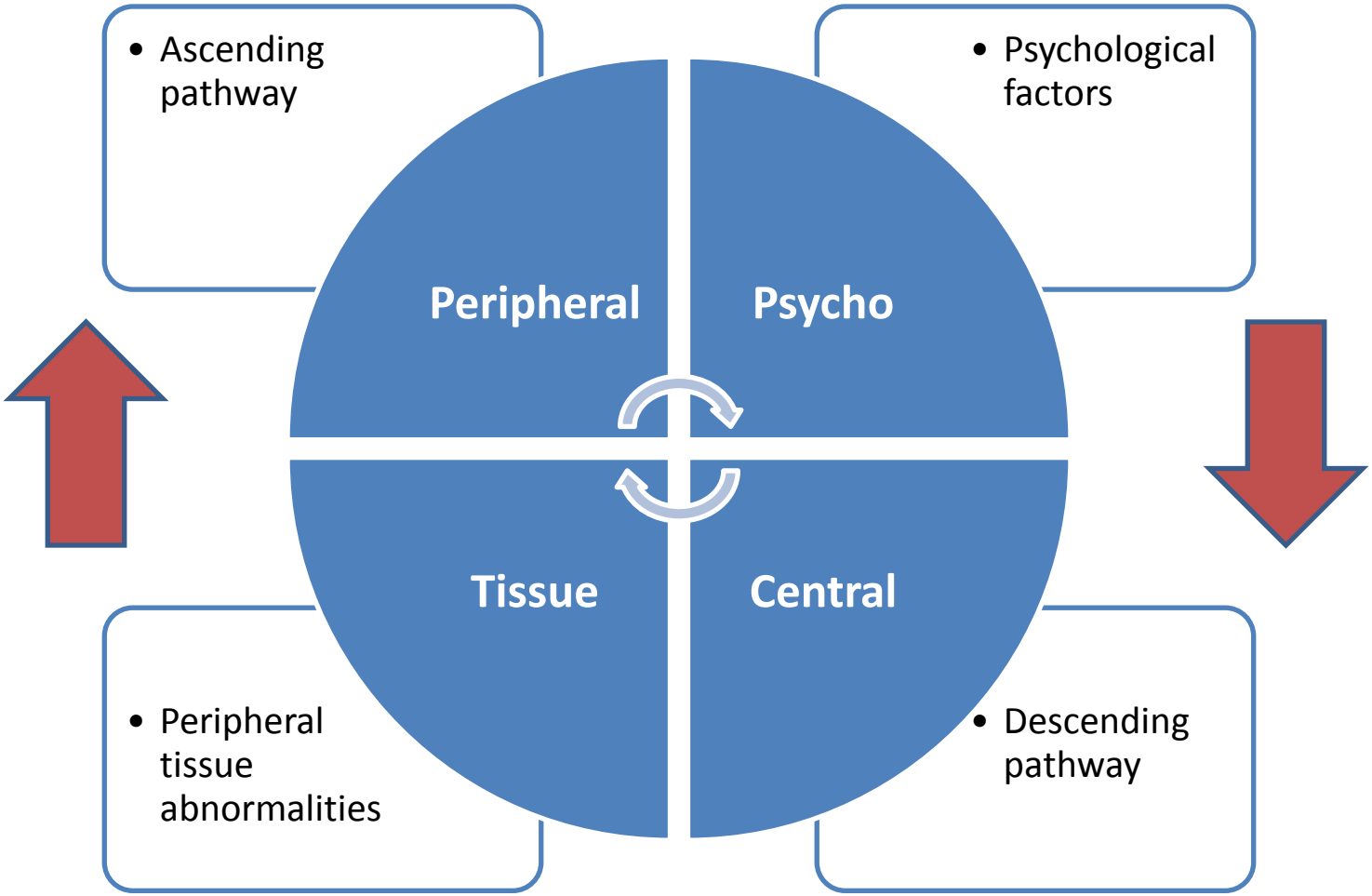
The amygdala has been implicated in fundamental functions for the survival of the organism, such as fear and pain. In accord with this, several studies have shown increased amygdala activity during fear conditioning and the processing of fear-relevant material in human subjects. In contrast, functional neuroimaging studies of pain have shown a decreased amygdala activity.

…

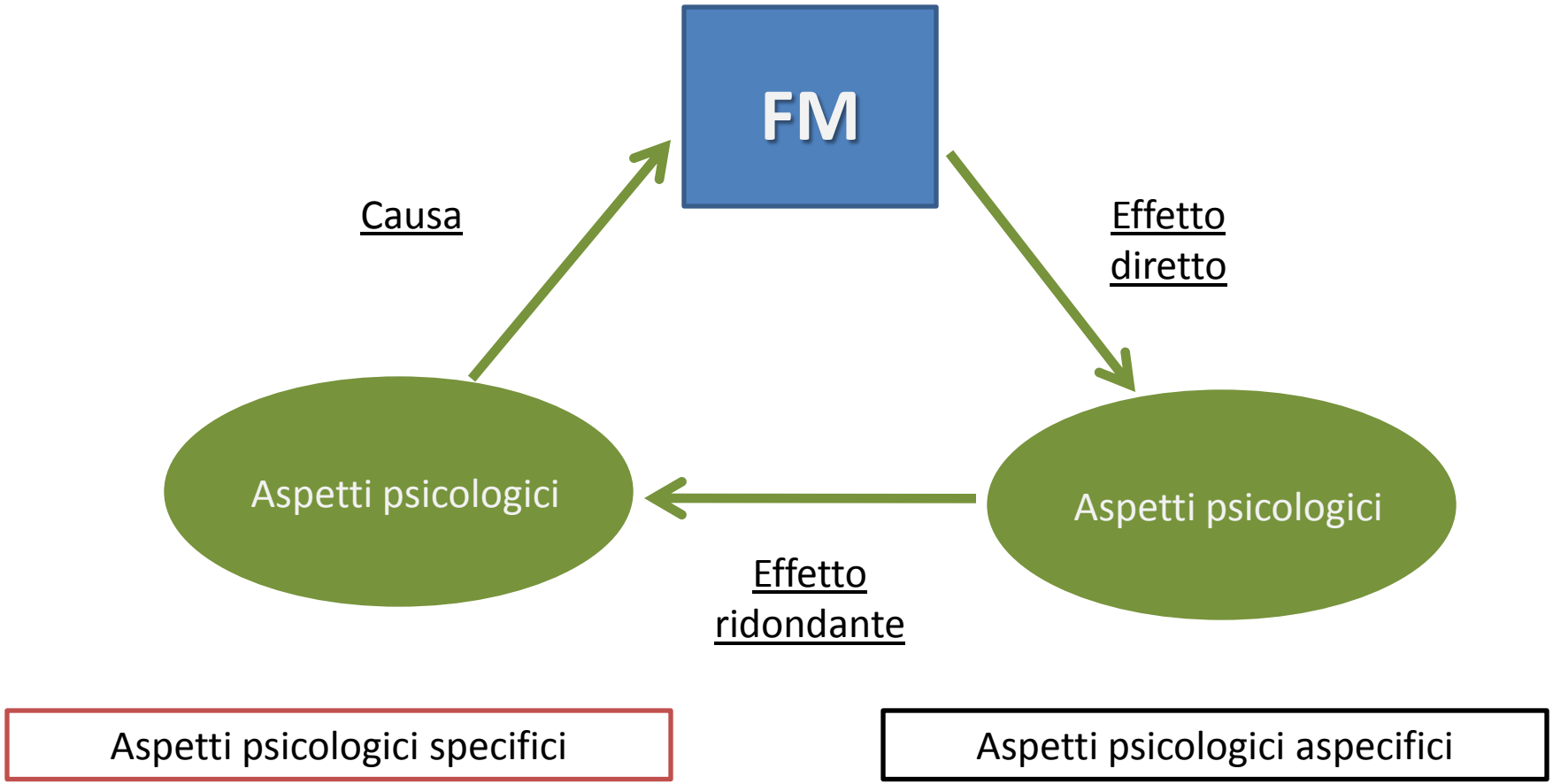
In this positron emission tomography study, we show that a simple contextual manipulation, immediately preceding a painful stimulation, that increases the anticipated duration of the painful event leads to a decrease in amygdala activity and modulates the autonomic response during the noxious stimulation. …

We suggest that the altered activity in the amygdala may be part of a mechanism to attenuate pain-related stress responses in a context that is perceived as being more aversive. The study also showed an increased activity in the rostral part of anterior cingulate cortex in the same context in which the amygdala activity decreased, further supporting the idea that this part of the cingulate cortex is involved in the modulation of emotional and pain networks.

Abnormal Pain processing in FM



Aspetti Psicologici della Fibromialgia


FM
Causa
Effetto diretto
Aspetti psicologici
Aspetti psicologici
Effetto ridondante
Aspetti psicologici specifici
Aspetti psicologici aspecifici

Episodio depressivo maggiore

almeno cinque dei seguenti sintomi devono essere presenti per almeno due settimane e rappresentano un cambiamento rispetto al precedente livello di funzionamento; almeno uno dei sintomi è costituito da 1) umore depresso o 2) perdita di interesse o piacere.

1. umore depresso per la maggior parte del giorno, quasi ogni giorno, come riportato dal soggetto o come osservato dagli altri (per es., appare lamentoso).
2. marcata diminuzione di interesse o piacere per tutte o quasi tutte le attività per la maggior parte del giorno, quasi ogni giorno.
3. significativa perdita di peso, senza essere a dieta, o aumento di peso (per es., un cambiamento superiore del 5% del peso corporeo in un mese), oppure diminuzione o aumento dell'appetito quasi ogni giorno.
4. insonnia o ipersonnia quasi ogni giorno.
5. agitazione o rallentamento psicomotorio quasi ogni giorno
6. faticabilità o mancanza di energia quasi ogni giorno
7. sentimenti di autosvalutazione o di colpa eccessivi o inappropriati quasi ogni giorno
8. ridotta capacità di pensare o di concentrarsi, o indecisione, quasi ogni giorno
9. pensieri ricorrenti di morte (non solo paura di morire), ricorrente ideazione suicidaria senza un piano specifico, o un tentativo di suicidio, o l'ideazione di un piano specifico per commettere suicidio.

Disturbo di panico

A) Entrambi 1. e 2.:

1. Attacchi di Panico inaspettati ricorrenti

2. almeno uno degli attacchi è stato seguito da 1 mese (o più) di uno (o più) dei seguenti sintomi:

a. preoccupazione persistente di avere altri attacchi

b. preoccupazione a proposito delle implicazioni dell'attacco o delle sue conseguenze (per es., perdere il controllo, avere un attacco cardiaco, "impazzire")

c. significativa alterazione del comportamento correlata agli attacchi.

B) Presenza o assenza di Agorafobia (D. di Panico con o senza Agorafobia)

C) Gli Attacchi di Panico non sono dovuti agli effetti fisiologici diretti di una sostanza (per es., una droga di abuso, un farmaco) o di una condizione medica generale (per es., ipertiroidismo).

D) Gli Attacchi di Panico non sono meglio giustificati da un altro disturbo mentale, come Fobia Sociale (per es., si manifestano in seguito all'esposizione a situazioni sociali temute), Fobia Specifica (per es., in seguito all'esposizione ad una specifica situazione fobica), Disturbo Ossessivo-Compulsivo (per es., in seguito all'esposizione allo sporco in soggetto con ossessioni di contaminazione), Disturbo Post-traumatico da Stress (per es., in risposta a stimoli associati con un grave evento stressante) o Disturbo d'Ansia di Separazione (per es., in risposta all'essere fuori casa o lontano da congiunti stretti).

American Psychiatric Association (2000). **DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders** , Fourth Edition, Text Revision. *Edizione Italiana: Masson, Milano.*

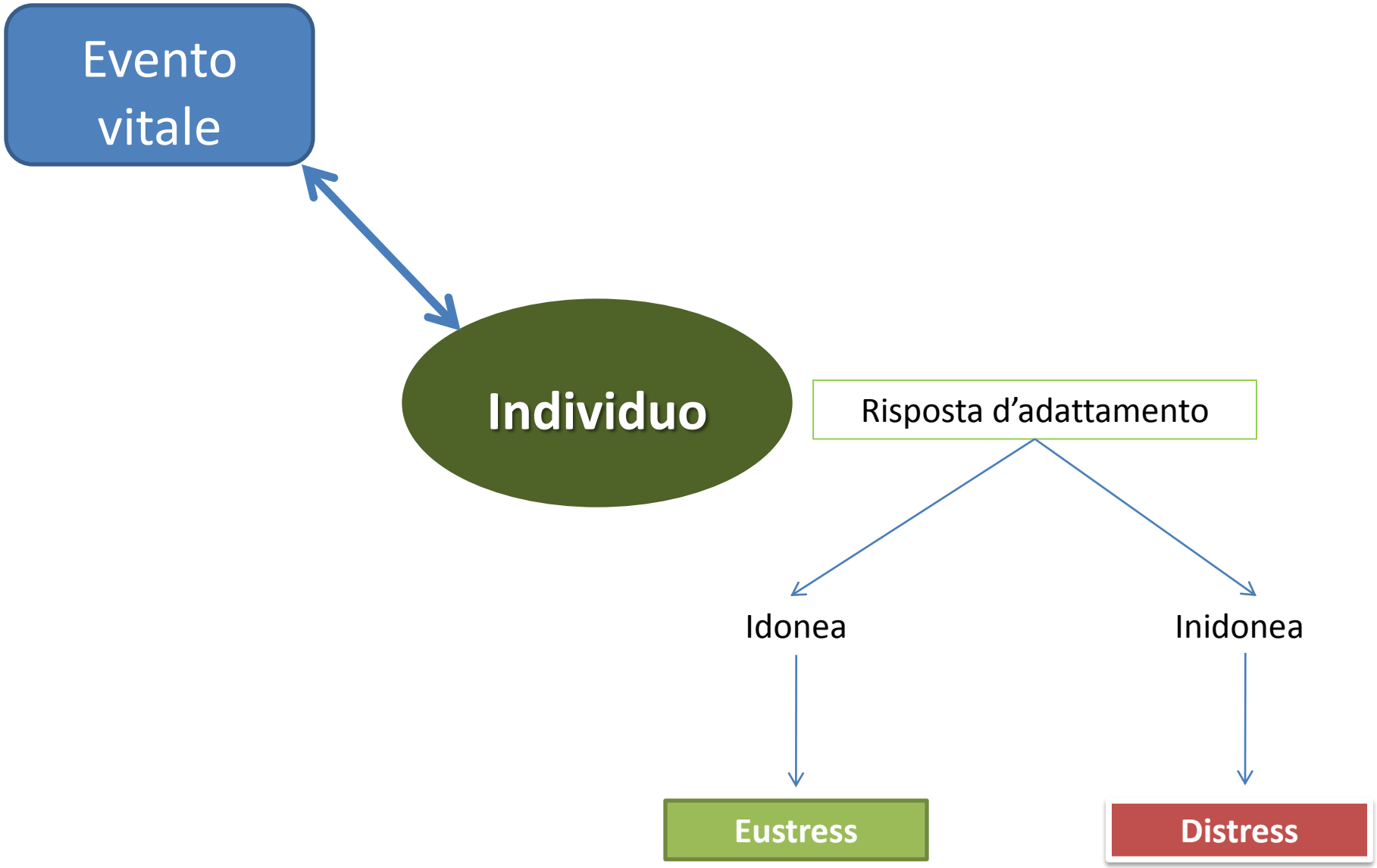
Disturbo fobico specifico

Criterio A. "paura marcata e persistente, eccessiva o irragionevole, provocata dalla presenza o dall'attesa di un oggetto o situazione specifici (per es., volare, altezze, animali, etc.)".
Oltre questo criterio diagnostico (A) è necessaria la presenza di un set di altri sei criteri:
Criterio B. L'esposizione allo stimolo fobico quasi invariabilmente provoca una risposta ansiosa immediata, che può prendere forma di Attacco di Panico situazionale o sensibile alla situazione.
Criterio C. La persona riconosce che la paura è eccessiva o irragionevole.
Criterio D. La situazione (o le situazioni) fobica viene evitata oppure sopportata con intensa ansia o disagio.
Criterio E. L'evitamento, l'ansia anticipatoria o il disagio nella situazione (situazioni) temuta interferiscono in modo significativo con la normale routine della persona, con il funzionamento lavorativo (o scolastico), o con le attività o le relazioni sociali, oppure è presente disagio marcato per il fatto di avere la fobia.
Criterio F. Negli individui al di sotto dei 18 anni la durata è di almeno 6 mesi.
Criterio G. L'ansia, gli attacchi di panico o l'evitamento fobico associati con l'oggetto o situazione specifici non sono meglio giustificati da un altro disturbo mentale, come il Disturbo Ossessivo-Compulsivo, Disturbo Post-traumatico da Stress, Disturbo d'Ansia di Separazione, Fobia Sociale, Disturbo di Panico con Agorafobia o Agorafobia senza Anamnesi di Disturbo di Panico.

Stress, possibile risposta dell'individuo agli eventi vitali

- **Lo "*stress*" può essere definito come una minaccia percepita dal nostro organismo verso la propria omeostasi, riflettente il bisogno di conservare stabilità passando attraverso un cambiamento.** Questa minaccia percepita può consistere in una minaccia fisica (biological stress) o in un carico emozionale (psychosocial stress) – che attiva, in modo geneticamente determinato programmi neuronali, ormonali e comportamentali (stress response system), allo scopo di preservare e ripristinare l'equilibrio.

Van Houdenhovea B, Egle U.T. - **Fibromyalgia: a stress disorder? - Psychother Psychosom 2004;73:267–275**


Evento vitale
Individuo
Risposta d'adattamento
Idonea
Inidonea
Eustress
Distress

Evento vitale

•Episodio depressivo maggiore
•Disturbo di panico
•Disturbo fobico specifico

Individuo

Risposta d'adattamento

Idonea

Inidonea

Eustress

Distress

www.nature.com/clinicalpractice/rheum

Mechanisms of Disease: pain in fibromyalgia syndrome

Roland Staud* and Miguel E Rodriguez

SUMMARY

Despite extensive research, the pathogenesis of pain in fibromyalgia syndrome is incompletely understood. Fibromyalgia pain is consistently felt in deep tissues including ligaments, joints and muscles. Increasing evidence points towards these tissues as relevant contributors of nociceptive input that might either initiate or maintain central sensitization, or both. Persistent or intense nociception can lead to transcriptional and translational changes in the spinal cord and brain resulting in central sensitization and pain. This mechanism represents a hallmark of fibromyalgia and many other chronic pain syndromes, including irritable bowel syndrome, temporomandibular disorder, migraine, and low back pain. Importantly, after central sensitization has been established, only minimal nociceptive input is required for the maintenance of the chronic pain state. Other factors, including pain-related negative affect, have been shown to significantly contribute to clinical fibromyalgia pain. An improved understanding of the mechanisms that characterize central sensitization and clinical pain will provide new approaches for the prevention and treatment of fibromyalgia and other chronic pain syndromes.

KEYWORDS central sensitization, fibromyalgia syndrome, pain, peripheral sensitization, temporal summation

REVIEW CRITERIA

All articles were identified by searching the MEDLINE and PubMed databases. The search keywords, used in different combinations, were "fibromyalgia", "pain", "central sensitization", "peripheral sensitization", "negative affect", "windup" and "spatial summation". All referenced articles were full-text, English-language papers, published between the years 1980 and 2004. We searched the articles' bibliographies and our own database for further relevant papers.

R Staud is a Professor of Medicine at the Evelyn F and William L McKnight Brain Institute and the Division of Rheumatology & Clinical Immunology, and ME Rodriguez is a Postdoctoral Rheumatology Fellow at the Division of Rheumatology & Clinical Immunology, of the University of Florida, Gainesville, USA.

Correspondence
*McKnight Brain Institute and Department of Medicine, University of Florida College of Medicine, Gainesville, FL 32610-0221, USA
staudr@ufl.edu

Received 29 June 2005 Accepted 20 October 2005
www.nature.com/clinicalpractice
doi:10.1038/ncprheum0091

INTRODUCTION

Fibromyalgia is a chronic pain syndrome that is defined by generalized pain for more than 3 months and the presence of more than 10 tender points,[1] in addition to disturbed sleep, distress and pronounced fatigue (Box 1). Pain in fibromyalgia is consistently felt in the musculature and is related to sensitization of central nervous system (CNS) pain pathways. The pathogenesis of fibromyalgia is unknown, although abnormal concentration of CNS neuropeptides and alterations of the hypothalamic–pituitary–adrenal axis have been described.[2] There is a large body of evidence for a generalized lowering of pressure-pain thresholds in patients with fibromyalgia,[3] but the mechanical ALLODYNIA of these patients is not limited to tender points and appears to be widespread.[4] In addition, almost all studies of patients with fibromyalgia have shown abnormalities of pain sensitivity while using different methods of sensory testing. Fibromyalgia represents the extreme end of the spectrum of chronic widespread pain syndromes in the general population and disproportionably affects women (9:1 ratio of women to men affected).[5] Like many other syndromes, fibromyalgia has no single specific feature but represents a symptom complex of self-reported or elicited findings.

Although relevant for many clinical pain syndromes like fibromyalgia, NOCICEPTION alone cannot sufficiently explain human pain, which can be altered by conscious and unconscious mental activity.[6] Whereas activated nociceptors, neurons and genes are highly useful in animal models of pain, sociocultural influences appear to be critical in shaping the human pain experience. In addition, beliefs or biases can strongly influence pain, particularly those related to cause, control, duration, outcome and blame. These beliefs are frequently linked to negative emotions, including anger, fear and depression. Thus, pain is a personal experience that can only be partially captured by definitions. The International Association for the Study of Pain defined pain as an "unpleasant sensory and

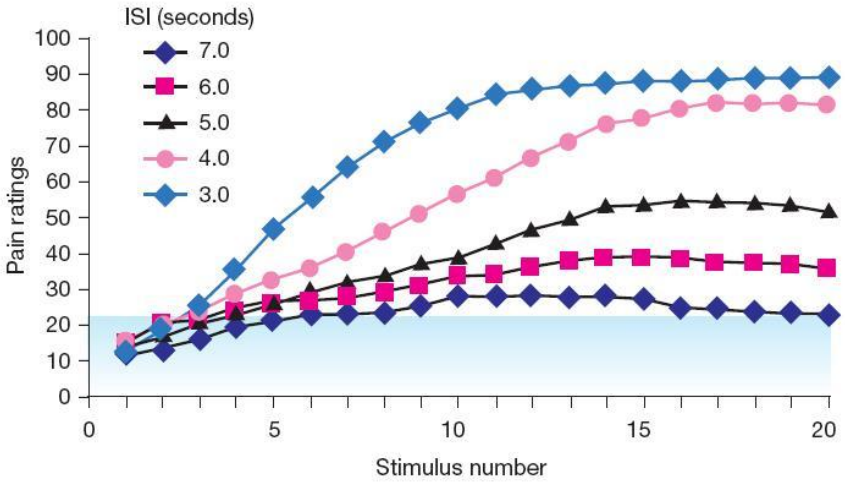
Pain pathways

Descending facilitation

Ascending facilitation

Pain amplification

Termed temporal sommation or Wind-up of second pain

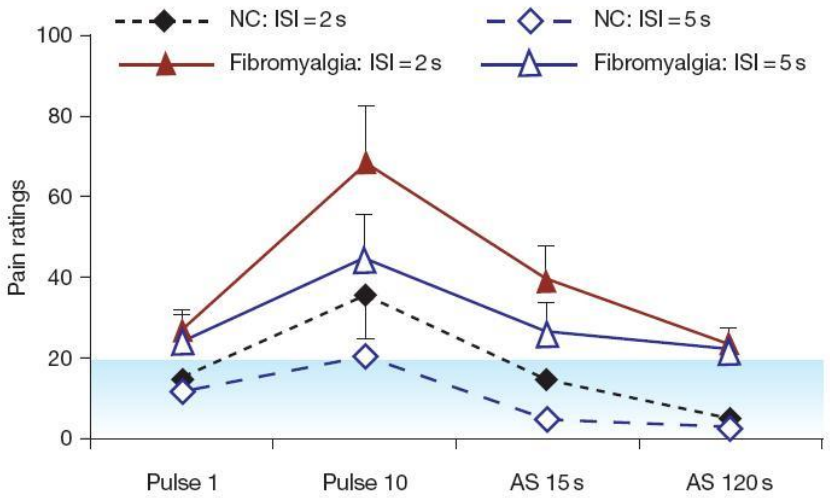


Staud R, Rodriguez ME. Mechanisms of disease: pain in fibromyalgia syndrome. *Nat Clin Pract Rheumatol*. 2006 Feb;2(2):90-8

Wind-up of second pain (Mendell and Wall)

- An important test of central pain amplification relies on detection of second pain by the study subjects and is termed temporal summation, or wind-up, of second pain.
- This technique reveals sensitivity to input from unmyelinated (C) afferents and the status of the NMDA receptor systems that are implicated in a variety of chronic pain conditions. Thermal, mechanical, or electrical second pain stimuli can be applied to the skin or musculature of patients using neuro sensory stimulators, which are readily available for assessing wind-up.
- This important mechanism of pain amplification in the dorsal-horn neurons of the spinal cord is related to temporal summation, or wind-up, of second pain.

Pain amplification in FM



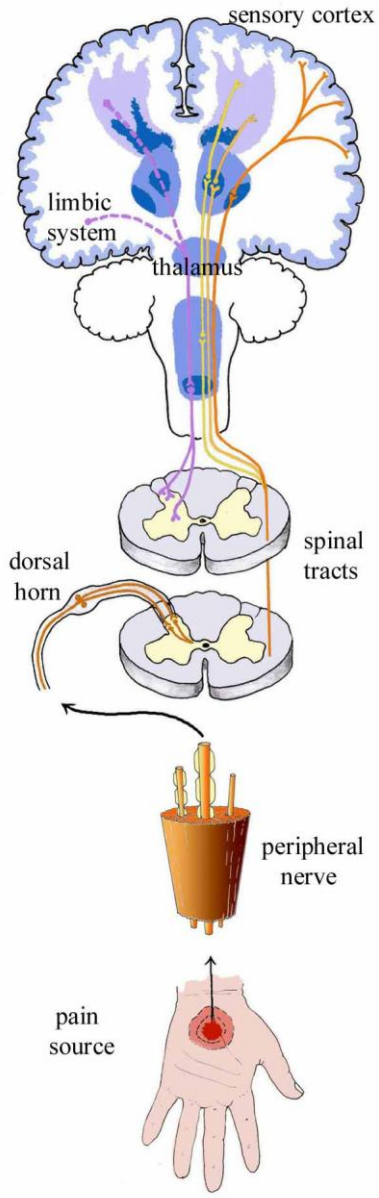
Wind-up comparisons between normal controls and patients with fibromyalgia. During this experiment, patients with fibromyalgia and normal control subjects received 10 identical heat pulses (51 ºC) to the hands at interstimulatory intervals of 2 s and 5 s. Pain after-sensations representing the decay of wind-up of second pain, were obtained after 15 s and 120 s.

A numerical pain scale (0–100) was used, with 20 representing the pain threshold. The shaded area indicates ratings of nonpainful warmth. This figure illustrates several important aspects of central sensitization that are detectable in fibromyalgia: first, patients with fibromyalgia show **secondary hyperalgesia to the first thermal stimulus**; second, **wind-up of second pain is abnormally increased in fibromyalgia**, indicating immediate central sensitization; and third, **wind-up of second pain decay is significantly prolonged** in patients with fibromyalgia, consistent with delayed central sensitization.

AS, after-sensations; ISI, interstimulatory interval; NC, normal control.

Inibitory pathway

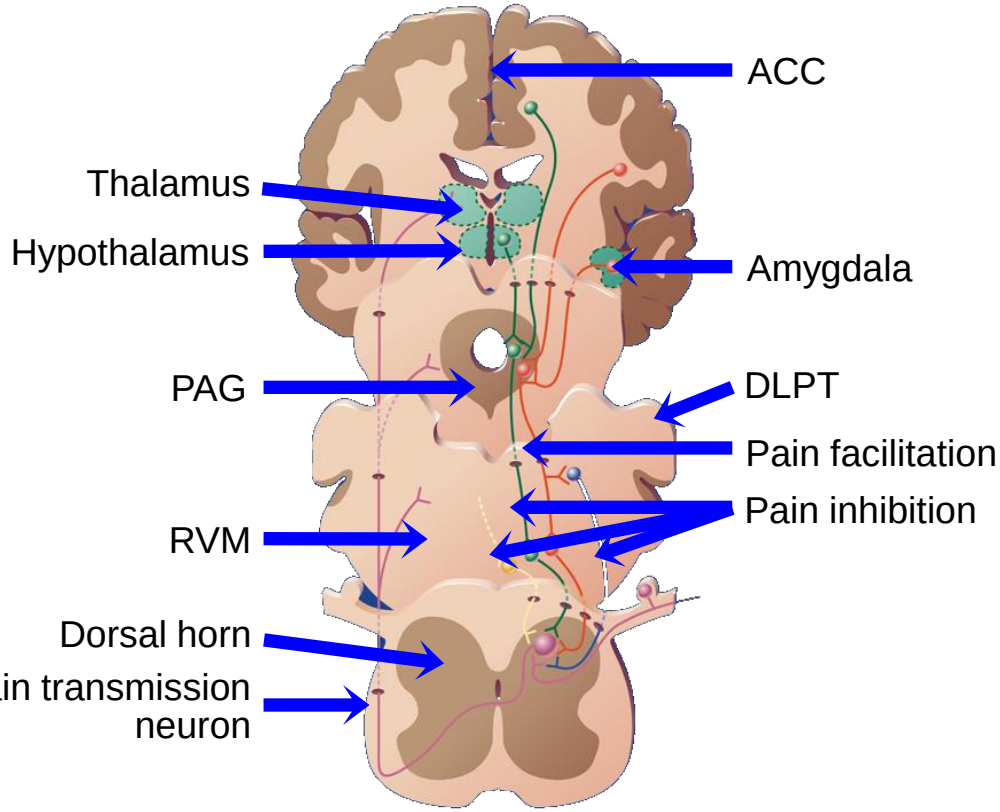
- The afferent (incoming) pain signals reach the dorsal root ganglion, cross the synapse to a higher neuron horn of the spinal cord and connect in the dorsal horn with interneuron cells. This is far from a simple, passive, one-to-one transmission. The signal processing in the dorsal root ganglion and the dorsal horn is complex and only partly understood. There are many factors, including: (1) descending stimulatory (shown in yellow) and inhibitory (shown in purple) signals from the brain; (2) production, release, reception, and modulation of neurotransmitter substances; and (3) other, less well-defined processes that are postulated in order to explain clinical findings, but not yet proven. These processes are thought to be both excitatory and inhibitory.



Descending modulation

- Neuropathic pain is associated with increased excitation and decreased inhibition of ascending pain pathways
- Descending pathways modulate ascending signals
- **NE and 5-HT are key neurotransmitters in descending inhibitory pain pathways**
- Increasing the availability of NE and 5-HT may promote pain inhibition centrally

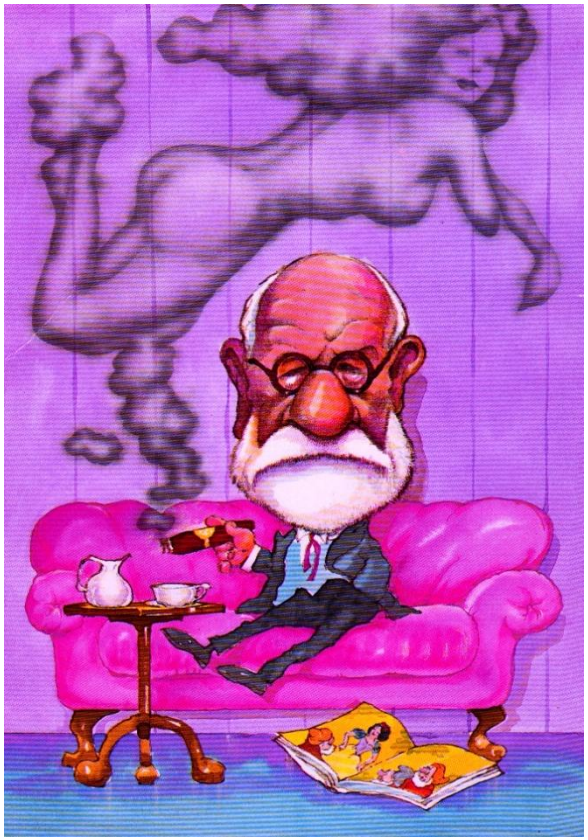
Descending modulation → PAG indirectly controls pain transmission in the dorsal horn

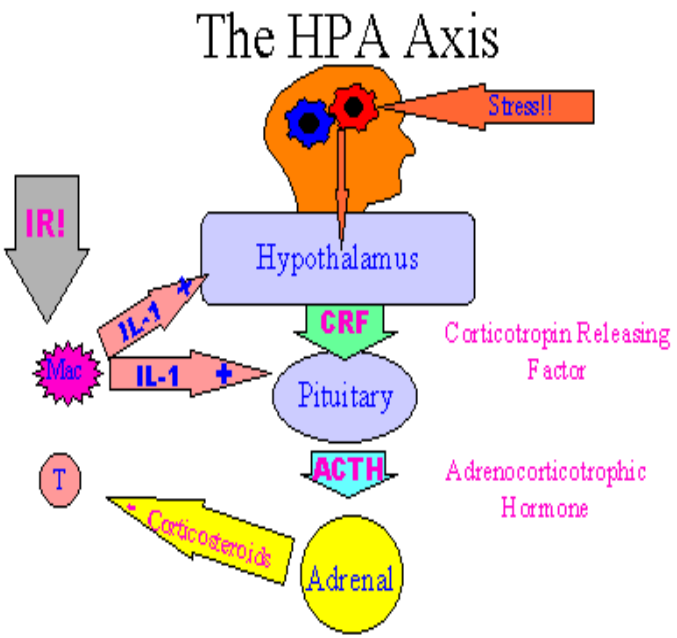


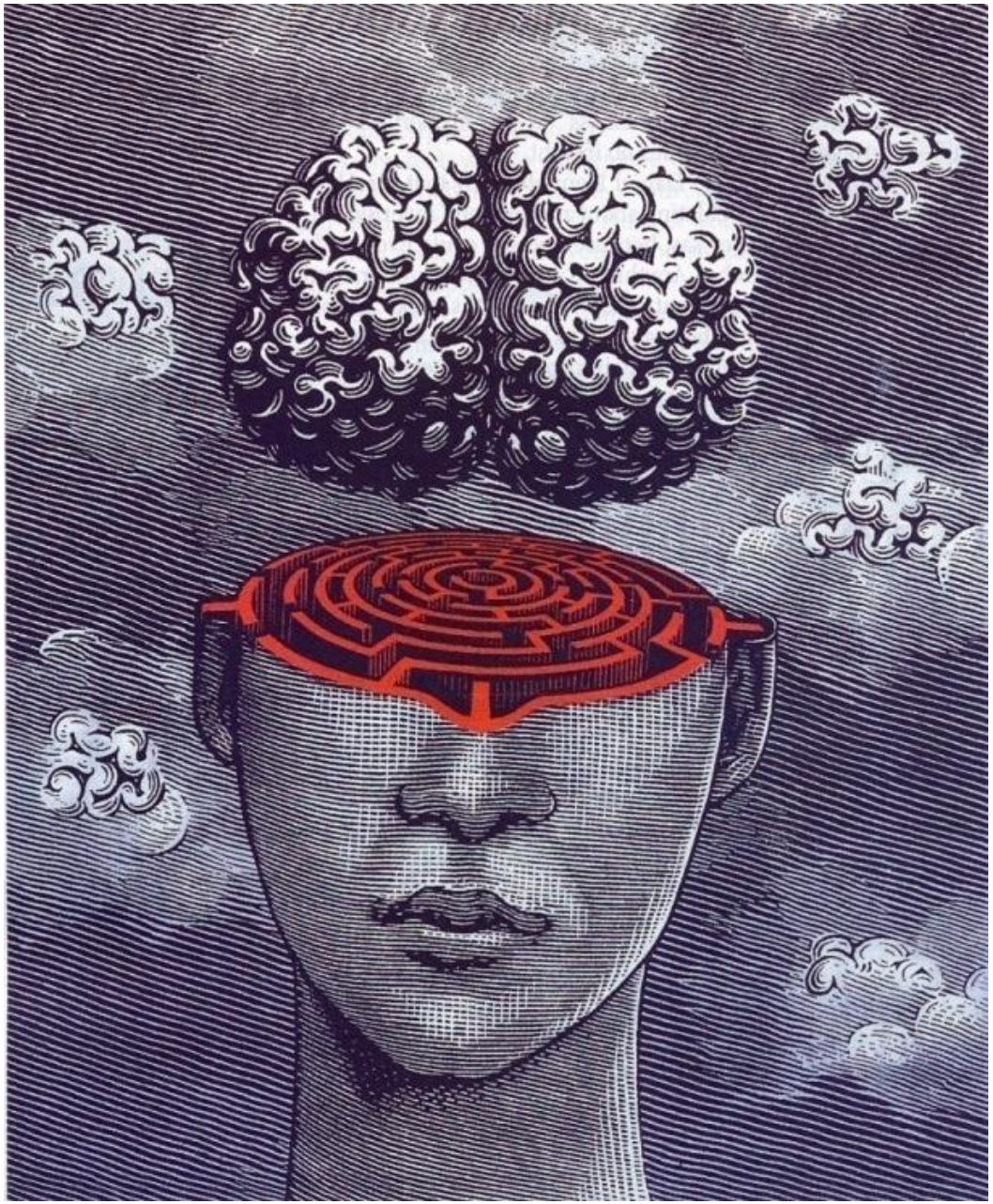
ACC: Anterior cingulate cortex
PAG: Periaqueductal gray (5-HT)
DLPT: Dorsolateral pontine tegmentum (NE)
RVM: Rostroventral medulla (5-HT)

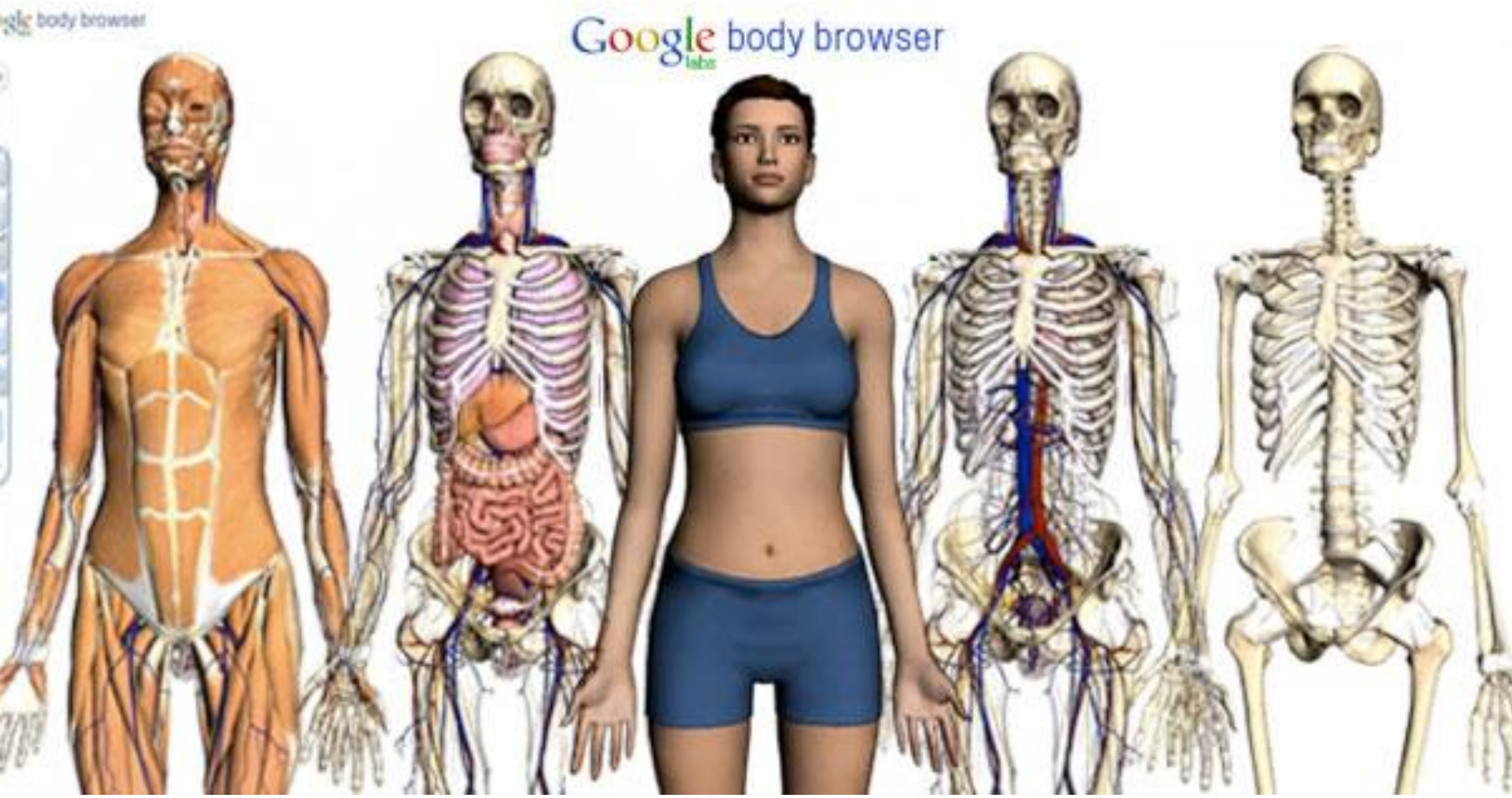
1. Staley K. *Nature Medicine*. 2003;**9**:1110–1111; 2. Ossipov MH, Porreca F. *NeuroRX*. 2005;**2**:650–661;
3. Fields HL, et al. *Annu Rev Neurosci.* 1991;**14**:219–245; 4. Fields HL, Basbaum AI. In: Wall PD, Melzack R, eds. *Textbook of Pain*; 2006:126.

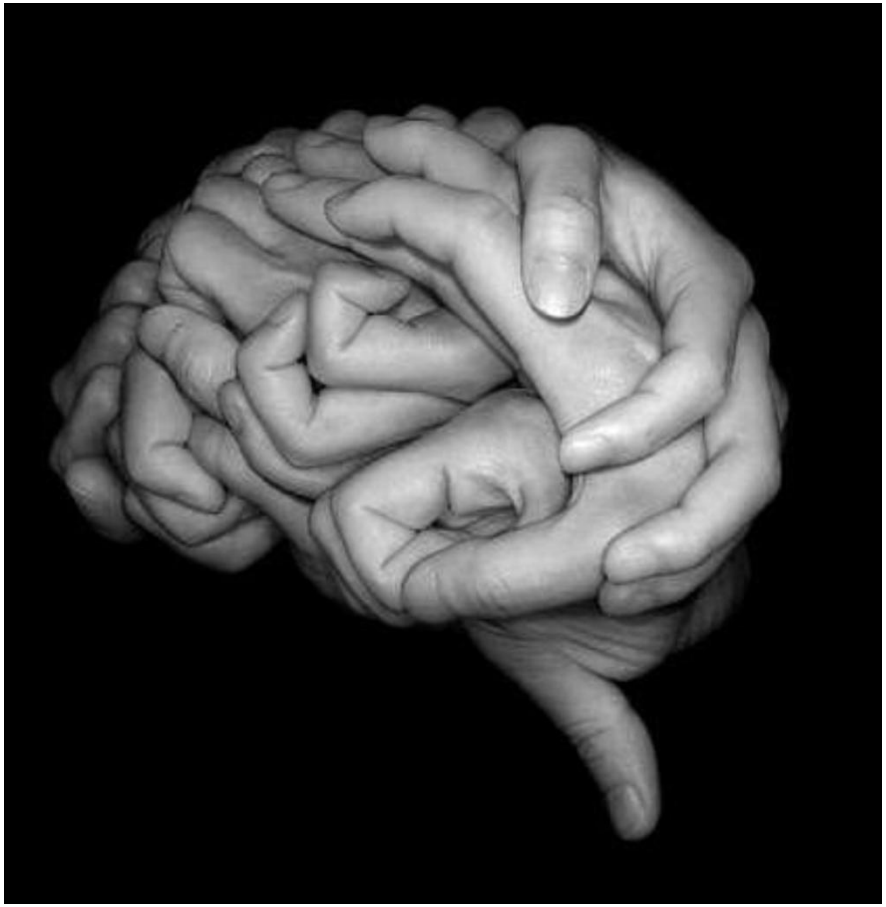
Malattia psico-neuroendocrino-algologica








Google body browser
labs

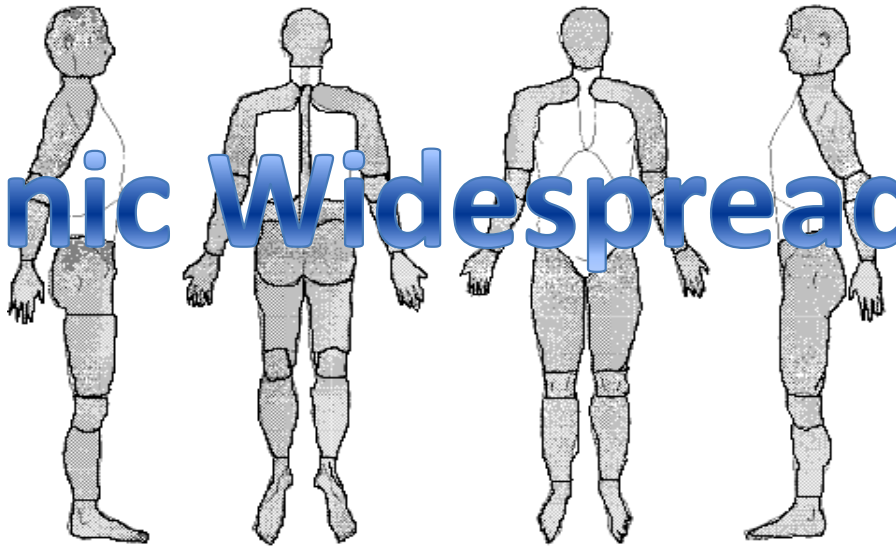


… ma il dolore non intende prestare ascolto alla ragione, perché il dolore ha una sua propria ragione che non è ragionevole.

Milan Kundera

Soffre di dolore dappertutto da almeno 3 mesi?

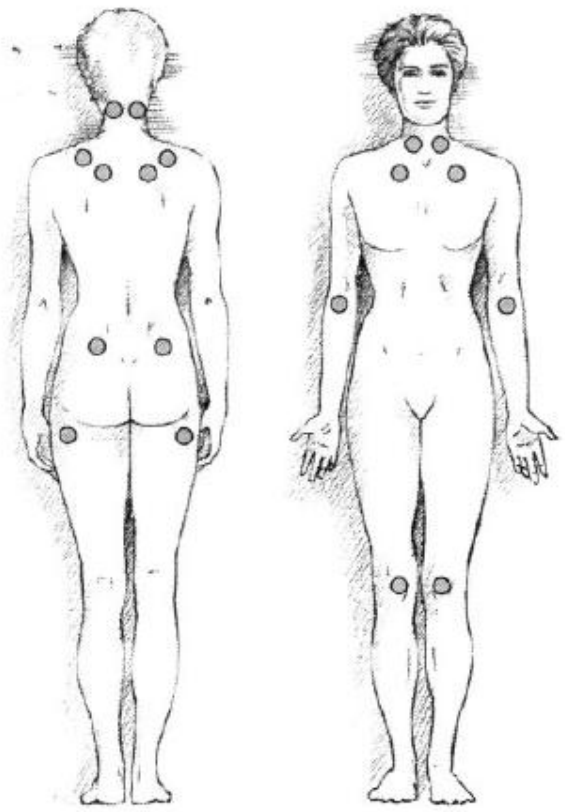
SI



Chronic Widespread Pain

Dolore riferito dal paziente in almeno 2 sezioni per ogni arto e della colonna, da almeno 3 mesi

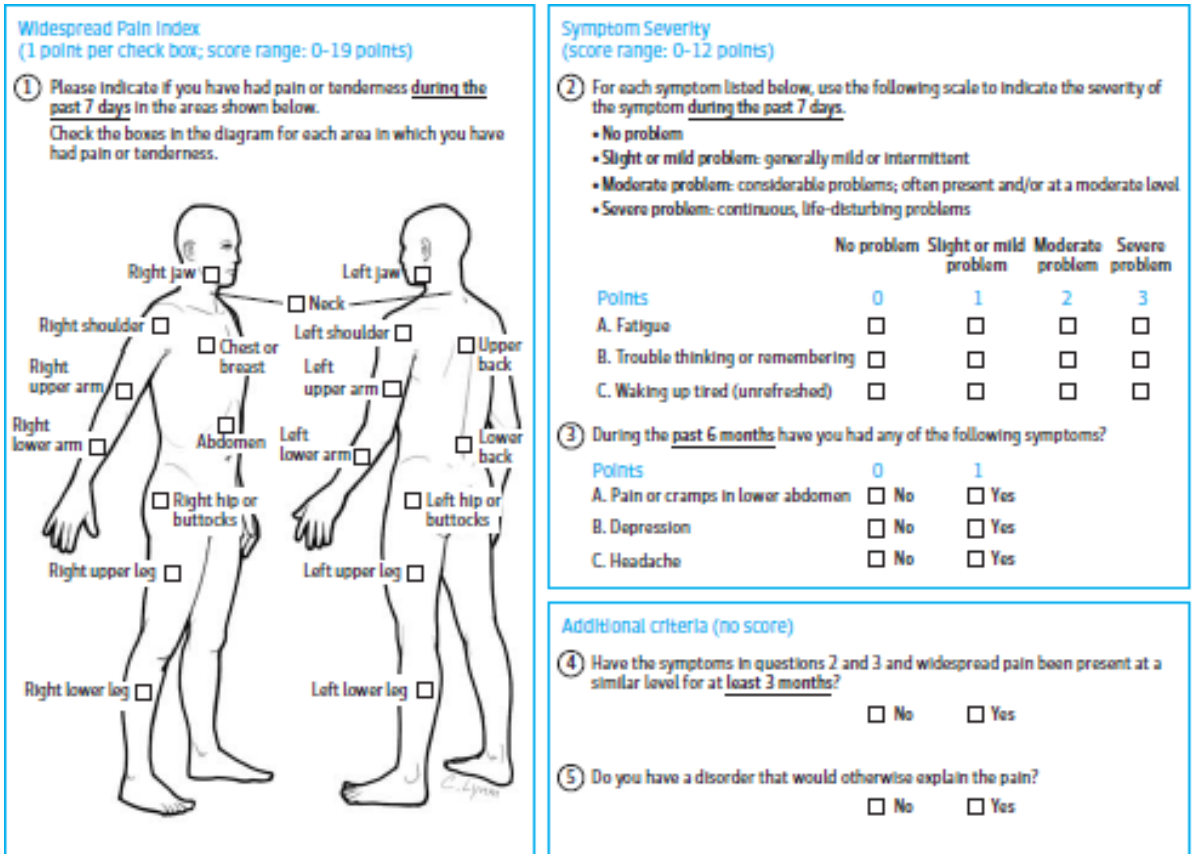
E’ una Fibromialgia?



SI **Anamnesi caratteristica** (dolore diffuso da almeno tre mesi, sonno disturbato, astenia, parestesie)

- Rilievo all’esame obiettivo di **dolorabilità alla palpazione** (di 4 kg/cm^2) di almeno 11/18 tender-points individuati come tipici della patologia, presenti su entrambi gli emisomi e sulla metà superiore e inferiore del corpo.

ACR-Criteria FM-2011



Widespread Pain Index
(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.

Right jaw ☐ Left jaw ☐
Neck ☐
Right shoulder ☐ Left shoulder ☐
Chest or breast ☐ Upper back ☐
Right upper arm ☐ Left upper arm ☐
Right lower arm ☐ Abdomen ☐ Left lower arm ☐ Lower back ☐
Right hip or buttocks ☐ Left hip or buttocks ☐
Right upper leg ☐ Left upper leg ☐
Right lower leg ☐ Left lower leg ☐

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 blue. The possible score ranges from 0 to 31 points; a score13 points is consistent with a diagnosis of fibromyalgia.

Diffidate di una diagnosi di FM:

1. **In soggetti > 70 aa**
2. **Nei maschi**

A SIMPLE ANAMNESTIC TEST CAN HELP US TO DIAGNOSE FIBROMYALGIA?

S. Stisi[1],*, C. Venditti[1], R. Murgia[2], B. Simonetti[3]

[1]Rheumatology, Rummo Hospital, [2]Rheumatolgy, Rheumatology Center Kinesis, Cagliari, Italy, [3]Department of Analysis of Business and Social Sciences, University of Sannio, Benevento

Background:

Fibromyalgia (FM) is a clinical construct characterized by widespread pain, that has been developed since 1990 American College of Rheumatology's Criteria[1]. There are many similar painful syndromes and there are not specific biological or imaging's markers safe for diagnosis, which therefore is only clinical. General practitioners are quite unfamiliar with the diagnostic criteria of FM (2) but it's diagnosis is sometimes difficult. In last years there was several attemps[3,4] to look for a diagnostic tool to aid diagnosis of fibromyalgia, but they have been poor circulation because have low specificity.

Objectives:

In order to create an help to diagnosis FM with high specificity for the general practitioners, we have designed a Fibromyalgia Help Diagnosis Test (FM-HDT), subjecting the patients to a semi quantitative questionnaire for the most frequent and characteristic symptoms of FM syndrome: widespread pain, sleep disturbances, fatigue/asthenia, paresthesia, previous history of psychological disorder and dysfunctional syndromes.

Patients and Methods:

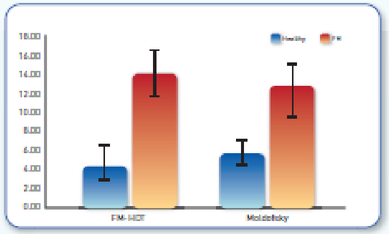
We interviewed a group of 70 healthy subjects (65 F; 5 M) mean age 42.9 and 114 fibromyalgia ACR-1990 consecutive patients (113 F; 1M) mean age 48.1, subjecting them to FM-HDT and to a previous similar Moldofsky's test[4]. We excluded all those who suffer of any other painful disease (visceral or muscle skeletal pain). FM-HDT assessed six items each with multiple choice and score (0-3); the simple sum of scores of each item was FM-HDT score (0-18). Identical subjects were administered Moldofsky's test (score 0-18). The statistical data were processed by the descriptive (t-test) and the Goodman-Kruskal asymmetrical association measure test.

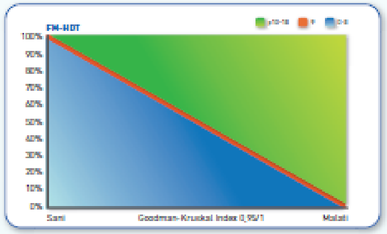
Results:

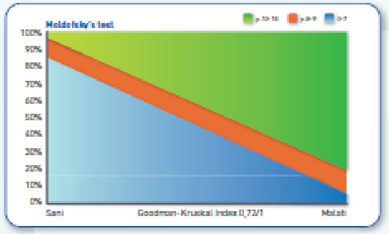
The mean score was significantly higher (p=< 0,0001) in FM patients compared with healthy related subjects evaluated with both tests (*see graph 1*). The FM-HDT normal values, constructed with Goodman-Kruskal index, found to be 0-8, while FM patients scored between 10 and 18. The score 9 was to be considered doubtful. FM-HDT and Moldofsky's tests were very sensitive (both 99%), but FM-HDT showed a significantly better specificity (97% vs 61%), as Goodman-Kruskal index 0,95 (range 0-1) vs 0,72 of Moldofsky's test. Also positive predictive value (98% vs 82%) showed how reliable was the FM-HDT.

Conclusion:

Due to obtained results we think that a specific and reliable test as FM-HDT, which can be easily administered in less than a minute, to a patient with "pain all over", may be indeed an help to clinical diagnosis of fibromyalgia in general practitioners activities.







Discriminant Analysis

FM-HDT

From/to	FM	Healts	Total	% Correct
FM	113	1	114	99,12%
Healts	2	68	70	97,14%
Total	115	69	184	98,37%

Moldofsky test

From/to	FM	Healts	Total	% Correct
FM	100	14	114	87,72%
Healts	6	64	70	91,43%
Total	106	78	184	89,13%

References:

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990 Feb;33(2):160-72.
2. Shleyfer E, Jotkowitz A, Karmon A, Nevzorov R, Cohen H, Buskila D. Accuracy of the diagnosis of fibromyalgia by family physicians: is the pendulum shifting? J Rheumatol. 2009 Jan;36(1):170-3.
3. Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. Arthritis Rheum. 2006 Jan;54(1):169-76.
4. Moldofsky H, Bouscatto S, Roak-Le Kay. Fibromyalgia Moldofsky Questionnaire (FMQ): use of a tool to aid diagnosis. Abst THU0387. Annual European Congress of Rheumatology-EULAR 2008. Paris, 11-14 June 2008

E’ una forma primaria di FM?

Anamnesi caratteristica per FM

Età < 70 aa	Fattori rischio	Età > 70 aa
SI → Tests Laboratorio di 1° istanza	*Psicologici* *Infettivi* *Cardiovascolari* *Metabolici* •Mini-Mental Test 5.0.0 •Test infettivologici •Holter pressorio 24h •Glicemia, Hb glicata, Colesterolo, Trigliceridi •Vitamina D, Calcemia	

Tests di prima istanza

Reumatismo, 2008; 60: Supplemento 1: 3-14

ORIGINAL ARTICLE

Fibromyalgia syndrome: definition and diagnostic aspects

La sindrome fibromialgica: definizione ed aspetti diagnostici

M. Cazzola[1], P. Sarzi Puttini[2], S. Stisi[3], M. Di Franco[4], L. Bazzichi[5], R. Carignola[6], R.H. Gracely[7], F. Salaffi[8], F. Marinangeli[9], R. Torta[10], M.A. Giamberardino[11], D. Buskila[12], M. Spath[13], G. Biasi[14], G. Cassisi[15], R. Casale[16], L. Altomonte[17], G. Arioli[18], A. Alciati[19], A. Marsico[20], F. Ceccherelli[21], G. Leardini[22], R. Gorla[23], F. Atzeni[2] (Italian Fibromyalgia Network)

Table II - Laboratory tests recommended at first observation.

Symptom onset <12 months	*Symptom onset >12 months*
ESR	ERS
CRP	Hemochrome
Hemochrome	TSH
ANA	
CPK	
TSH	
Liver and renal function	

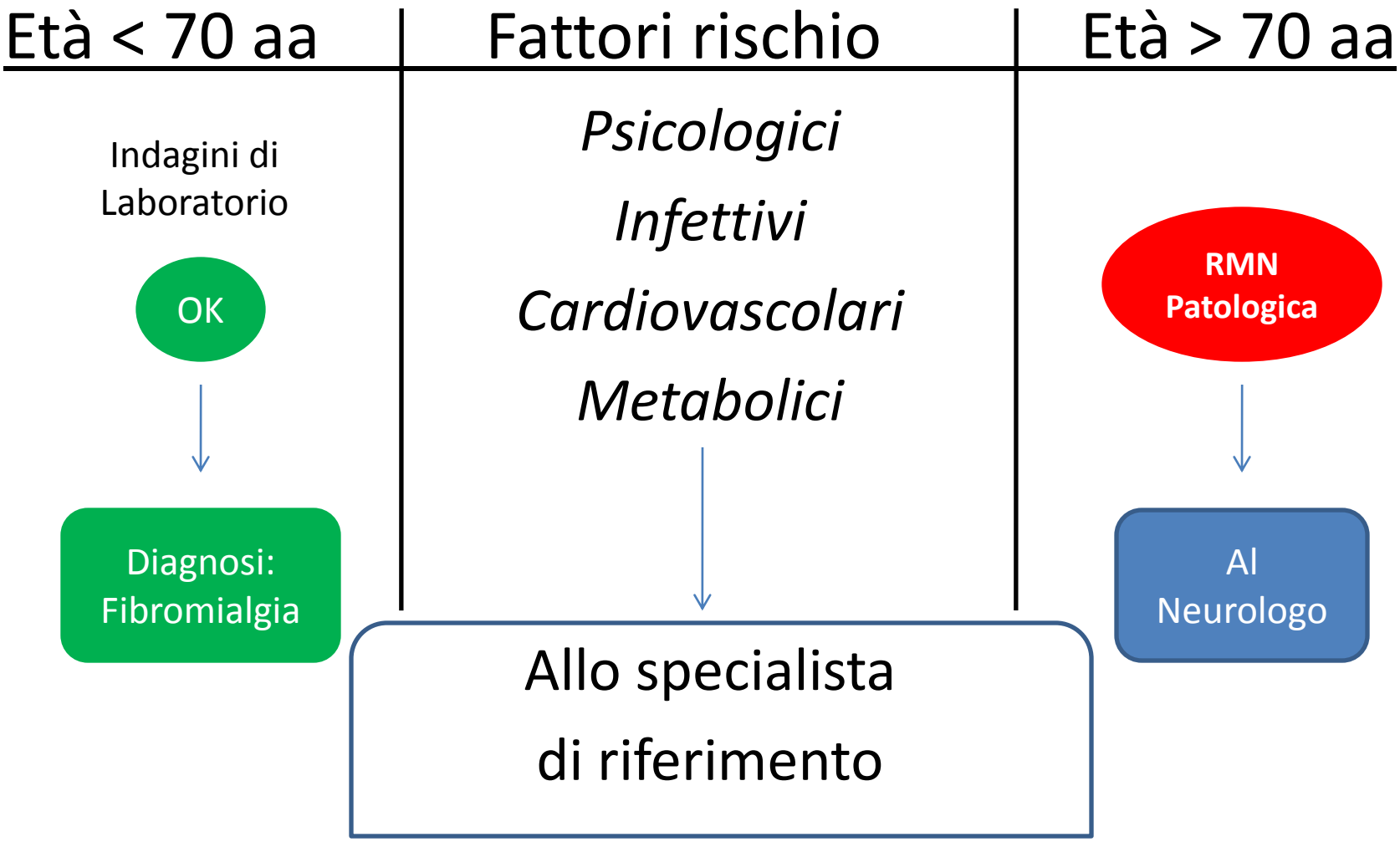
E’ una forma primaria di FM?

Anamnesi caratteristica per FM

Età < 70 aa	Fattori rischio	Età > 70 aa
	Psicologici *Infettivi* *Cardiovascolari* *Metabolici*	SI → Imaging Neurologico (RMN)

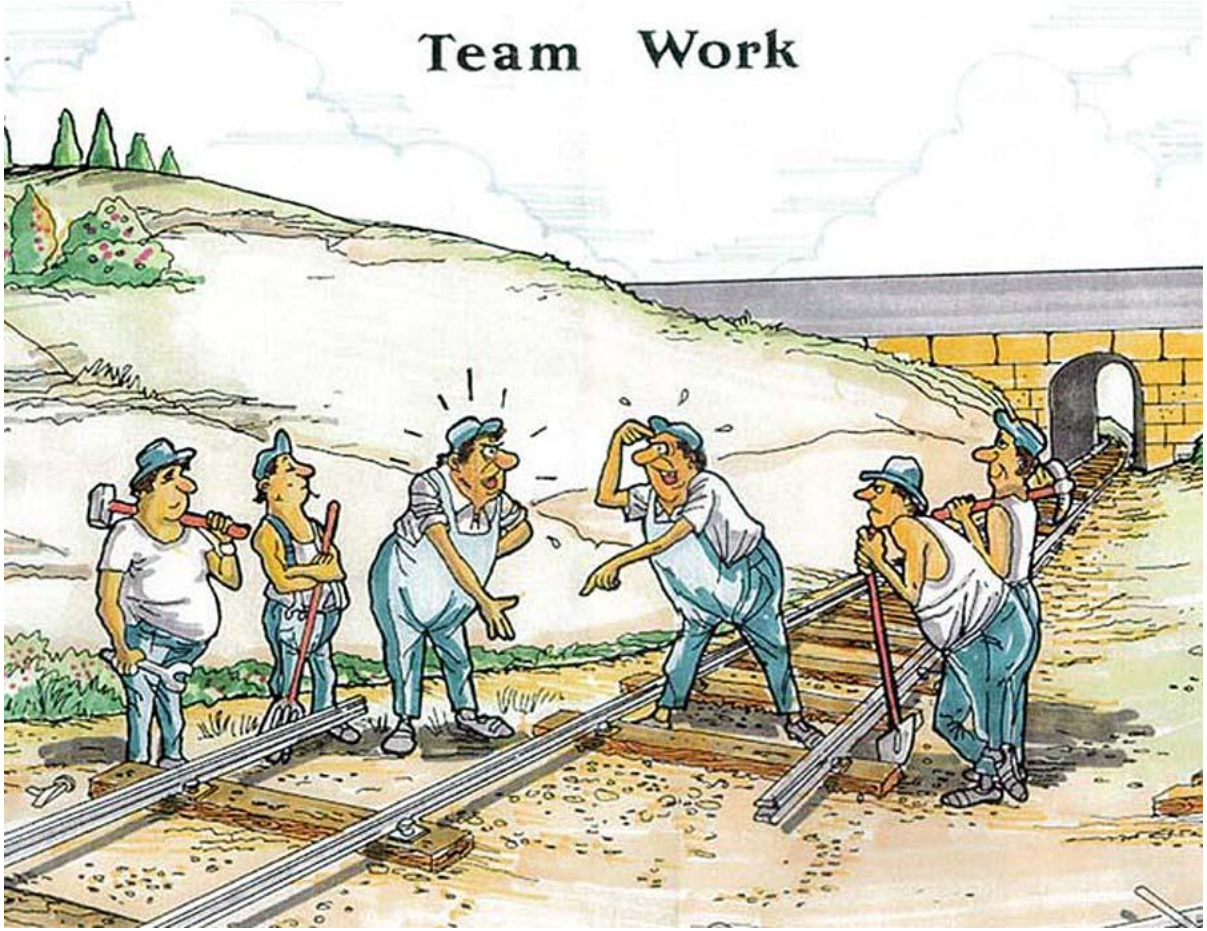
- Mini-Mental Test 5.0.0
- Test infettivologici
- Holter pressorio 24h
- Glicemia, Hb glicata, Colesterolo, Trigliceridi
- Vitamina D, Calcemia

Chiusura dello screening

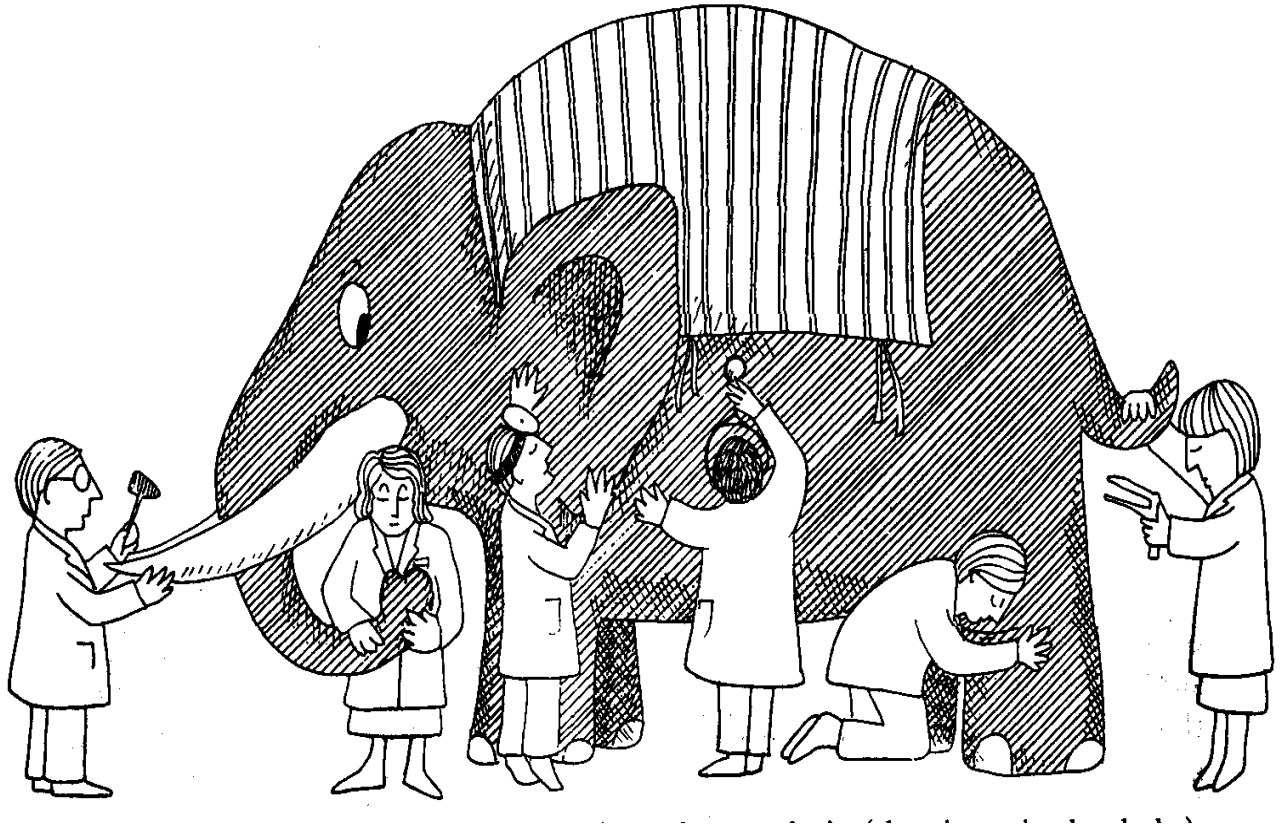


Siamo sempre noi lo specialista giusto?

Lavorare con altri specialisti aumenta la possibilità di successo terapeutico?



The blind physicians and the elephant



The neurologist (chronic tension headache), the gastroenterologist (irritable bowel syndrome), the otorhinolaryngologist (temporo-mandibular syndrome), the cardiologist (costochondritis), the rheumatologist (FMS), and the gynaecologist (primary dismenorrhoea syndrome).

E.Nüesch, W. Häuser, K.Bernardy, J. Barth, P. Jüni
***Ann Rheum Dis. 2012 Jun* 27.**

EXTENDED REPORT

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]

► Additional data are published online only. To view the files please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2011-201249).

[1]Institute of Social and Preventive Medicine (ISPM), University of Bern, and CTU Bern, Bern University Hospital, Bern, Switzerland
[2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, University of London, London, UK
[3]Department of Internal Medicine 1, Klinikum Saarbrücken, Saarbrücken, Germany
[4]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, München, Germany
[5]Department of Internal Medicine, Complementary and Integrative Medicine, University of Duisburg-Essen, Kliniken Essen-Mitte, Essen, Germany
[6]Department of Pain Management, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil, Ruhr University Bochum, Bochum, Germany

Correspondence to
Dr Eveline Nüesch, Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern 3012, Switzerland; enueesch@ispm.unibe.ch

Received 25 December 2011
Accepted 31 May 2012

ABSTRACT

Objectives To synthesise the available evidence on pharmacological and non-pharmacological interventions recommended for fibromyalgia syndrome (FMS).

Methods Electronic databases including MEDLINE, PsycINFO, Scopus, the Cochrane Controlled Trials Registry and the Cochrane Library were searched for randomised controlled trials comparing any therapeutic approach as recommended in FMS guidelines (except complementary and alternative medicine) with control interventions in patients with FMS. Primary outcomes were pain and quality of life. Data extraction was done using standardised forms.

Results 102 trials in 14 982 patients and eight active interventions (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors (SNRIs), the gamma-amino butyric acid analogue pregabalin, aerobic exercise, balneotherapy, cognitive behavioural therapy (CBT), multicomponent therapy) were included. Most of the trials were small and hampered by methodological quality, introducing heterogeneity and inconsistency in the network. When restricted to large trials with ≥100 patients per group, heterogeneity was low and benefits for SNRIs and pregabalin compared with placebo were statistically significant, but small and not clinically relevant. For non-pharmacological interventions, only one large trial of CBT was available. In medium-sized trials with ≥50 patients per group, multicomponent therapy showed small to moderate benefits over placebo, followed by aerobic exercise and CBT.

Conclusions Benefits of pharmacological treatments in FMS are of questionable clinical relevance and evidence for benefits of non-pharmacological interventions is limited. A combination of pregabalin or SNRIs as pharmacological interventions and multicomponent therapy, aerobic exercise and CBT as non-pharmacological interventions seems most promising for the management of FMS.

INTRODUCTION

Key symptoms of fibromyalgia syndrome (FMS) are chronic widespread pain associated with cognitive dysfunction, sleep disturbances and physical fatigue.[1 2] Patients often report high levels of disability and poor quality of life, and an extensive use of medical care.[3] In the absence of suitable laboratory tests, diagnosis is established by a history of key symptoms and the exclusion of somatic diseases sufficiently explaining these symptoms.[2 4] The estimated overall prevalence of FMS is 2.9% in the general population of five European countries.[5] The definite aetiology of FMS remains unknown.[4] Since specific treatment aimed at altering the pathogenesis is not possible, the therapeutic focus is on symptom reduction.

Systematic reviews and evidence-based guidelines provide healthcare professionals and patients with a guide through the large variety of pharmacological and non-pharmacological treatment options offered to and used by patients with FMS.[6] The American Pain Society[7] and the Association of Scientific Medical Societies in Germany[4] strongly recommend a pharmacological intervention (amitriptyline) and several non-pharmacological treatments (aerobic exercise, cognitive behavioural therapy (CBT), multicomponent therapy). Conversely, the European League Against Rheumatism (EULAR) have given only a strong recommendation for a variety of pharmacological therapies (eg, tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), serotonin reuptake inhibitors (SSRIs), gamma-amino butyric acid analogues (GABA) such as pregabalin) but weak recommendations for non-pharmacological therapies such as aerobic exercise, CBT and multicomponent therapy.[8] Recommendations for first-line treatment options of FMS, however, are hampered by the lack of head-to-head comparisons of pharmacological versus non-pharmacological treatments.

Network meta-analyses allow a unified coherent analysis of all randomised controlled trials comparing pharmacological and non-pharmacological treatments head-to-head or with a control intervention, while fully respecting randomisation.[9–11] We performed a systematic review with network meta-analysis of randomised trials in patients with FMS evaluating effects of pharmacological and non-pharmacological interventions recommended in FMS guidelines on pain and quality of life. We provide an overall synthesis of available data that can be used to guide treatment decisions and examined the potential for bias due to methodological flaws or small-study effects.[12–15]

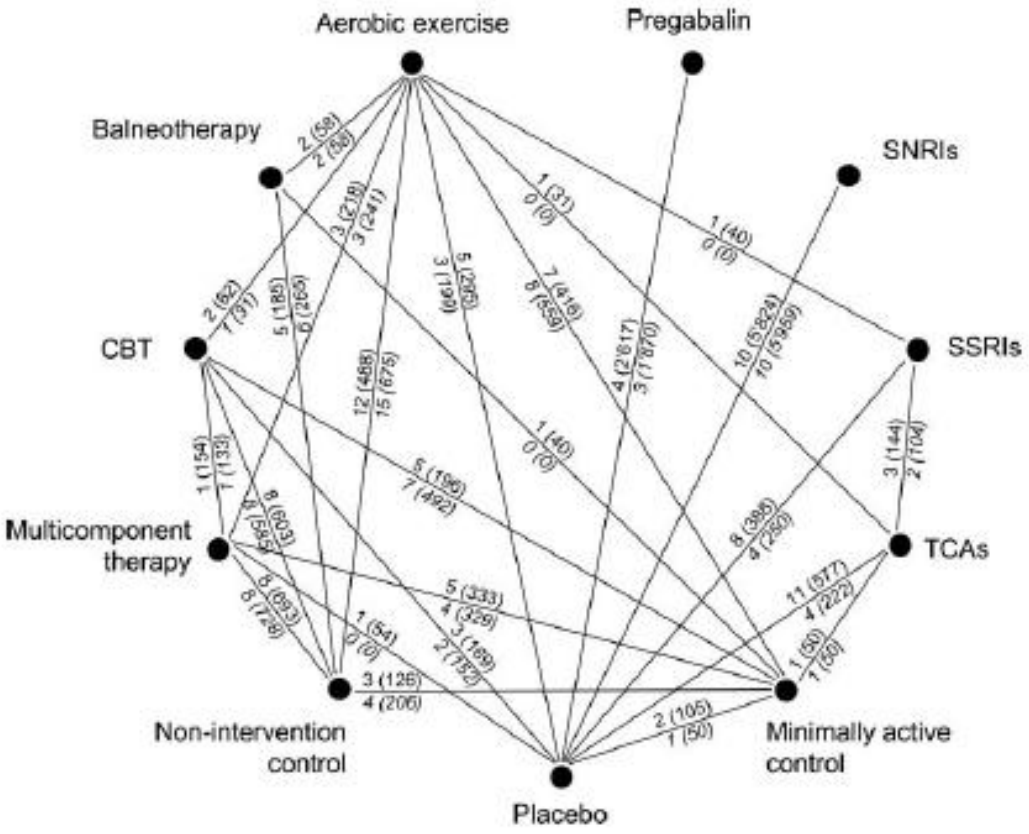
METHODS

Literature search and trial selection

We searched MEDLINE, PsycINFO, Scopus, the Cochrane Controlled Trials Registry and the Cochrane Library, all from inception through 31 December 2011. The search strategy has been previously described.[16–21] We included treatment

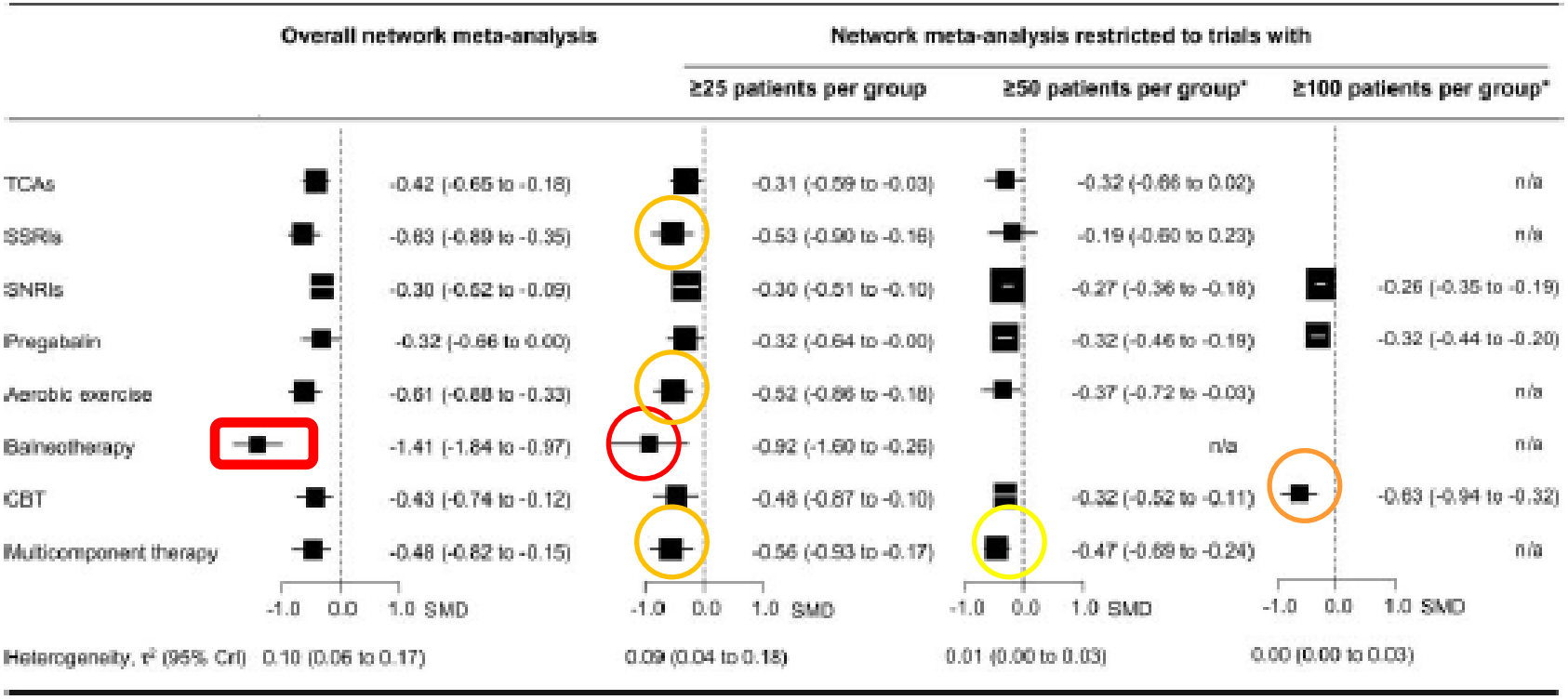
Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis

E.Nüesch, W. Häuser, K.Bernardy, J. Barth, P. Jüni
Ann Rheum Dis. 2012 Jun 27.



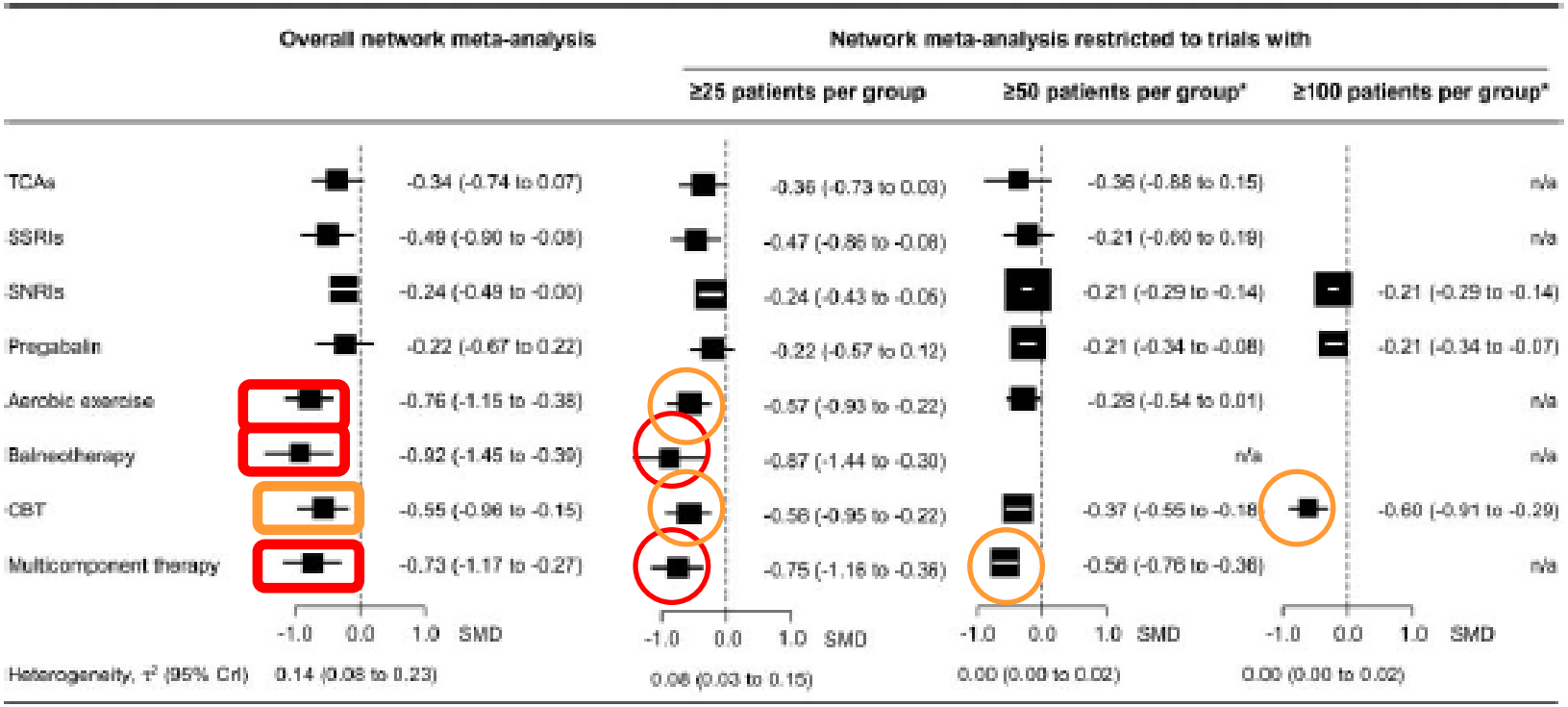
Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis

Pain



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

Quality ol life



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

- In conclusion, evidence about **effective and clinically relevant treatments** for FMS **is limited**.
- **Additional large-scale randomised trials** of high methodological quality of promising nonpharmacological interventions such as **CBT, aerobic exercise and multicomponent therapy** are warranted.
- In view of the currently available evidence, **a combination of pregabalin or SNRIs as pharmacological interventions and multicomponent therapy, aerobic exercise or CBT as non-pharmacological interventions seems most promising**.

Di Franco M. et al.
Pharmacological treatment of fibromyalgia.
Clin Exp Rheumatol. 2010 Nov-Dec;28(6 Suppl 63):S110-6

- The best treatment should be individualised and combined with patient education and non-pharmacological therapy.

frontiers in
PHARMACOLOGY

REVIEW ARTICLE
published: 31 March 2011
doi: 10.3389/fphar.2011.00017

Pharmacotherapy for fibromyalgia

Howard S. Smith[1], Donna Bracken[2] and Joshua M. Smith[3]*

[1] Department of Anesthesiology, Albany Medical College, Albany, NY, USA
[2] Medical School, Albany Medical College, Albany, NY, USA
[3] Pharmaceutical Research Institute, Albany, NY, USA

Edited by:
Arpad Szallasi, Monmouth Medical Center, USA

Reviewed by:
Marco Pappagallo, Mount Sinai School of Medicine, USA
Tobias Moeller-Bertram, University of California, USA
Troels Jensen, Aarhus University Hospital, Denmark

***Correspondence:**
Howard S. Smith, Department of Anesthesiology, Albany Medical College, 47 New Scotland Avenue, MC-131, Albany, NY 12208, USA.
e-mail: smithh@mail.amc.edu

Fibromyalgia (FM) is a chronic disorder characterized by multifocal pain and other associated somatic symptoms including fatigue, insomnia, cognitive/memory problems, and even psychological distress. It appears that 2–4% of the general population suffers from FM. FM negatively impacts the physical functioning of its patients, as evidenced by difficulties with multiple daily activities, as well as affecting emotional health, social functioning, and health related quality of life. This review will discuss the potential theories that possibly contribute to the pathogenesis of FM, although the precise mechanism is unknown. The evolution of the assessment of FM will also be examined, with the waning use of tender point examinations and the appearance of new simple, practical diagnostic criteria. Although non-pharmacologic therapeutic options (exercise, education, cognitive–behavioral therapy) have been shown to be extremely effective in FM, the focus of this article will be on pharmacologic strategies. Non-Food and Drug Administration (FDA) approved as well as FDA approved agents will be presented. Each agent's therapeutic "niche" in FM management will be discussed based on its pharmacologic profile, patient responsiveness, and tolerability. Finally a clinical algorithm will be presented for the step-wise management of pain and other associated symptoms of FM.

Keywords: pharmacotherapy, fibromyalgia, pregabalin, duloxetine, milnacipran, efficacy, pain

INTRODUCTION

Fibromyalgia (FM) is a central pain disorder that seems to involve altered afferent processing, resulting in augmentation of peripheral stimuli, especially the nociceptive types. The "core" symptoms seen in FM and many other central sensitization disorders include multifocal pain, fatigue, insomnia, cognitive/memory problems, and psychological distress. However, FM patients may experience a multitude of other symptoms, including dysesthesias, stiffness, poor balance, oral/ocular symptoms (e.g., keratoconjunctivitis sicca), headaches, sexual dysfunction, and impaired physical function (**Figure 1**).

Chronic widespread pain (CWP) may occur with no other associated symptoms, generally referring to persistent pain ≥3 months with multiple locations in multiple extremities (usually upper and lower/right and left side of body), spine/axial skeleton, head, and/or thoraco abdominopelvic regions. FM includes CWP, but also includes other symptoms, notably fatigue, sleep disturbance, stiffness, hyperalgesia, impaired functioning, and cognitive or memory problems.

There is growing support that FM is part of a much larger continuum that has been called many things, including functional somatic syndromes, medically unexplained symptoms, chronic multisymptom illnesses, somatoform disorders, and perhaps most appropriately, central sensitivity syndromes (CSS; Smith et al., 2011). Yunus (1984) showed FM to be associated with tension type headache, migraine, and irritable bowel syndrome (IBS). There may be a fair amount of clinical overlap between these syndromes. The more recent term CSS as proposed by Yunus (2008) is the preferred term to globally group these entities together in, because it is felt that this may represent the best nosological term at present for these syndromes [e.g., chronic fatigue syndrome, vulvodynia/chronic pelvic pain, IBS, interstitial cystitis, temporomandibular disorder (TMD), FM].

Groups of individuals with these CSS conditions (e.g., FM, IBS, interstitial cystitis, headaches, TMD, etc.) display diffuse hyperalgesia (increased pain in response to normally painful stimuli) and/or allodynia (pain in response to normally non-painful stimuli; Langemark et al., 1989; Maixner et al., 1995; Clauw et al., 1997; Giesecke et al., 2004, 2005; Ness et al., 2005; Rodrigues et al., 2005). Many of these conditions have also been shown to demonstrate more sensitivity to many stimuli other than pain (i.e., auditory, Gerster and Hadj-Djilani, 1984; Geisser et al., 2007, visual), and the aggregate data suggest that these individuals have a fundamental problem with pain or sensory amplification rather than an structural or inflammatory condition in the specific body region where the pain is being experienced (Smith et al., 2011).

Non-pharmacologic therapeutic options are extremely important in the management of this disorder, however we will briefly touch upon this aspect of treatment as pharmacologic strategies are the focus of this article. In this narrative review of the current available literature, the authors each separately performed a review using MEDLINE/PubMed, and EMBASE as sources in a non-systematic fashion and search terms (FM, pathophysiology, treatment, criteria). Abstracts were screened for relevance with additional sources identified via manual search of bibliographies and reference lists. The searches were restricted to the English language. Observational studies (e.g., cohort and case control studies) and open-label studies were excluded from the review.

Smith HS, Bracken D, Smith JM.
Front Pharmacol. 2011;2:17

Smith HS, Bracken D, Smith JM.

Pharmacotherapy for fibromyalgia

Front Pharmacol. 2011;2:17

- Non-FDA approved agents, such as amitriptyline and cyclobenzaprine, have been utilized in the "off-label" management of FM.
- There is evidence to support the short-term use of **amitriptyline 25 mg/day**, but higher doses for longer periods do not appear to be efficacious (Nishishinya et al., 2008).
- **Cyclobenzaprine**, which is structurally similar to amitriptyline, seems to be effective for the musculoskeletal component and improves sleep (Goldenberg, 1989).

Smith HS, Bracken D, Smith JM.
Pharmacotherapy for fibromyalgia
Front Pharmacol. 2011;2:17

- Agents such as **SSRIs** (Otto et al., 2008) and **opioids** appear to demonstrate little efficacy in FM.
- The three FDA approved agents, **pregabalin**, **duloxetine**, and **milnacipran**, were shown to be superior to placebo except for the following symptom-types: duloxetine for fatigue, milnacipran for sleep disturbances, and pregabalin for depressed mood (Häuser et al., 2010).

Smith HS, Bracken D, Smith JM.

Pharmacotherapy for fibromyalgia

Front Pharmacol. 2011;2:17

- Other centrally acting agents may also show benefit in FM patients with a predominant symptom-type. For example, **γ-hydroxybutyrate**, (*ossibato di sodio*) with its strong sedative qualities, may be clinically useful for FM patients with insomnia/sleep disturbance (Scharf et al., 2003; Russell et al., 2009).
- **Pramipexole**, a dopamine agonist used for Parkinson's disease, could be potentially useful for FM patients with concomitant restless leg syndrome (Bennett, 2001; Holman and Myers, 2005).

Smith HS, Bracken D, Smith JM.
Pharmacotherapy for fibromyalgia
Front Pharmacol. 2011;2:17

- **Tramadol**, which possesses some analgesic activity, may be utilized for FM patients with a significant pain component to their disease (Russell et al., 2000; Bennett, 2001; Bennett et al., 2003).
- **Tizanidine**, an alpha-2-adrenergic agonist muscle relaxant, could be potentially used for FM patients with spasticity.

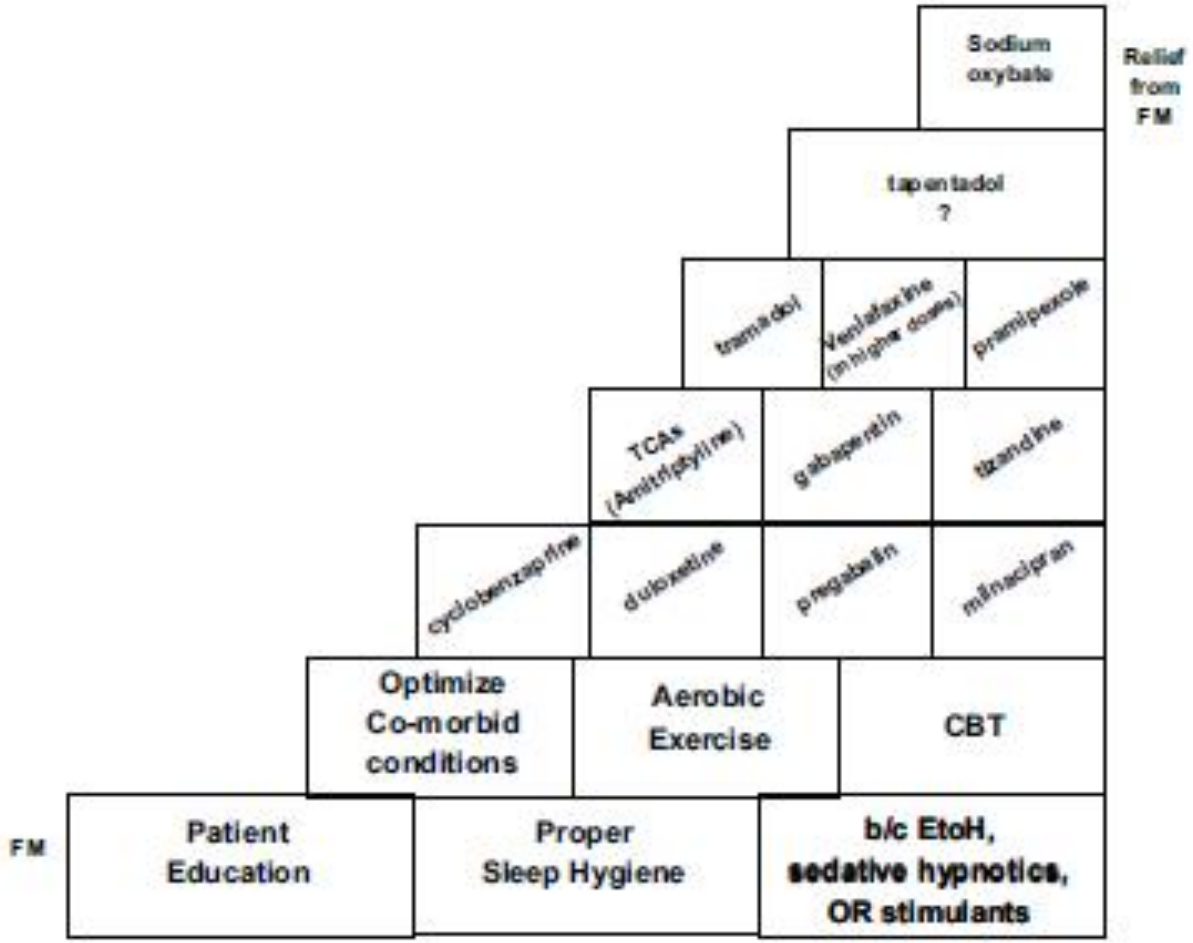
Smith HS, Bracken D, Smith JM.
Pharmacotherapy for fibromyalgia
Front Pharmacol. 2011;2:17

- Based on these observations, **choice of treatment medication should be tailored to fit individual patient needs and preferences**.

Smith HS, Bracken D, Smith JM.

Pharmacotherapy for fibromyalgia

Front Pharmacol. 2011;2:17



Princìpi di trattamento farmacologico

- Un approccio ad un trattamento completo ritagliato sulle esigenze del singolo paziente è indispensabile.
- Preavvisare il paziente sugli eventuali effetti indesiderati e rassicurarlo a tal proposito, evitando principi la cui maneggevolezza è limitata.
- Al paziente deve essere specificato un tempo ed un obiettivo di trattamento.

Wolfe, 1996 The Vancouver Fibromyalgia Consensus Group

Taglio pratico - Generalità

- Attenti alla diagnosi differenziale!
- Il controllo del paziente deve essere frequente (tight control 4 vv/anno) e finalizzato al raggiungimento progressivo di singoli obiettivi.
- **Primo obiettivo è la riduzione del dolore!**
- Il secondo obiettivo è il raggiungimento di una **qualità di vita giudicata dal paziente soddisfacente**, e confacente all'età!!

Taglio pratico - Obiettivi

Giovane

- 1 Dolore; 2 Qualità di vita

Maturo

- 1 Dolore; 2 Reinserimento sociale

Anziano

- 1 Dolore; 2 Recupero disabilità

Taglio pratico – Primo step dolore

- Ciclobenzaprina+eserc.aerobico
- Tramadolo+SNRI+CTB
- Pregabalin+SSRI+Balneoterapia

Taglio pratico – Indicatori

Dolore

- VAS; numero e score dei Tender-points

Qualità di vita

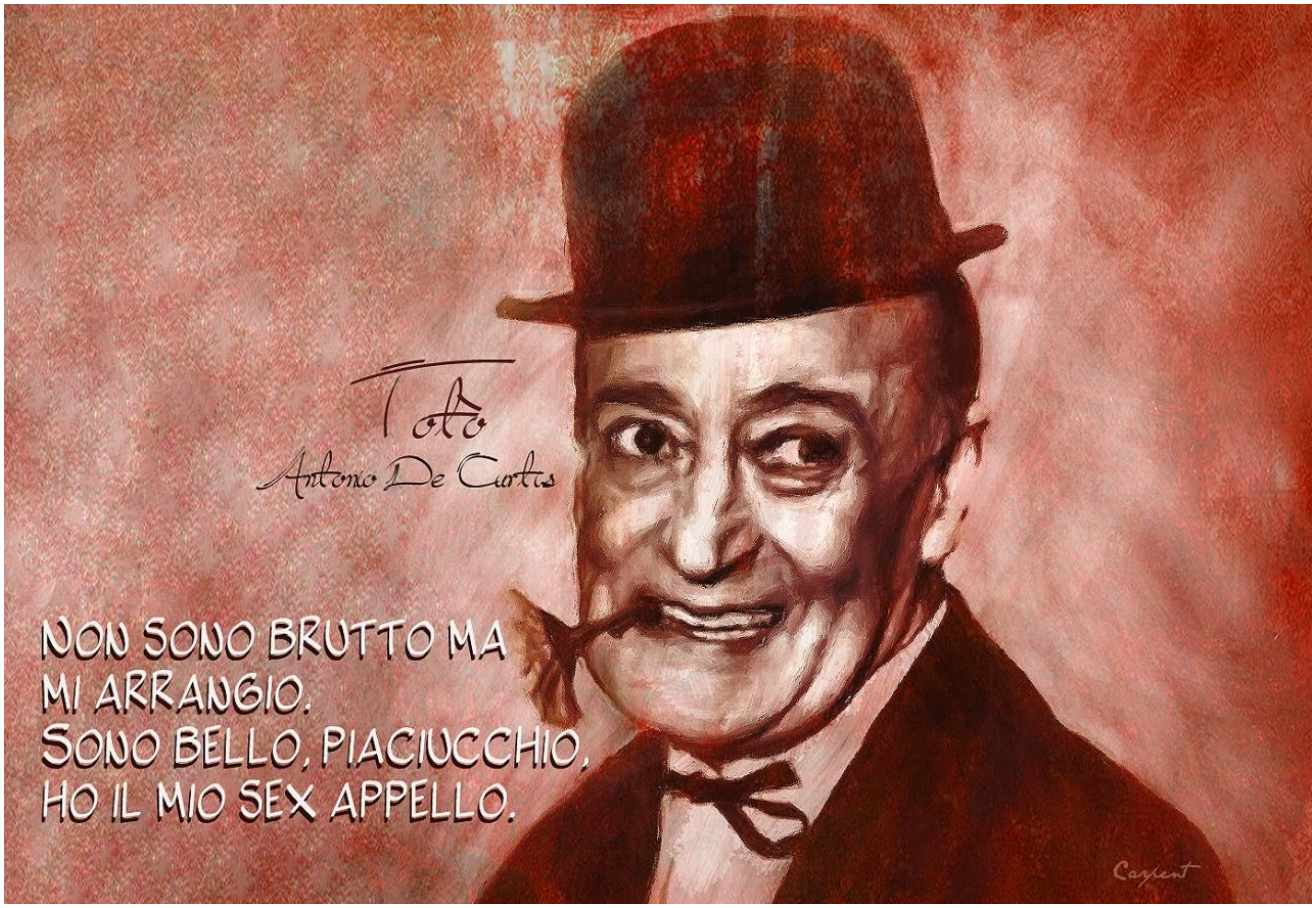
- rFIQ (Bennett, 2009)

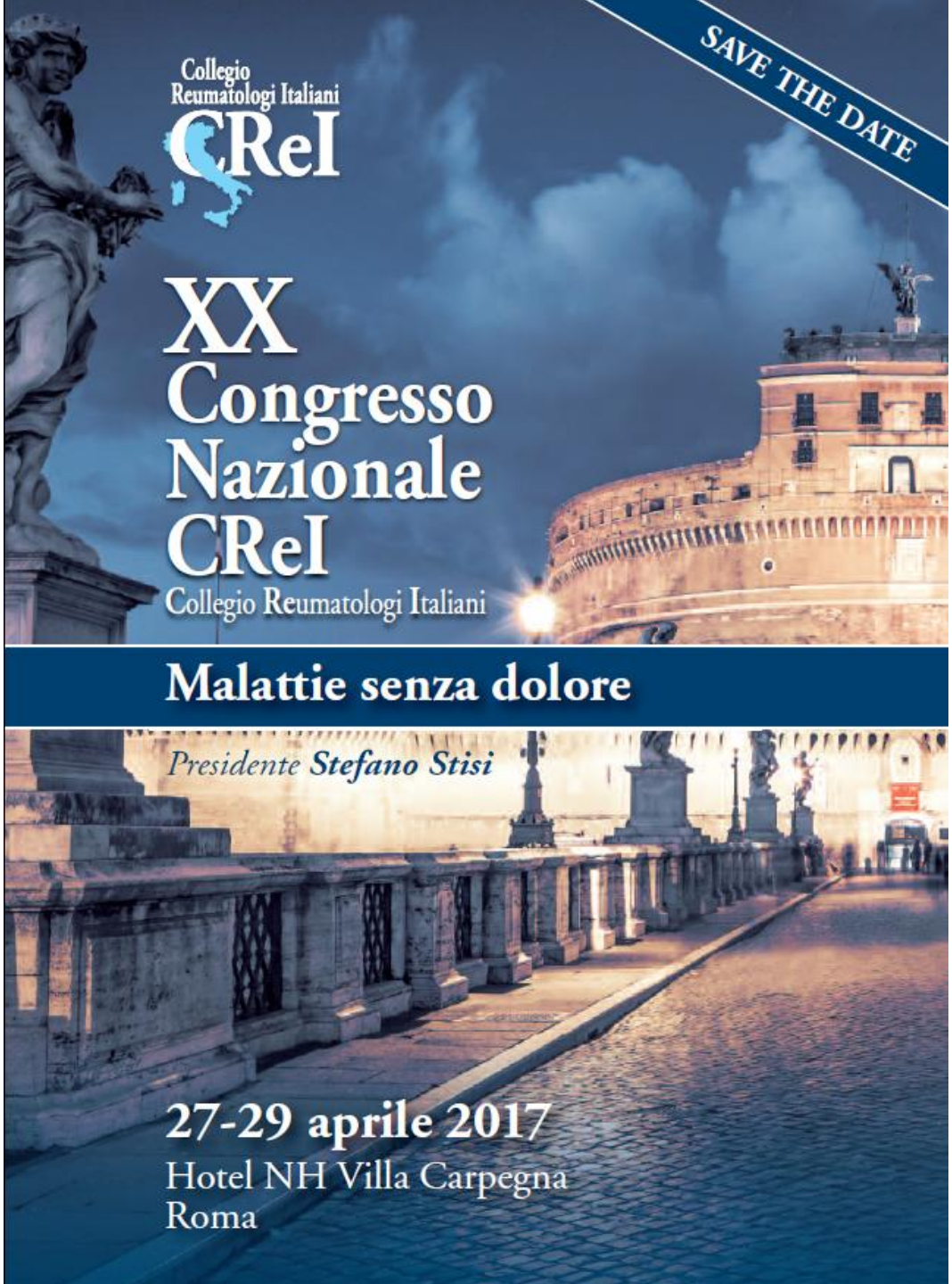
Disabilità

- SF-36

- **Un cuore felice è come una medicina.**

Proverbi 17; 22




Collegio
Reumatologi Italiani
CReI
SAVE THE DATE
XX
Congresso
Nazionale
CReI
Collegio Reumatologi Italiani
Malattie senza dolore
Presidente Stefano Stisi
27-29 aprile 2017
Hotel NH Villa Carpegna
Roma