Utilizzo delle varie classi di farmaci nella terapia del dolore, dal miorilassante all'analgesico

Filomena Puntillo

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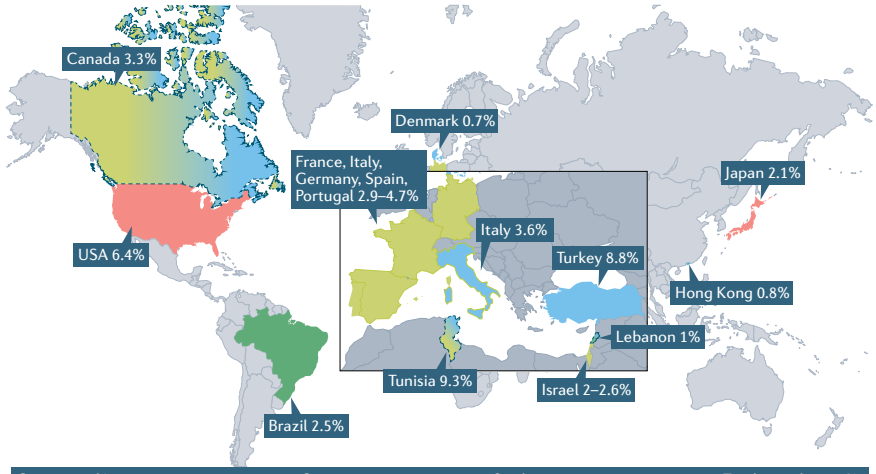
Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment

Piercarlo Sarzi-Puttini[1] ✉, *Valeria Giorgi*[1], *Daniela Marotto*[2] *and Fabiola Atzeni*[3]

Fibromyalgia or fibromyalgia syndrome is one of the most common causes of chronic widespread pain

Prevalence



Criteria and/or questionnaire	Country or region	Study	Total prevalence (%)
1990 ACR	Hong Kong	Scudds et al. (2006)[13]	0.8
	Denmark	Prescott et al. (1993)[15]	0.7
	Italy	Salaffi et al. (2005)[16]	3.6
	Turkey	Turhanoglu et al. (2008)[8]	8.8
The 2010 ACR criteria	Japan	Nakamura et al. (2014)[7]	2.1
	USA	Vincent et al. (2013)[12]	6.4
LFESSQ	Israel	Ablin et al. (2012)[14]	LFESSQ-4: 2.6 LFESSQ-6: 2.0
	France, Italy, Germany, Spain and Portugal	Branco et al. (2009)[5]	LFESSQ-4: 4.7 LFESSQ-6: 2.9
COPCORD	Brazil	Rodrigues Senna et al. (2004)[10]	2.5
LFESSQ and the 1990 ACR criteria	Canada	White et al. (1999)[11]	3.3
	Tunisia*	Guermazi et al. (2008)[9]	9.3
COPCORD and the 1990 ACR criteria	Lebanon	Chaaya et al. (2011)[6]	1
	World	Queiroz (2013)[1]	2.7

FIbromialgia

Fibromyalgia is the **third** most common musculoskeletal condition in terms of prevalence, after lumbar pain and osteoarthritis

Prevalence is proportional to the age of the population, peaking at **50–60** years old

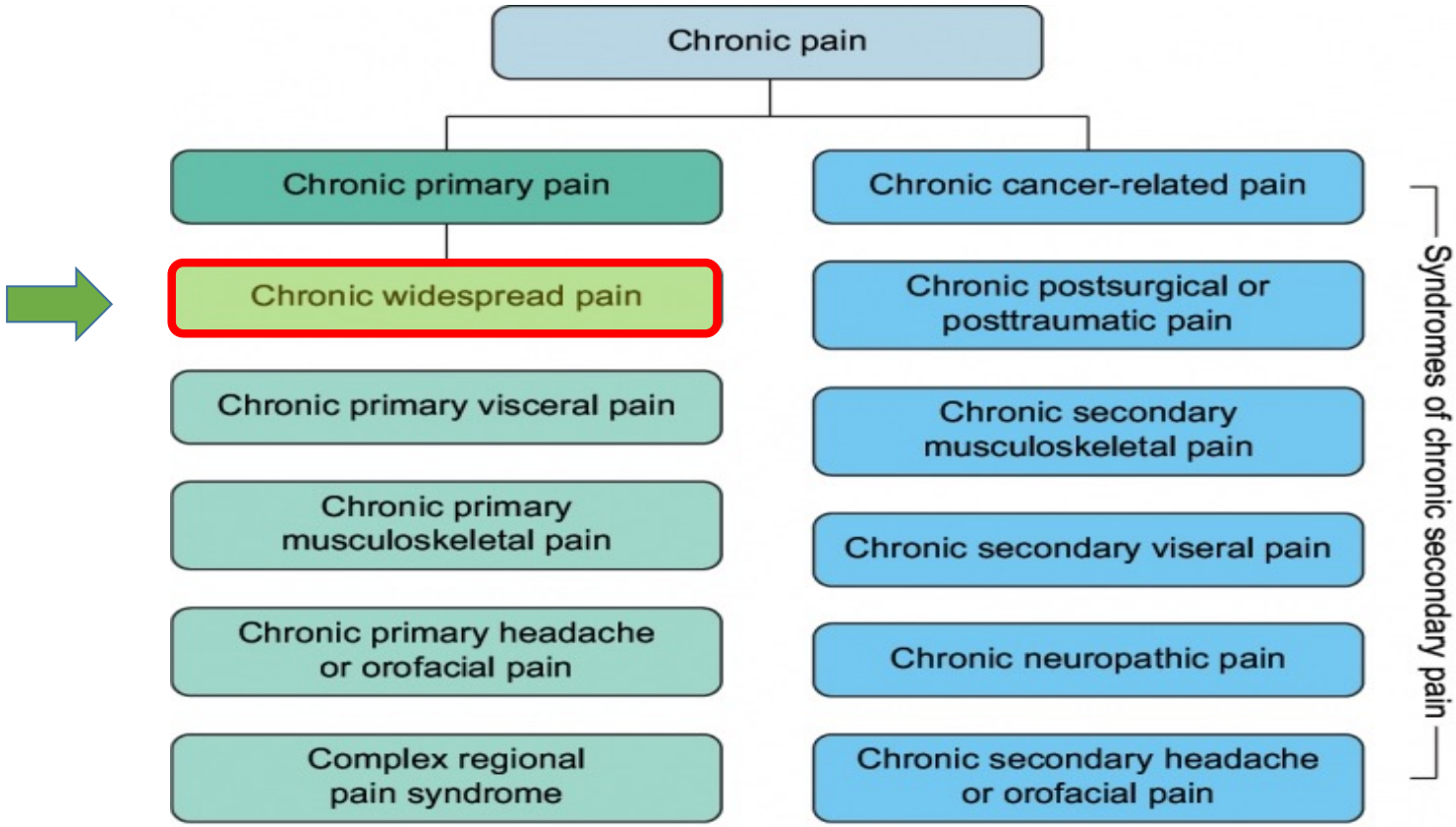


Figure 1. Chronic pain in the ICD-11. 1

Primario
ad eziologia non nota
a patogenesi non nota

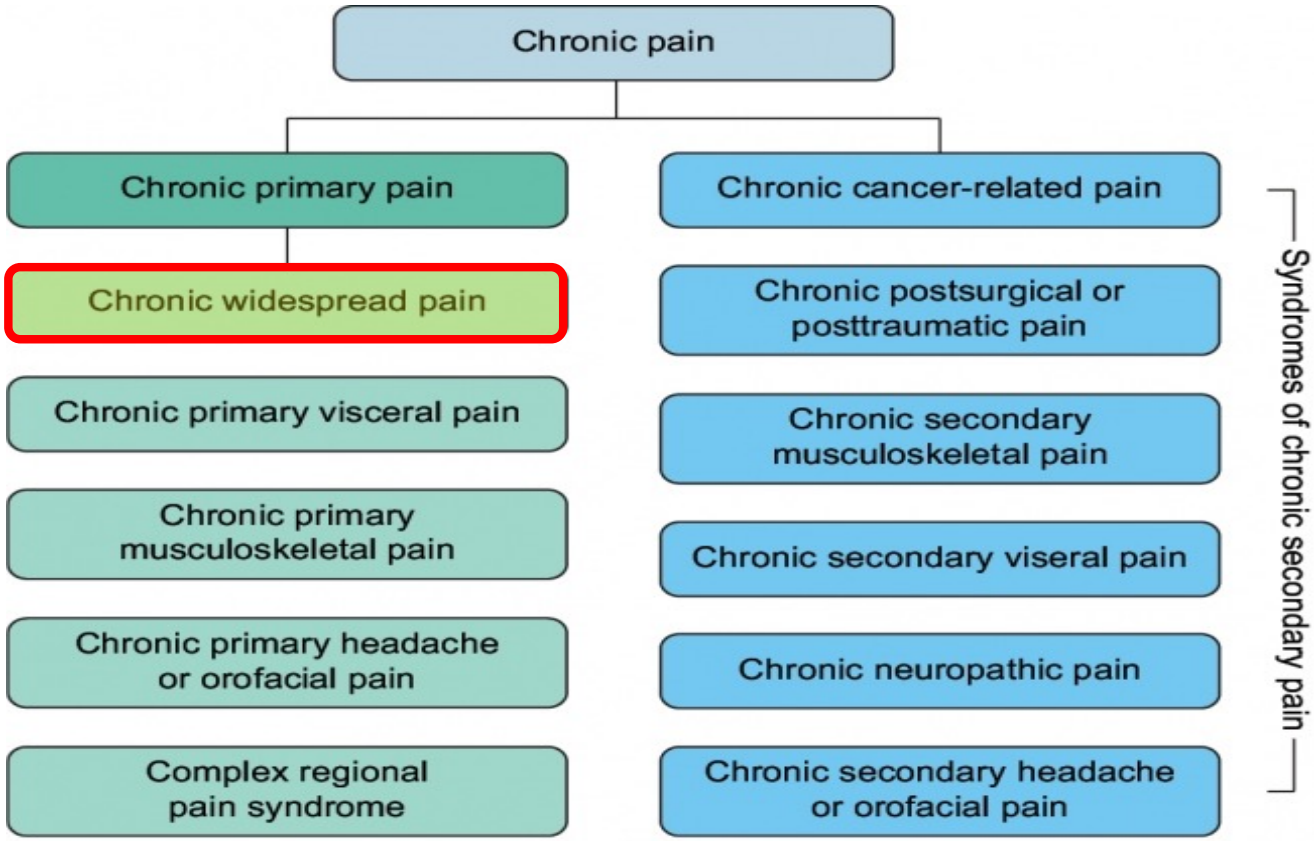


Figure 1. Chronic pain in the ICD-11. 1

Secondario
ad eziologia nota
a patogenesi nota

Primario
ad eziologia non nota
a patogenesi non nota

Secondario
ad eziologia nota
a patogenesi nota

Nociplastico

Nocicettiva

Infiammatoria

Neuropatica

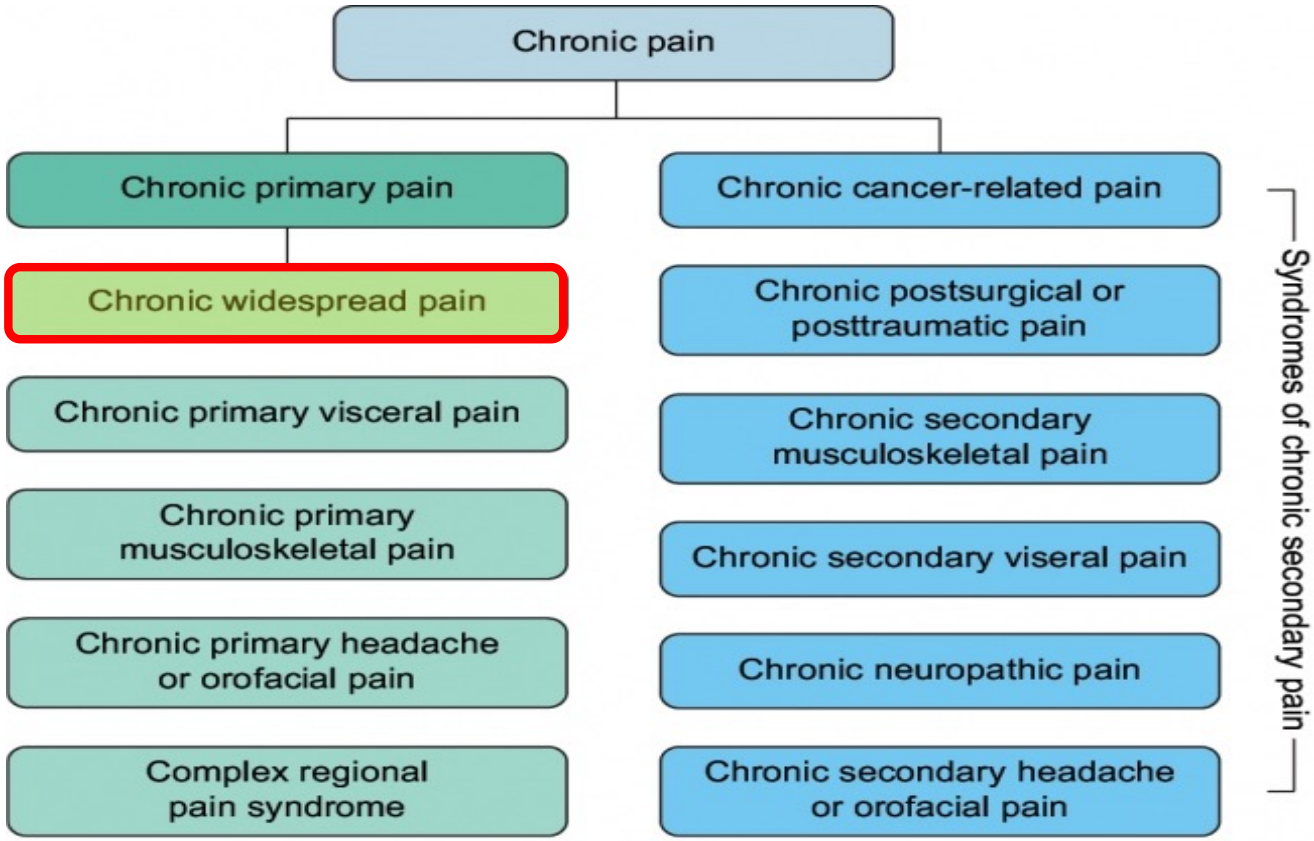


Figure 1. Chronic pain in the ICD-11.1

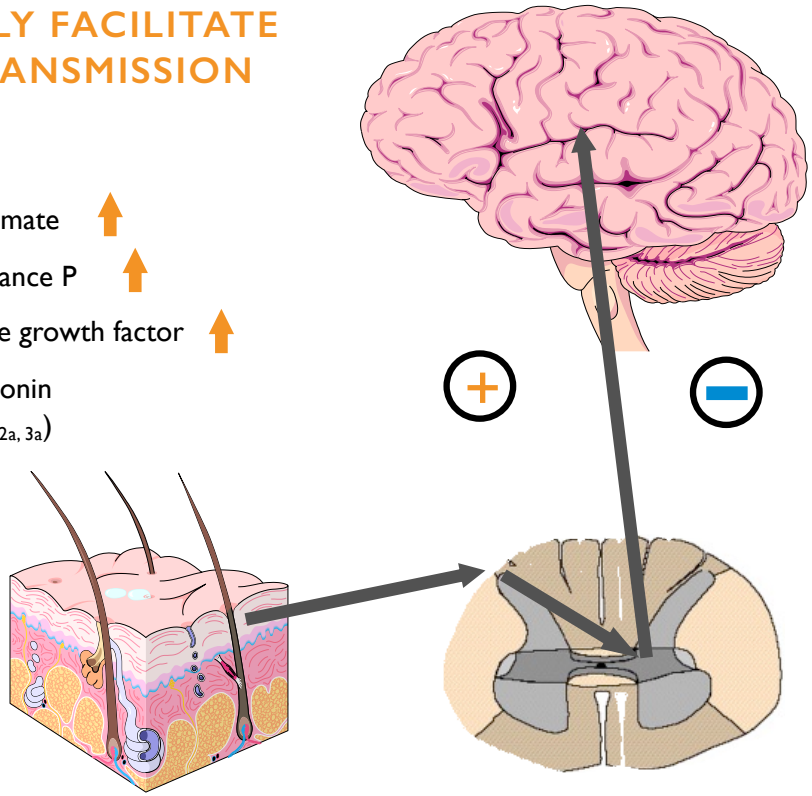
Nociplastic pain

Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain

squilibrio tra il sistema nocicettivo ed anti-nocicettivo

GENERALLY FACILITATE PAIN TRANSMISSION

- Glutamate ↑
- Substance P ↑
- Nerve growth factor ↑
- Serotonin ($5HT_{2a, 3a}$)



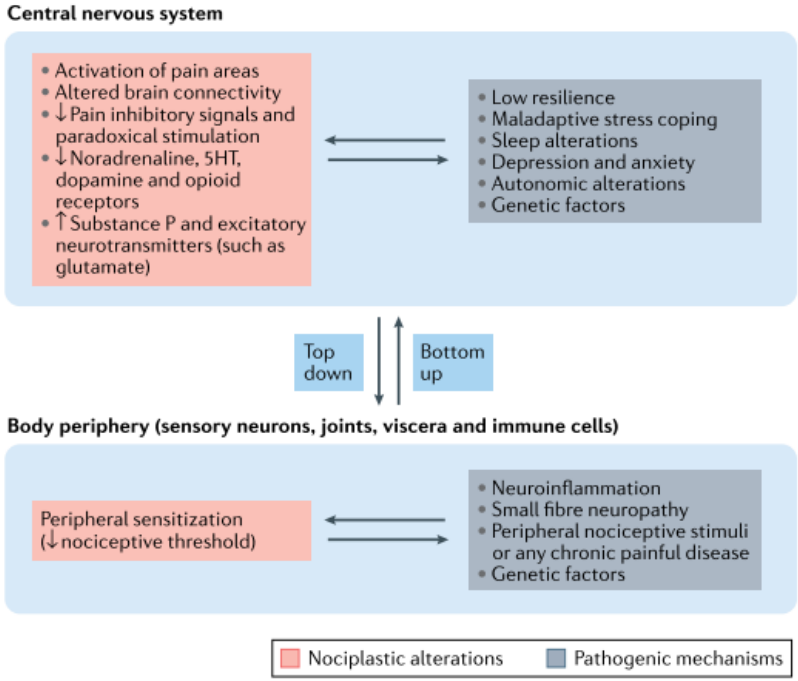
GENERALLY INHIBIT PAIN TRANSMISSION

- **Descending anti-nociceptive pathways**
  - ↓ Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
  - ↓ Opioids receptors
  - Cannabanoid
  - ↓ GABA

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

EZIOPATOGENESI DELLA FIBROMIALGIA: IN SUMMARY

interplay between potential pathogenic mechanisms and nociplastic alterations in fibromyalgia.



Sarzi-puttini P, Giorgi V, Marotto D, Atzeni F. Nat Rev Rheumatol. 2020; 16:645–660.

Peripheral (nociceptive)

- Inflammation or mechanical damage in all tissues
- NSAID, opioid responsive
- Responds to procedures

Classic examples

- Osteoarthritis
- Rheumatoid arthritis
- Cancer pain

Peripheral and central Neuropathic

- Damage of peripheral nerves and/or CNS
- Responds to both peripheral (anesthetics, opioids, Na channel blockers) and centrally acting pharmacological therapies

Classical examples

- Diabetic neuropathic pain
- Post-herpetic neuralgia
- Stroke pain

Nociplastic

- Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)
- Responsive to neuroactive compound altering level of neurotransmitters involved in pan transmission

Classic examples

- Fibromyalgia
- Irritable bowel syndrome
- Tension headache
- Idiopathic low back pain

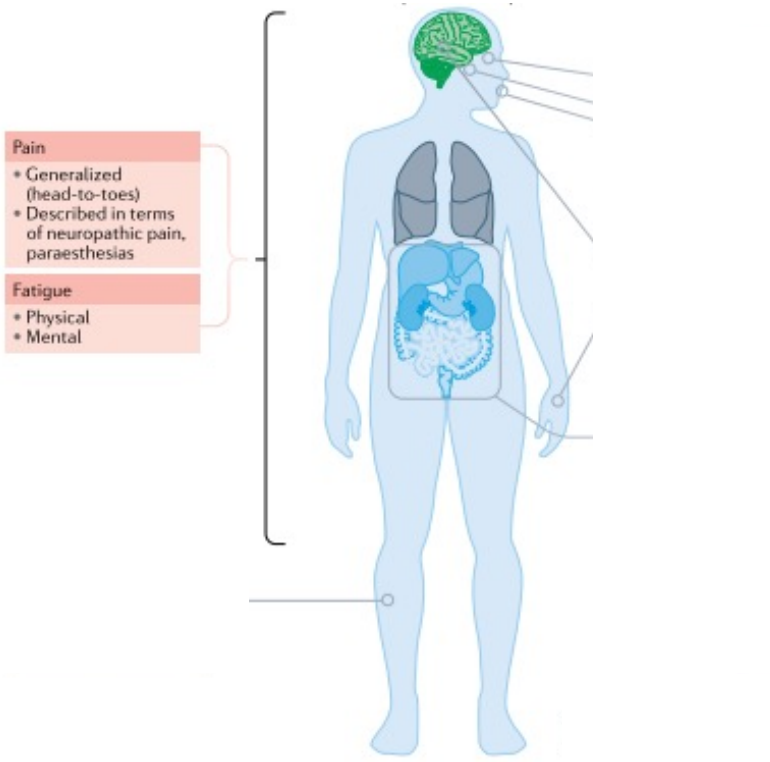
Modified from Clauw, Best Prac Res Clin Rheum 2011

SINTOMI

20–30% of patients report **paraesthesia** in the limbs, hands or trunk, which is commonly described as a tingling sensation or pins-and-needles.

The type, location and severity of pain depends on a number of modulating factors, the most important of which are working activities, comorbidities (such as obesity) and variations in temperature.

Physical or mental stress is also a known factor associated with worsening pain



Sarzi-puttini P, Giorgi V, Marotto D, Atzeni F. Nat Rev *Rheumatol*. 2020;16:645–660.

Features of FM

Clinically, fibromyalgia has many of the features of central sensitization (also known as central hyperactivation) : hyperalgesia, allodynia , temporal summation and hypersensitivity to various external stimuli such as sounds or lights

Preliminary identification of key clinical domains for outcome evaluation in fibromyalgia using Delphi methods: the Italian experience

F. Salaffi[1], A. Ciapetti[1], P. Sarzi Puttini[2], F. Atzeni[2], C. Iannuccelli[3], M. Di Franco[3], M. Cazzola[4], L. Bazzichi[5]

Reumatismo, 2012; 64 (1): 28-35

DOMINI CLASSIFICATI PER RILEVANZA DAI PAZIENTI

Dominio	Items	Frequency	Mean importance (MI)	Frequency importance product (FIP)
1. Dolore	Dolore o disagio fisico; articolazioni dolenti; dolorabilità alla palpazione	97.3	2.9	282.2
2. Fatica	Stanchezza; scarsa energia	93.6	2.7	252.7
3. Qualità del sonno	Difficoltà ad addormentarsi; insonnia; risvegli frequenti	90.1	2.6	234.3
4. Funzione multidimensionale	Difficoltà nei movimenti, nel camminare o svolgere esercizi; difficoltà nello svolgere normali attività, compromissione dell'attività lavorativa, scolastica ed impatto nella vita quotidiana	89,8	2.6	233,5
5. Depressione	Sentirsi tristi, demotivati, pessimisti, isolati, svogliati	81.5	2.4	195.6
6. Sensibilità a stimoli esterni	Sensibilità a suoni, luci, odori e/o al freddo	78.3	2.4	187.9
7. Ansia	Sentirsi frustrati; essere preoccupati; avere paura	76.1	2.3	175.0
8. Disturbi cognitivi	Difficoltà nel ricordare o pensare; perdita di memoria; difficoltà nel concentrarsi	74.7	2.1	156.9

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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 20, No 6 (June), 2019: pp 611–628
Available online at www.jpain.org and www.sciencedirect.com

Critical Reviews

AAPT Diagnostic Criteria for Fibromyalgia

Lesley M. Arnold,* Robert M. Bennett,† Leslie J. Crofford,‡ Linda E. Dean,§ Daniel J. Clauw,¶ Don L. Goldenberg,‖ Mary-Ann Fitzcharles,** Eduardo S. Paiva,†† Roland Staud,‡‡ Piercarlo Sarzi-Puttini,§§ Dan Buskila,¶¶ and Gary J. Macfarlane§

ACTTION-APS Pain Taxonomy (AAPT)

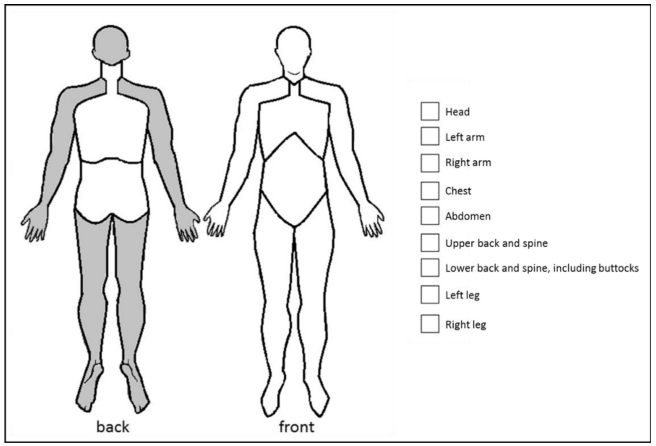


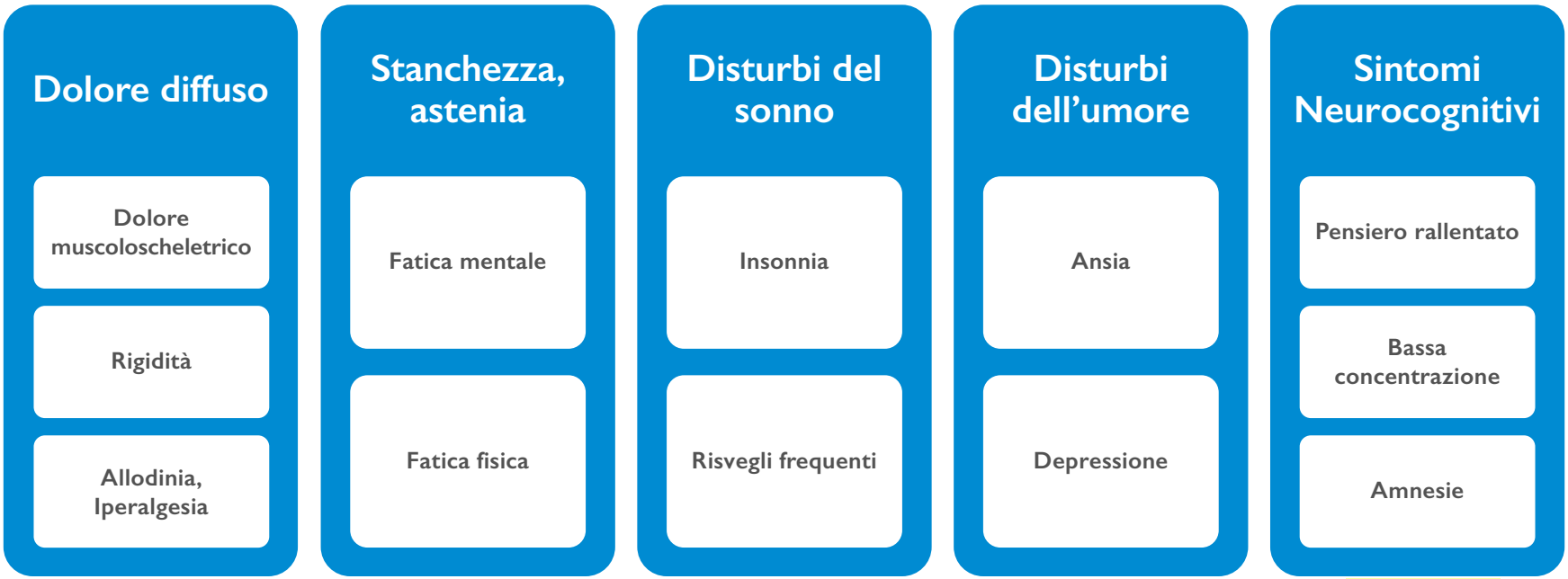
Figure 1. Number of painful body sites.
Patients are asked to check the areas in which they experience pain on the 2-view manikins (ignoring the pre-shaded areas). Alternatively, patients may use the checklist of body sites.
The number of separate sites are summed from a maximum of 9 body sites.

Table 1. AAPT Diagnostic Criteria for Fibromyalgia

Dimension 1: Core Diagnostic Criteria

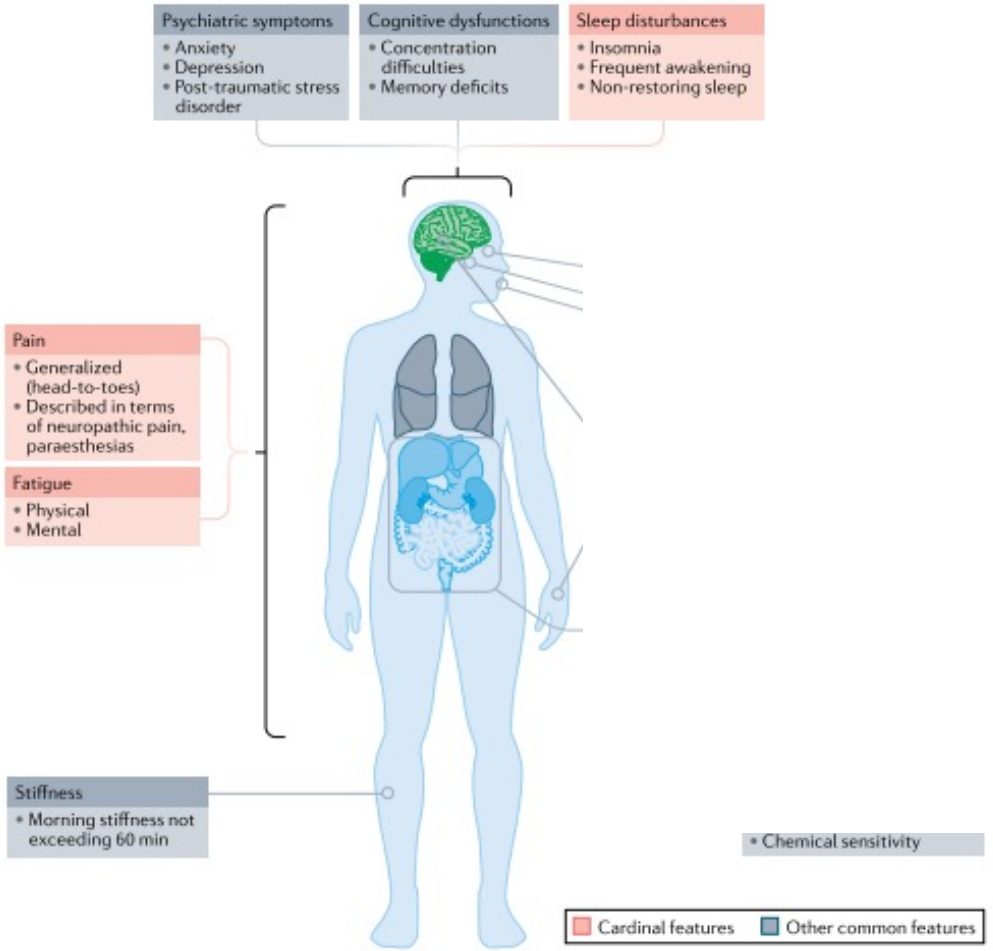
1. MSP defined as 6 or more pain sites from a total of 9 possible sites (see Fig 1)
2. Moderate to severe sleep problems OR fatigue
3. MSP plus fatigue or sleep problems must have been present for at least 3 months

SINTOMI



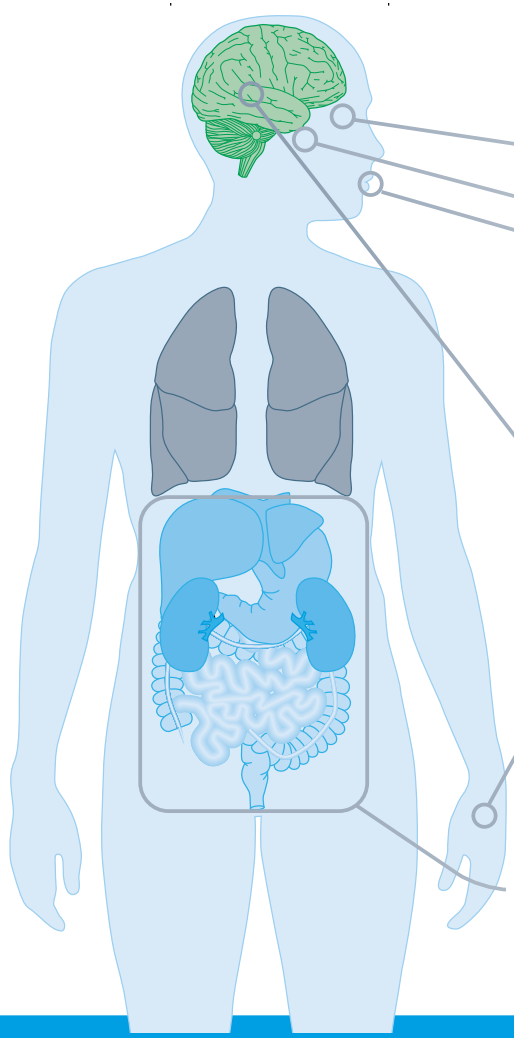
fibro-fog

SINTOMI



Sarzi-puttini P, Giorgi V, Marotto D, Atzeni F. Nat Rev *Rheumatol*. 2020; 16:645–660.

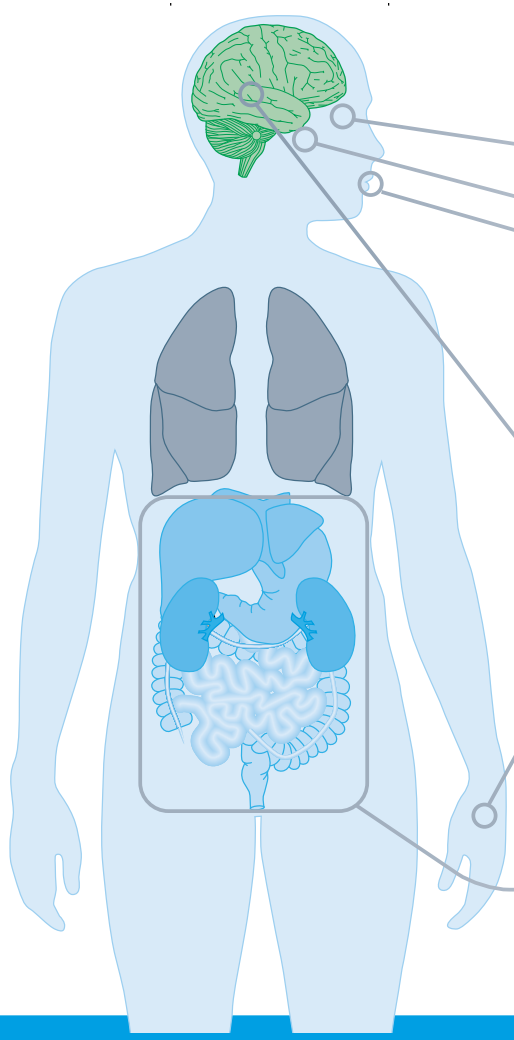
Musculoskeletal stiffness is experienced, in varying degrees, by all FM patients Interestingly, stiffness in FM patients is difficult to distinguish from the stiffness in conditions such as rheumatoid arthritis, polymyalgia rheumatica, and ankylosing spondylitis. FM-related stiffness, like that described in these other conditions, is typically more severe in the early morning and improves as the day goes on. However, unlike these other conditions, it is not responsive to corticosteroids.



Autonomic disturbances

- Blurred vision, photophobia and xerophthalmia
- Feeling of instability
- Xerostomia
- Variations in responses to cold at the extremities (including Raynaud phenomenon)
- Orthostatic hypotension

Impattare sulla terapia farmacologica



Autonomic disturbances

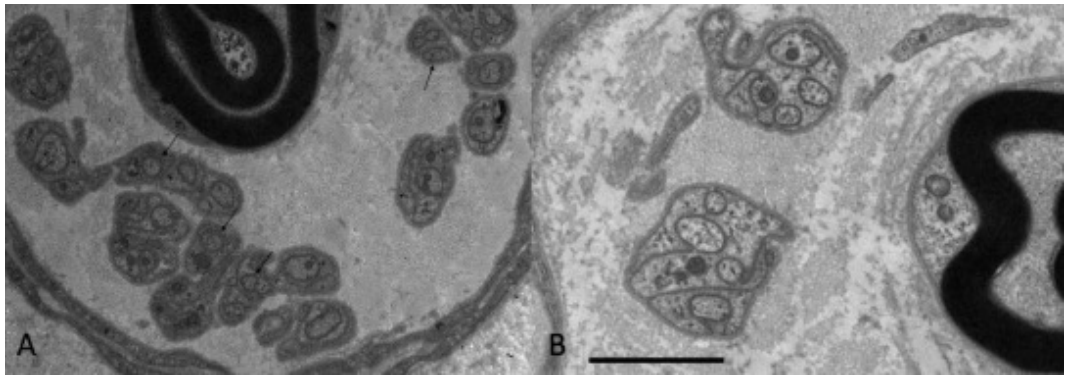
- Blurred vision, photophobia and xerophthalmia
- Feeling of instability
- Xerostomia
- Variations in responses to cold at the extremities (including Raynaud phenomenon)
- Orthostatic hypotension

Regional pain syndromes

- Migraine or headache
- Stomach ache or dyspepsia
- Abdominal pain or irritable bowel syndrome
- Dysmenorrhoea
- Vulvodynia
- Dysuria

Neuropatia delle piccole fibre

- Disestesie (formicolii, bruciore…)
- Sintomi autonomici



- A 2019 meta-analysis estimates a high prevalence of SFP, with 49% of people with fibromyalgia having a structural abnormality of the small nerve fibers
  - Significant variability for overall pooled data
  - Small sample sizes

Doppler, K., et al. (2015). Pain 156, 2319–2325.
Grayston R, et al. Semin Arthritis Rheum. 2019;48(5):933-940.
Farhad K. Curr Neurol Neurosci Rep. 2019;19(12):103.

Assessment and treatment

The assessment of fibromyalgia should be holistic and not only consider all of the symptoms experienced by patients but also alleviating or aggravating factors and the effect of fibromyalgia on everyday life, functional status and working ability.

PAIN® 150 (2010) 250–256

PAIN®

www.elsevier.com/locate/pain

Development and validation of the Fibromyalgia Rapid Screening Tool (FiRST)

Serge Perrot [a,b,c,*], Didier Bouhassira [a], Jacques Fermanian [c,d],
the CEDR (Cercle d'Etude de la Douleur en Rhumatologie)

No diagnosis and yreatment delay!!!

Screening tools: pts at risk

	FMS (%)	Non-FMS (%)	*p* value*
1 – Diffuse pain	84.5	53.5	0.001
2 – Continuous pain	90.5	87.5	0.77
3 – Fatigue	94.1	64.2	0.001
4 – Triggered pain	84.7	72.2	0.14
5 – Pain descriptors	92.9	33.9	0.0001
6 – Abnormal sensations	85.8	32.1	0.0001
7 – Associated somatic comorbidities	89.4	37.5	0.0001
8 – Sleep and cognition	98.8	82.1	0.01
9 – Social impact	76.4	82.1	0.07
10 – Morning stiffness	80.0	82.1	0.90

Terapia

- In generale, ci sono essenzialmente 4 pilastri del trattamento FM:

  1) Educazione del paziente

  2) attività fisica;

  3) trattamento farmacologico;

  4) psicoterapia.

Terapia

- In generale, ci sono essenzialmente 4 pilastri del trattamento FM:
  1) Educazione del paziente
  2) attività fisica;
  3) trattamento farmacologico; ➡ quando e con quali farmaci
  4) psicoterapia.

FDA approved drugs for FM

Three drugs are approved by the US Food and Drug Administration (FDA):
the gabapentinoid pregabalin (approved in 2007)
the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine (in 2008)
and milnacipran (in 2009).

Original Article

"Clinical Approach to Fibromyalgia: Synthesis of Evidence-based Recommendations, a Systematic Review"☆

Daniel Ángel García,* Ismael Martínez Nicolás, Pedro J. Saturno Hernández

Recommendations		EULAR 2008[14]		UoT 2009[15]		SHM 2011[16]		MSIC 2011[17]		AWMF 2012[3]		CPS 2012[18]	
		LOE	SOR	LOE	SOR	LOE	SOR	LOE	SOR	LOE	SOR	LOE	SOR
General	Patient education			A2[c]	A[c]	A2	B			C2	C		
	• Improve self-efficacy											A2	A
	• Online resources			A2	B								
	Multidisciplinary therapy					A1	A	A1	A	A1	A	A1	A
	Use of FIQ			A1	A								
Drug therapy	NSAID			D	I	C2	I			D	I	D	I
	Amitriptyline	A2	A	A1	A	A2	A	A1	A	A2	A	A2[a]	A[a]
	Anticonvulsive drugs	A2	A									A2	A
	• Gabapentin			A3	B			C2	C	C2	C		
	• Pregabalin			A2	A	A1	A	A2	A	A1	A		
	Cyclobenzaprine			A1	B	A1	A	A1	A	A2	B	A3	B
	Glucocorticoids					A3	D						
	SNRI (serotonin and noradrenaline reuptake inhibitors)	A2	A									A2[a]	A[a]
	• Duloxetine			A2	A	A1	A	A1	A	A1	B		
	• Milnacipran			A2	A	A3	B[b]			A2	D		
	SSRI (selective serotonin and reuptake inhibitors)	A2	A2									A2[a]	A[a]
	• Citalopram			C2	C								
	• Fluoxetine			A2	B	C2	C	A1	C	A2	B		
	• Paroxetine			A2	B					A2	B		
	Mild opioids	B1	D	C2	C					B1	D	C2	C
	• Tramadol	A2	A			A3	B	A3	B	C2	C	C2	C
	Paracetamol					D	I			D	I		

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Drug Therapy: An Ephemeral Ally

sulla base delle evidenze scientifiche disponibili, non si rileva un trattamento efficace nella remissione completa dei sintomi caratterizzanti la fibromialgia

l'uso della terapia farmacologica dovrebbe essere riservato a situazioni specifiche, per rispondere a sintomi incontrollati o al dolore intenso e irruente.

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Summaries of Recommendations Collected From the Guidelines.

	Recommendation	LOE
Strength of recommendation A (is recommended)		
General	The approach in patients with fibromyalgia should be multimodal and multidisciplinary.[3,18]	A1
	Control of the disease using specific scoring systems such as the FIQ is adequate for controlling the disease course and adapting the treatment.[15]	A1
Drug therapy	Amitriptyline can be used over short periods of time to relieve pain and improve sleep (10–50 mg/day).[3,17]	A1
Physiotherapy	Patients with fibromyalgia should follow a program of moderate to mild aerobic exercise. They should begin gradually. It is preferable that the exercise be chosen by the patients. Supervision is recommended. The patients should not overexert themselves to avoid making the symptoms worse. This exercise should be performed at least 2–3 times a week for a duration of at least 30 min.[3,18]	A1
	• Muscle strength training is a complement to be added to exercise programs for fibromialgia.[18]	A2
	• Relaxation after performing aerobic exercise helps to improve the symptoms in patients with fibromialgia.[3]	A2
Psychology	Cognitive-behavioral therapy, even over a short period, is useful in reducing fear of pain and of activity.[3,18]	A1
	• Interventions to build up self-efficacy are indicated to help patients to control their symptoms.[18]	A2

FIQ, Fibromyalgia Impact Questionnaire;

Original Article

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FIQ, Fibromyalgia Impact Questionnaire;

Summaries of Recommendations Collected From the Guidelines.

	Recommendation	LOE
Strength of recommendation B (can be recommended)		
General	Educating patients with fibromyalgia helps them to face the disease.	
	• Education is more effective when provided in combination with other therapies.[15]	A2
	• The offer of online resources for patients with fibromyalgia can help them to control the symptoms.[15]	A2
Drug therapy	Cyclobenzaprine at very low doses can be used in patients with fibromyalgia to improve nightly sleep.[3,18]	A1
	Antiepileptic drugs can be used to control the pain in patients with fibromyalgia (principally pregabalin; there is no evidence for gabapentin).[3,18]	A2
	• Pregabalin (50–450 mg/day) can be used for short periods of time, should treatment with amitriptyline not be possible or was not effective.[3,17]	A2
	Serotonin and norepinephrine reuptake inhibitors (SNRI) are indicated for a short period of time in patients with comorbid depression or anxiety, should amitriptyline not be tolerated or not be successful.[3,18]	A2
	• Duloxetine (60 mg/day) is the preferred SNRI for patients with fibromyalgia and comorbid depression or anxiety.[3,17]	A1
	Selective serotonin reuptake inhibitors (SSRI) (fluoxetine, 20–40 mg/day; paroxetine, 20–40 mg/day) can be considered in cases of coexistence of anxiety or depression disorder.[3,18]	A2
Physiotherapy	Stretching is indicated as part of the exercise program.[3]	A2
	Balneotherapy can reduce the symptoms in patients with fibromyalgia.[3,15]	A2
	Aquatic exercise are indicated in patients with fibromyalgia.[17]	A2
	Biofeedback can be used to reduce symptoms in patients with fibromyalgia.[3,15]	A2
	Exercise training can employ kinetics or functional training (in water or on land), twice a week, in groups monitored by a physiotherapist.[3]	B1
Psychology	Hypnosis or guided imagery can be used to reduce the symptoms of fibromialgia.[3,15]	A2

Summaries of Recommendations Collected From the Guidelines.

	Recommendation	LOE
Strength of recommendation C and I (cannot be recommended because there is not enough evidence or there is contradictory evidence)		
The following therapies cannot be recommended because there is not enough evidence or there is contradictory evidence: mild opioids, gabapentin, paracetamol, NSAID, milnacipran, acupuncture, trigger point therapy, TENS, magnetic field therapy, chiropractic care, therapeutic massage, Qi Gong, reiki, Tai Chi, homeopathy, transcranial direct current stimulation, relaxation with no accompanying therapy, therapeutic writing.		
Strength of recommendation D (not to be recommended)		
Drug therapy	Glucocorticoids are not recommended for the treatment of the symptoms of fibromyalgia because no study supports their efficacy; moreover, in continued treatment, secondary effects often develop.[16]	A3

Review Article

Treatment of Fibromyalgia Syndrome: Recommendations of Recent Evidence-Based Interdisciplinary Guidelines with Special Emphasis on Complementary and Alternative Therapies

Jacob Ablin,[1] Mary-Ann Fitzcharles,[2] Dan Buskila,[3] Yoram Shir,[4] Claudia Sommer,[5] and Winfried Häuser[6,7]

Table 2: Comparison of major positive treatment recommendations of the three guidelines.

	Canada		Germany		Israel	
	Level of evidence	Strength of recommendation	Level of evidence	Strength of recommendation	Level of evidence	Strength of recommendation
Aerobic exercise	Ia	A	Ia	A	Ia	A
Amitriptyline	Ia	A	Ia	B	Ia	A
Anticonvulsants (gabapentin, pregabalin)	Ia	A	Ia	C	Ia	A
Balneotherapy	No comment		Ia	B	Ia	C
Cognitive-behavioral therapy	Ia	A	Ia	A*	Ia	A
Multicomponent therapy	Ia	A	Ia	A	Ia	A
SNRI (duloxetine, milnacipran)	Ia	A	Ia	B/C**	Ia	A
SSRI	Ia	A	Ia	C	Neither positive nor negative recommendation	
Tramadol	IIa	C	No comment***		IIa	B

- A patient-tailored and stepwise treatment approach

  All three guidelines recommended that attention should be paid to individual symptoms (e.g., pain, sleep problems, fatigue, and depression) in a patient tailored approach

- The promotion of self-management strategies.

- Unrealistic (“cure”) and passive physical treatments (e.g., massage, “magic pill”) should be discouraged

EXTENDED REPORT

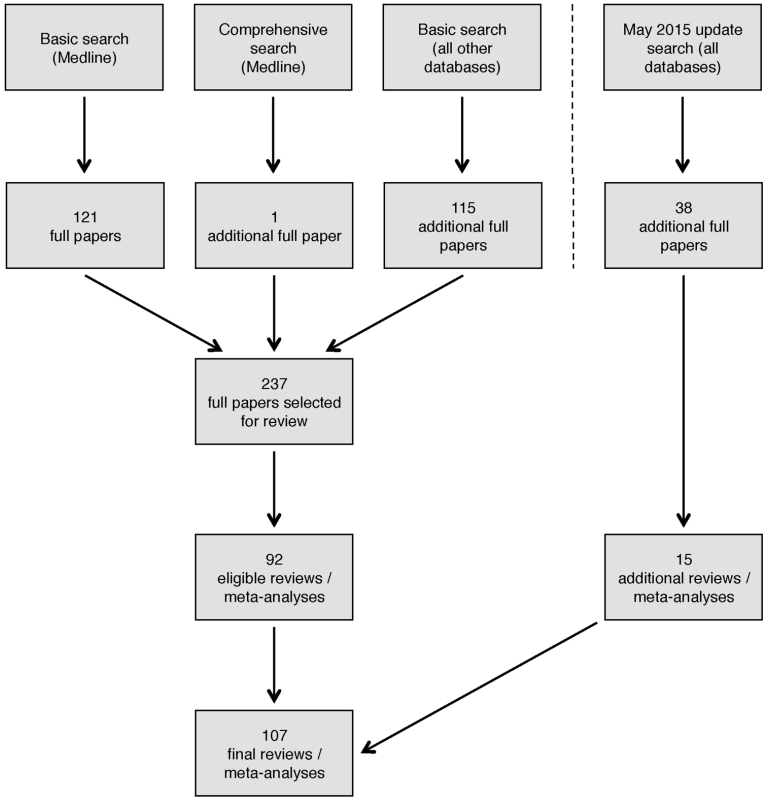
EULAR revised recommendations for the management of fibromyalgia

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

METHODS

Working group membership

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives and the allied health professions (nursing).



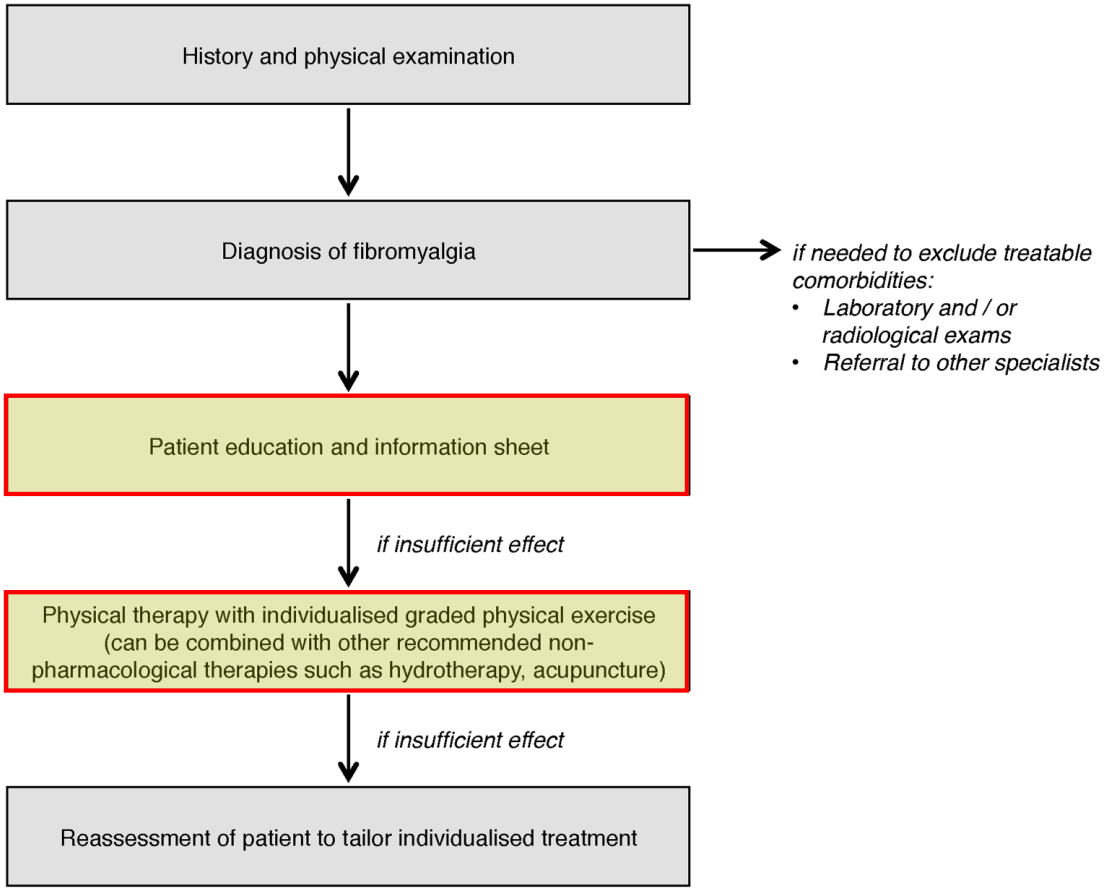
Macfarlane GJ, *et al*. *Ann Rheum Dis* 2017;**76**:318–328. doi:10.1136/annrheumdis-2016-209724

Recommendations

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

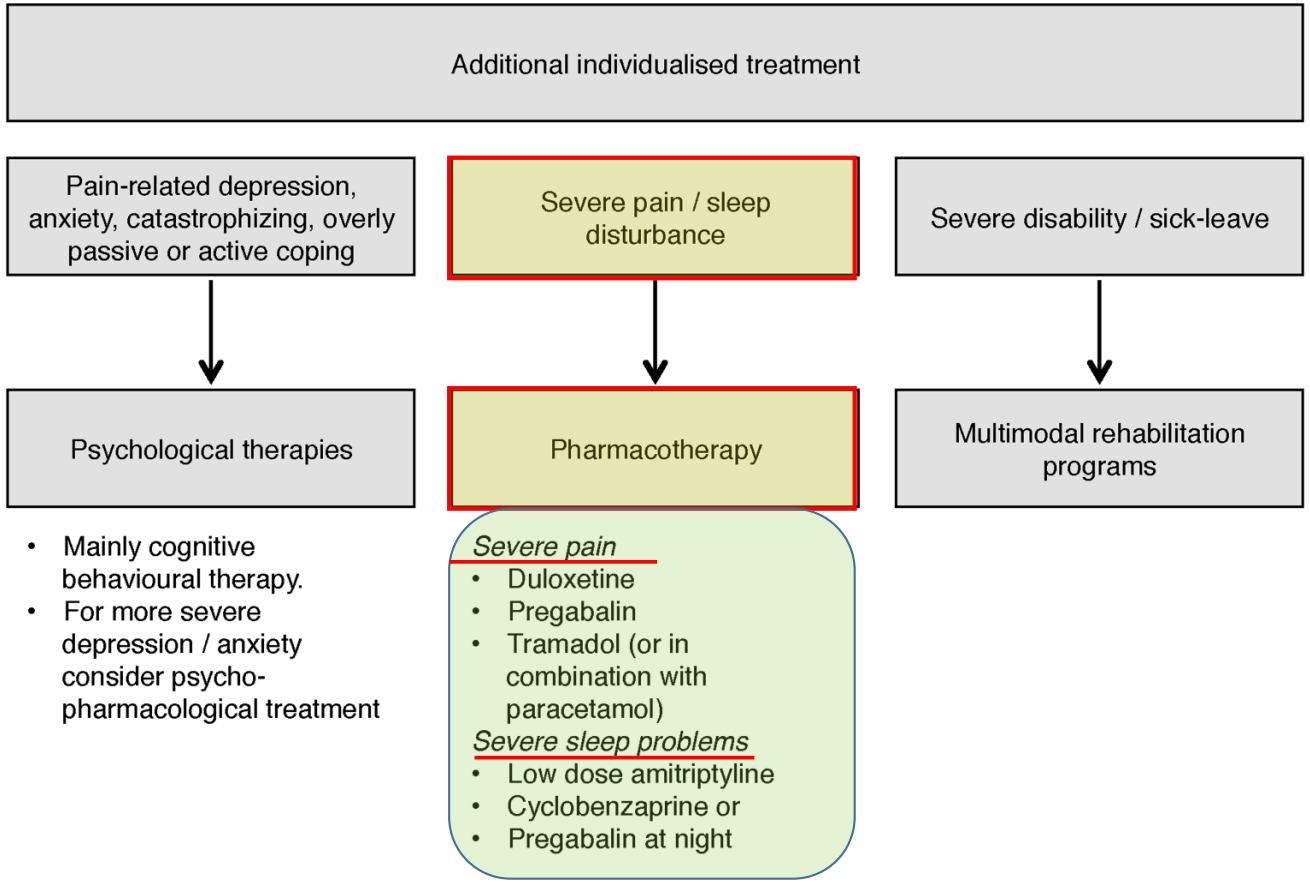
Macfarlane GJ, *et al*. *Ann Rheum Dis* 2017;**76**:318–328. doi:10.1136/annrheumdis-2016-209724

Recommendations



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

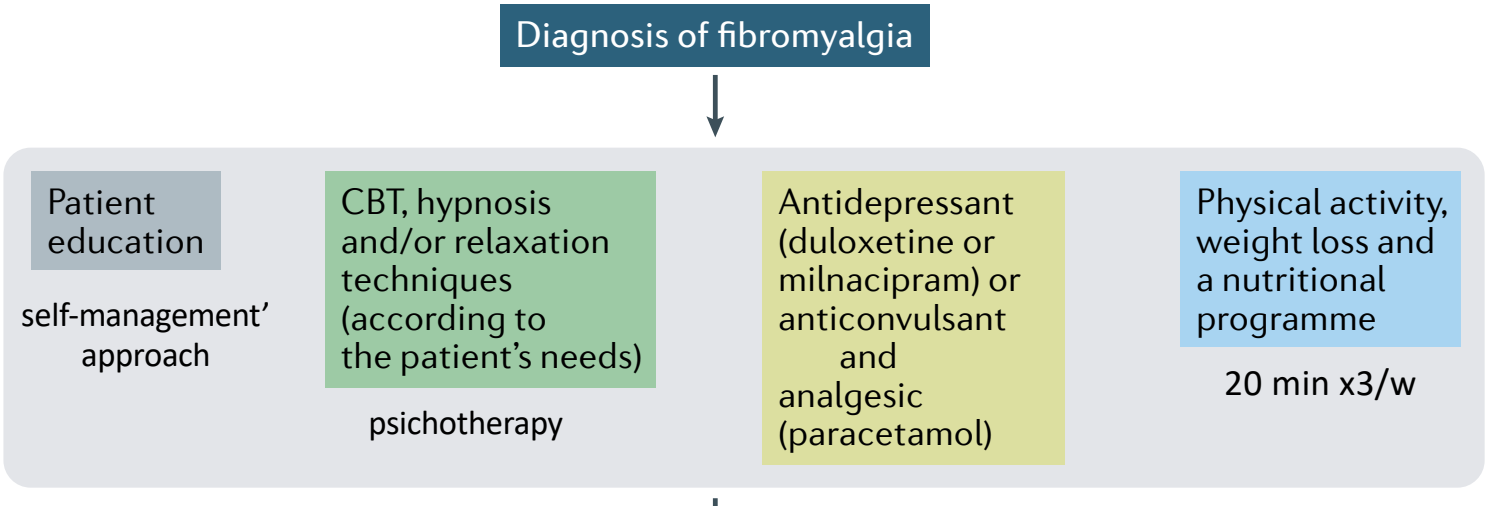
3 step



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

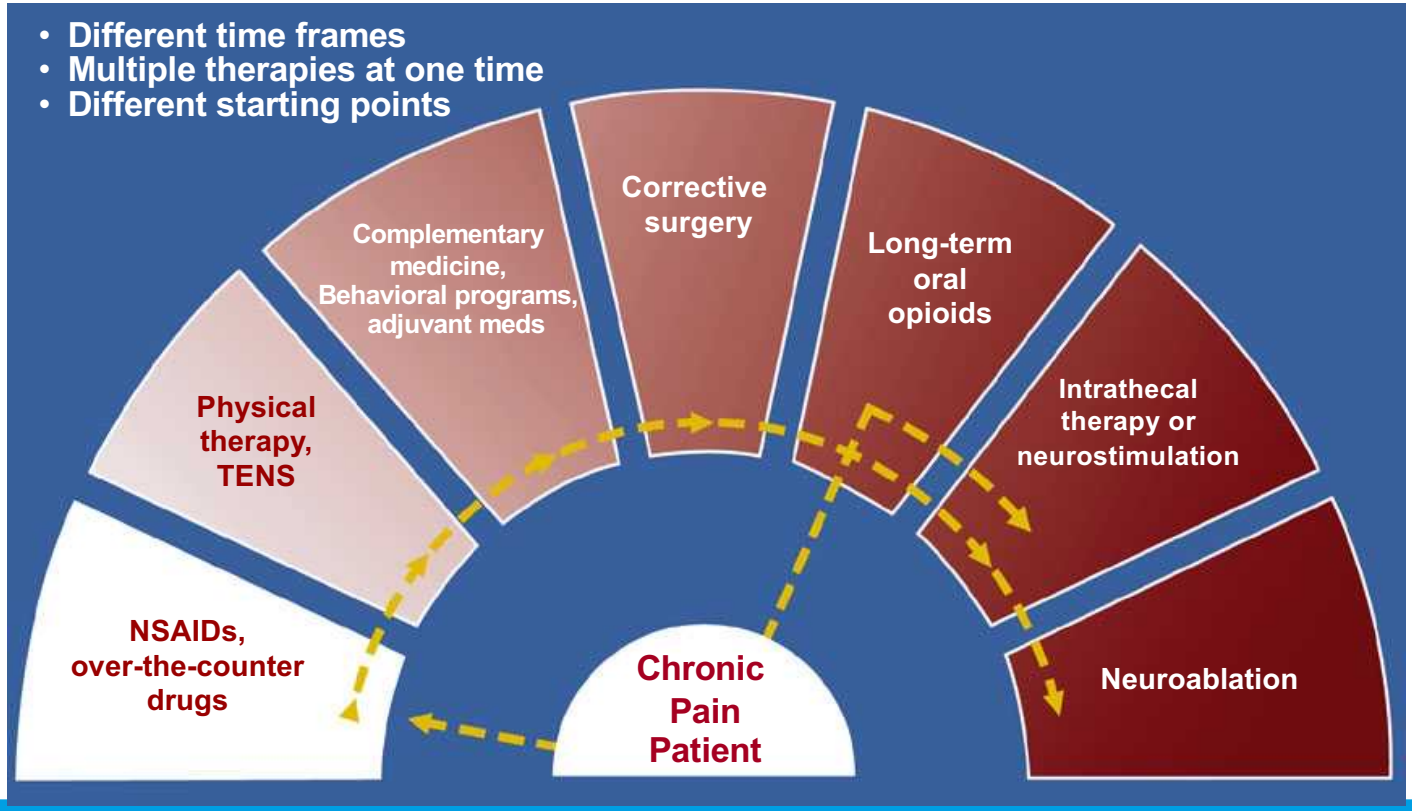
Classi di farmaci o singoli p.a.	LG EULAR 2017§	LG CRA 2012	LG SIGN 2013
paracetamolo	**Raccomandato SOLO in associaz. con tramadolo se presente dolore grave**	**1°scelta**	Non considerato
FANS / COXIB	**NO**	**1° scelta#**	NO
SSRI / SNRI	**Duloxetina** (se presente dolore grave) **NO SSRI**	**2° scelta (sia SSRI che SNRI)**	2° scelta Duloxetina Fluoxetina
antiepilettici	**Pregabalin** (se presente dolore grave o gravi alterazioni del sonno)	**2° scelta (gabapentin, pregabalin)**	1° scelta (pregabalin)
corticosteroidi sistemici	**NO**	**Non riportata alcuna racc.**	Non considerati
antidepressivi triciclici (TCA)	**Amitriptilina a basse dosi** (se presenti gravi alterazioni del sonno)	**2° scelta**	2° scelta Amitriptilina 25-125mg/die
oppioidi minori	**Tramadolo da solo o in associaz. con paracetamolo** (se presente dolore grave)	**2° scelta Tramadolo** (se dolore moderato/grave, non responsivo alle altre opzioni)	NO
oppioidi maggiori	**NO**	**NO**	NO
cannabinoidi	**NO**	**3° scelta Cannabinoidi** (se presenti importanti alterazioni del sonno)	Non considerati
miorilassanti	**Ciclobenzaprina** (se presenti gravi alterazioni del sonno)	**Non riportata alcuna racc.***	NO

4 pilastri della terapia

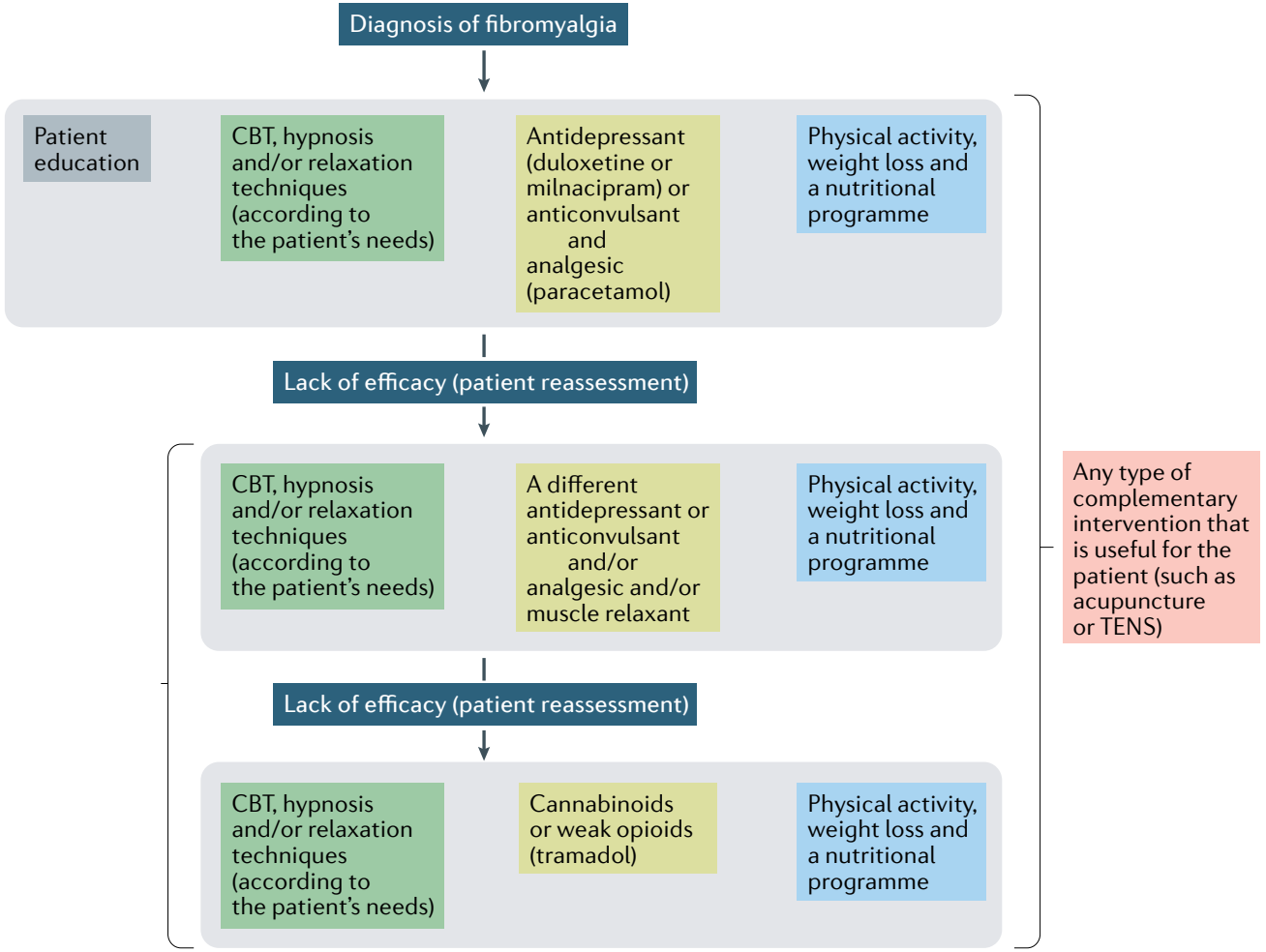


CBT: terapia cognitivo comportamentale

Ventaglio terapeutico del dolore cronico



* Prager J and Jacobs M. Evaluation of patients for implantable pain modalities: medical and behavioral assessment. Clin J Pain. 2001 Sep;17(3):206-14.


Diagnosis of fibromyalgia
Patient education
CBT, hypnosis and/or relaxation techniques (according to the patient's needs)
Antidepressant (duloxetine or milnacipram) or anticonvulsant and analgesic (paracetamol)
Physical activity, weight loss and a nutritional programme
Lack of efficacy (patient reassessment)
CBT, hypnosis and/or relaxation techniques (according to the patient's needs)
A different antidepressant or anticonvulsant and/or analgesic and/or muscle relaxant
Physical activity, weight loss and a nutritional programme
Lack of efficacy (patient reassessment)
CBT, hypnosis and/or relaxation techniques (according to the patient's needs)
Cannabinoids or weak opioids (tramadol)
Physical activity, weight loss and a nutritional programme
Any type of complementary intervention that is useful for the patient (such as acupuncture or TENS)
Patient education
Patient education and fitness
Psychotherapy
Additional options
Pharmacotherapy

Pain Research and Management
Volume 2022, Article ID 1217717, 8 pages
https://doi.org/10.1155/2022/1217717

Research Article

Analgesic Medication in Fibromyalgia Patients: A Cross-Sectional Study

H.-C. Aster,[1,2] D. Evdokimov,[1] A. Braun,[1] N. Üçeyler,[1] and C. Sommer[1]

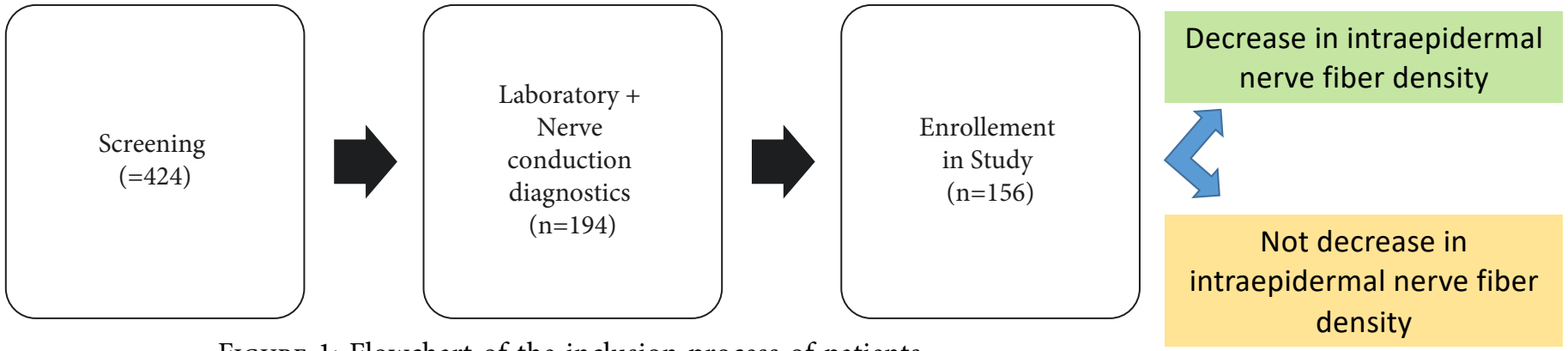


Figure 1: Flowchart of the inclusion process of patients.

One hundred and fifty-six patients (144 women, 12 men)

Medications

	Current use Number of patients currently using the drug (% patients)
NSAID	64 (41.0)
Metamizole	35 (22.4)
None	25 (16.0)
Amitriptyline	20 (12.8)
SNRI	18 (11.5)
Weak opioid	9 (5.8)
COX-2 inhibitor	8 (5.1)
Pregabalin	8 (5.1)
Muscle relaxant	7 (4.5)
Acetaminophen	6 (3.8)
Cannabinoid	4 (2.6)
Strong opioid	3 (1.9)
Guaifenesin	3 (1.9)
Triptan	3 (1.9)
Flupirtine	3 (1.9)
SSRI	3 (1.3)
Corticosteroid	1 (0.6)
Lidocaine	1 (0.6)
Magnesium	1 (0.6)
Mirtazapine	1 (0.6)

Treatment regimen for each category of medications

	On demand (%)	Fixed daily regime (%)
NSAID	97.0	3.0
Metamizole	82.4	17.6
Amitriptyline	5.3	94.7
SNRI	0.0	100.0
Weak opioid	55.6	44.4
Pregabalin	0.0	100.0
Strong opioid	14.0	86.0
COX-2 inhibitor	71.4	28.6
Muscle relaxant	28.6	71.4
Acetaminophen	100.0	0.0
Cannabinoid	25.0	75.0
Guaifenesin	0.0	100.0
Triptans	100.0	0.0
Flupirtine	100.0	0.0
SSRI	0.0	100.0
Corticosteroid	100.0	0.0
Lidocaine	0.0	100.0
Magnesium	0.0	100.0
All	60.3	39.4

Table 3: Effect of the medication on pain relief.

	Percentage of patient replies indicating pain reduction by x points on the NRS with a given drug (retrospective evaluation).									N
	0	1	2	3	4	5	6	8	Pain reduction in NRS (median, range)	
NSAID	6.2	18.5	38.5	16.9	16.9	3.1	0.0	0.0	2.3 (2, 0–5)	64
Metamizole	12.1	15.2	51.5	15.2	0.0	3.0	0.0	3.0	2.0 (2, 0–8)	33
Amitriptyline	45.0	15.0	15.0	20.0	5.0	0.0	0.0	0.0	1.3 (1, 0–4)	20
SNRI	38.9	33.3	16.7	11.1	0.0	0.0	0.0	0.0	1.0 (1, 0–3)	18
Drugs taken by < 15 patients										
Weak opioid	0.0	22.2	44.4	0.0	22.4	11.0	0.0	0.0	2.6 (2, 1–5)	9
Pregabalin	12.5	0.0	50.0	37.5	0.0	0.0	0.0	0.0	2.1 (2, 0–3)	8
Strong opioid	0.0	14.3	0.0	71.4	0.0	14.3	0.0	0.0	3.0 (3, 1–5)	7
COX-2 inhibitor	0.0	14.3	28.6	42.9	14.3	0.0	0.0	0.0	2.6 (3, 1–4)	7
Muscle relaxant	33.3	16.7	33.3	0.0	16.7	0.0	0.0	0.0	1.5 (2, 0–4)	6
Acetaminophen	16.7	16.7	33.3	16.7	16.7	0.0	0.0	0.0	2.0 (2, 0–4)	6
Cannabinoid	0.0	0.0	25.0	25.0	25.0	0.0	25.0	0.0	3.7 (4, 2–6)	4
Guaifenesin	33.3	0.0	0.0	0.0	33.3	0.0	33.3	0.0	3.3 (4, 0–6)	3
Flupirtine	0.0	33.3	33.3	0.0	33.3	0.0	0.0	0.0	2.3 (2, 1–4)	3
SSRI	0.0	50.0	0.0	50.0	0.0	0.0	0.0	0.0	2.0 (2, 1–3)	2
Triptans[1]	0.0	0.0	0.0	50.0	50.0	0.0	0.0	0.0	3.5 (3.5, 3-4)	2
Corticosteroid	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	4.0 (4)	1
Lidocaine	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	4.0 (4)	1
All									2.1 (2, 0–8)	195

N, the number of patients' replies when asked about a given drug. [1]Used in migraine attacks.

Table 4: Effect of the medication categories (current treatment) on pain relief in NRS-points, in the subgroups with and without reduction of skin innervation.

	Reduced IENFD		Normal IENFD			All	
	N	Response (median, range)	*N*	Response (median, range)	*P*	*N*	Response (median, range)
NSAID	16	2, 0–5	21	2, 0–4	0.33	65	2, 0–5
Metamizole	9	2, 0–3	5	2, 1–3	0.36	33	2, 0–8
Amitriptyline	5	0, 0–2	6	1, 0–4	0.24	20	1, 0–4
SNRI	8	1, 0–2	3	0, 0	0.13	18	1, 0–3

N, the number of patients replies when asked about a given drug; IENFD, normal and reduced intraepidermal nerve density.

Table 5: Reasons for discontinuing medication given in % of treatment episodes.

	No effect (%)	Side effects (%)	No reason given (%)	*N*
Amitriptyline	42.3	57.7	8.8	57
NSAIDs	83.7	16.3	7.5	53
SNRI	42.4	57.6	0	33
Pregabalin	48.3	51.7	0	29
Weak opioids	74.1	25.9	0	27
Metamizole	57.1	28.6	14.3	14
Flupirtine	84.6	7.7	7.7	13
Acetaminophen	100.0	0.0	0	12
SSRI	81.8	18.2	0	11
Strong opioids	60.0	40.0	0	5
COX-2 inhibitors	100.0	0.0	0	2
Cyclobenzaprine	33.3	33.3	33.3	3
Corticosteroids	100.0	0.0	0	1
Lidocaine	100.0	0.0	0	1
All	60.1	34.1	5.8	261

N, the total number of treatments with the respective drug in the past.

Table 5: Reasons for discontinuing medication given in % of treatment episodes.

	No effect (%)	Side effects (%)	No reason given (%)	*N*
Amitriptyline	42.3	57.7	8.8	57
NSAIDs	83.7	16.3	7.5	53
SNRI	42.4	57.6	0	33
Pregabalin	48.3	51.7	0	29
Weak opioids	74.1	25.9	0	27
Metamizole	57.1	28.6	14.3	14
Flupirtine	84.6	7.7	7.7	13
Acetaminophen	100.0	0.0	0	12
SSRI	81.8	18.2	0	11
Strong opioids	60.0	40.0	0	5
COX-2 inhibitors	100.0	0.0	0	2
Cyclobenzaprine	33.3	33.3	33.3	3
Corticosteroids	100.0	0.0	0	1
Lidocaine	100.0	0.0	0	1
All	60.1	34.1	5.8	261

N, the total number of treatments with the respective drug in the past.

Cochrane Library

Cochrane Database of Systematic Reviews

Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults (Review)

Derry S, Wiffen PJ, Häuser W, Mücke M, Tölle TR, Bell RF, Moore RA

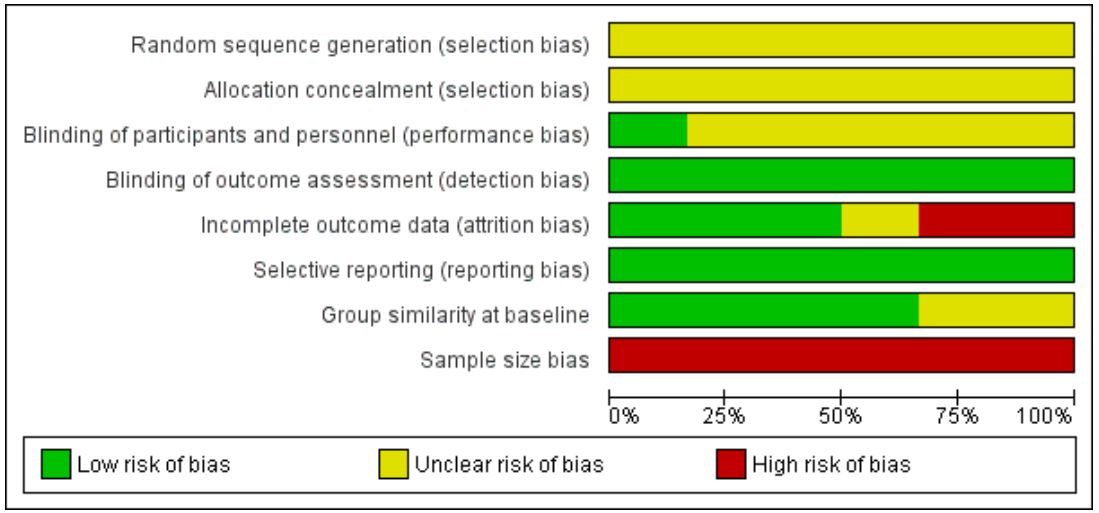
6 RCT

NSAIDs tested wer:
etoricoxib 90 mg daily,
ibuprofen 2400 mg daily,
naproxen 1000 mg daily, and
tenoxicam 20 mg daily;

146 participants received NSAID and 146 placebo.

The duration of treatment in the double-blind phase varied between three and eight weeks.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Non si sono osservate differenze statisticamente significative tra FANS e placebo nella percentuale di pazienti che hanno ottenuto una riduzione del punteggio del dolore di almeno:

- ✓ il 50% (differenza assoluta: -0,07, 95% CI da -0,18 a +0,04) (2 RCT, 146 pazienti)
- ✓ il 30% (differenza assoluta: -0,04, 95% CI da -0,16 a +0,08) (3 RCT, 192 pazienti);
- ✓ nelle interruzioni per eventi avversi (differenza assoluta 0,04, 95% CI da -0,02 a +0,09) (4 RCT, 230 pazienti);
- ✓ nella percentuale di pazienti che ha avuto reazioni avverse (differenza assoluta 0,08, 95% CI da -0,03 a +0,19) (4 RCT, 230 pazienti);
- ✓ nelle interruzioni per qualunque causa (differenza assoluta 0,03, 95% CI da -0,07 a +0,14) (3 RCT, 192 pazienti).

Authors' conclusions

There is only a modest amount of very low-quality evidence about the use of NSAIDs in fibromyalgia, and that comes from small, largely inadequate studies with potential risk of bias. That bias would normally be to increase the apparent benefits of NSAIDs, but no such benefits were seen. Consequently, NSAIDs cannot be regarded as useful for treating fibromyalgia.

Cochrane Database of Systematic Reviews 2018

Cochrane Database of Systematic Reviews

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia (Review)

Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W

Instituto Nacional de Salud Pública de México, Cuernavaca, Morelos, Mexico

Authors' conclusions

The update did not change the major findings of the previous review. Based on low- to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran.

JAMA Network Open

View Article

JAMA Netw Open. 2022 May; 5(5): e2212939.
Published online 2022 May 19. doi: 10.1001/jamanetworkopen.2022.12939: 10.1001/jamanetworkopen.2022.12939

PMCID: PMC9121190
PMID: 35587348

Comparison of Amitriptyline and US Food and Drug Administration–Approved Treatments for Fibromyalgia

A Systematic Review and Network Meta-analysis

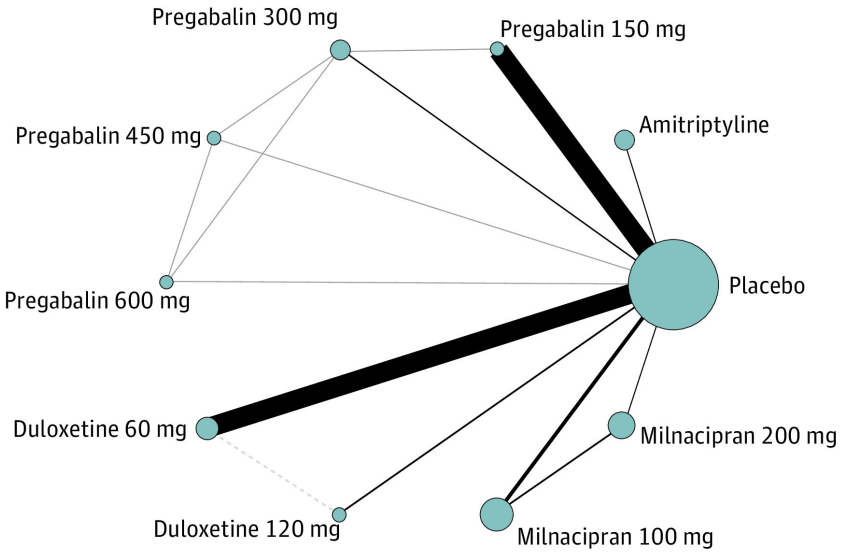
Hussein M. Farag, PharmD, MSc, PhD, [1] Ismaeel Yunusa, PharmD, PhD, [1,2] Hardik Goswami, BPharm, MSc, PhD, [1,3] Ihtisham Sultan, PharmD, [1,4] Joanne A. Doucette, MSc, MSLIS, [1] and Tewodros Eguale, MD, PhD [1,5]

Question

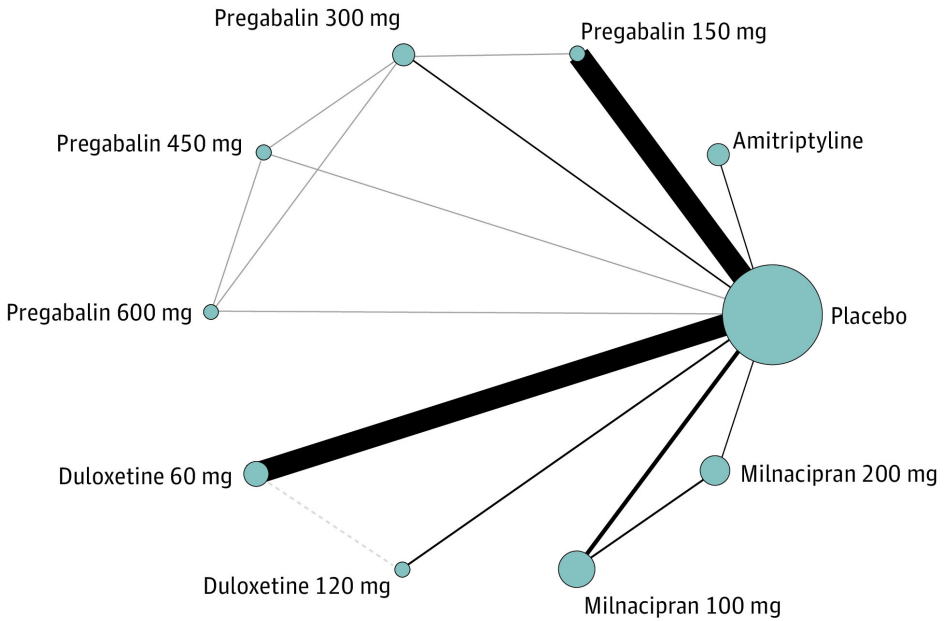
What pharmacological treatments for adults with fibromyalgia are associated with the highest efficacy and acceptability?

Network Diagrams

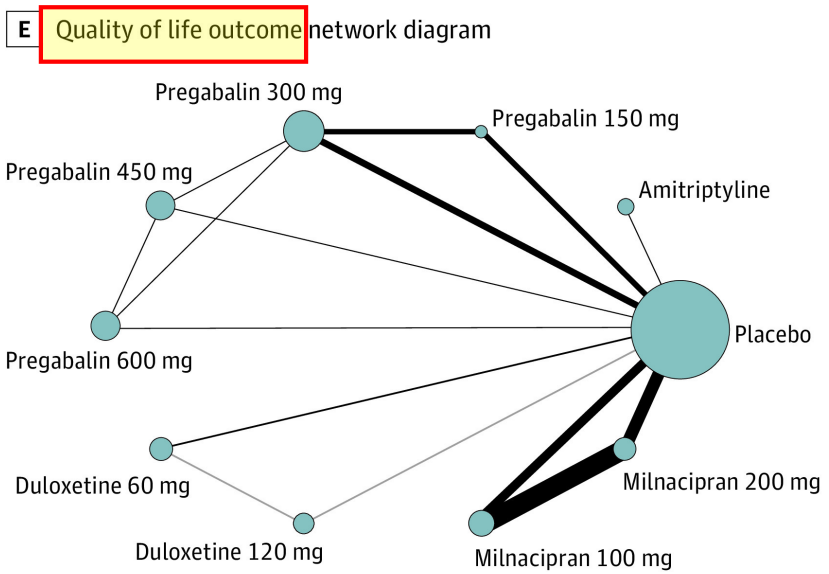
C Depression outcome network diagram

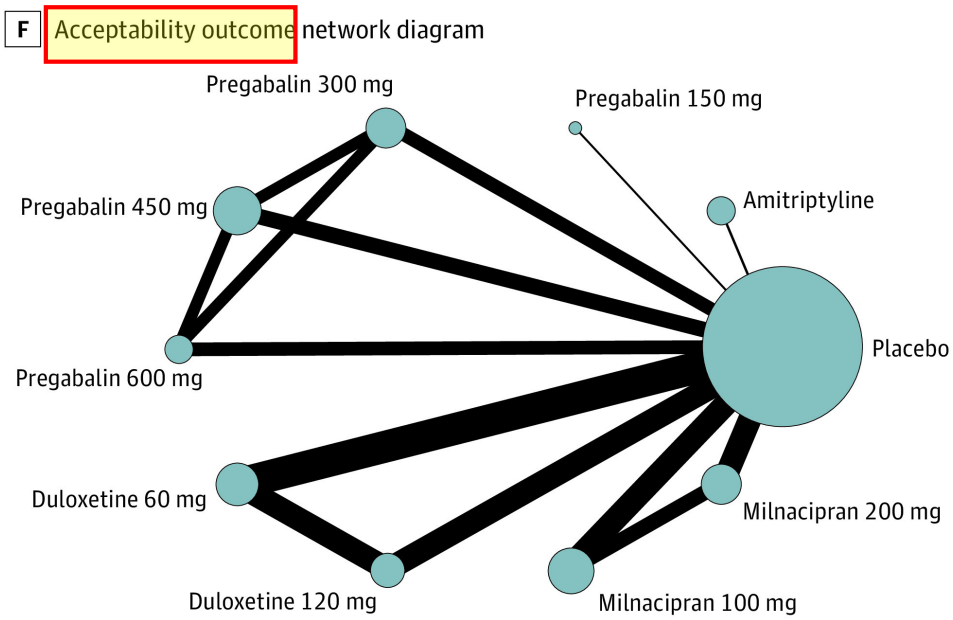


D Fatigue outcome network diagram



Network Diagrams





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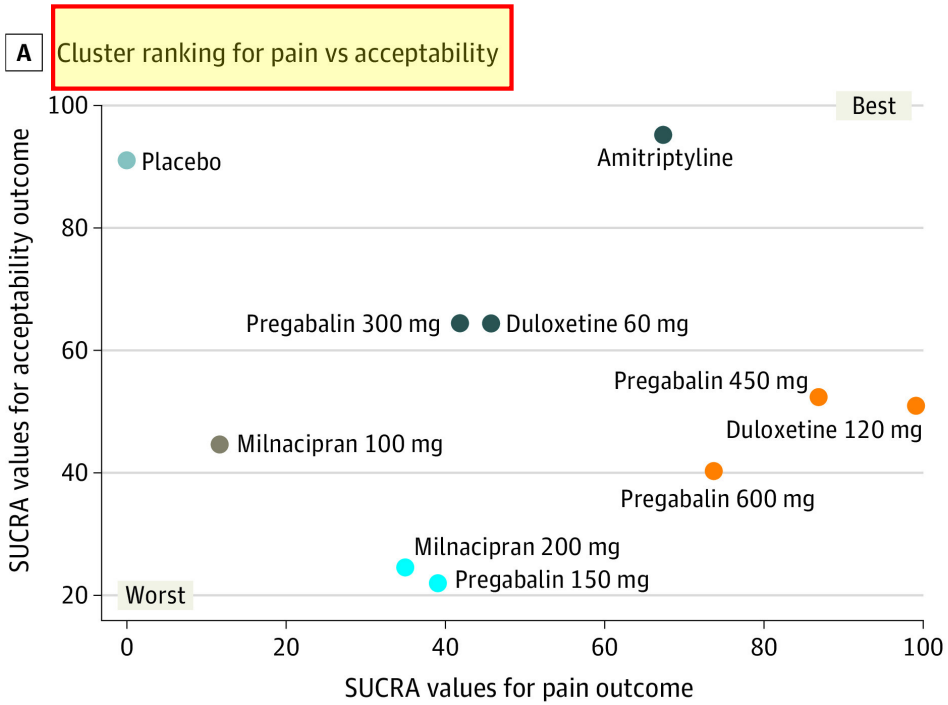
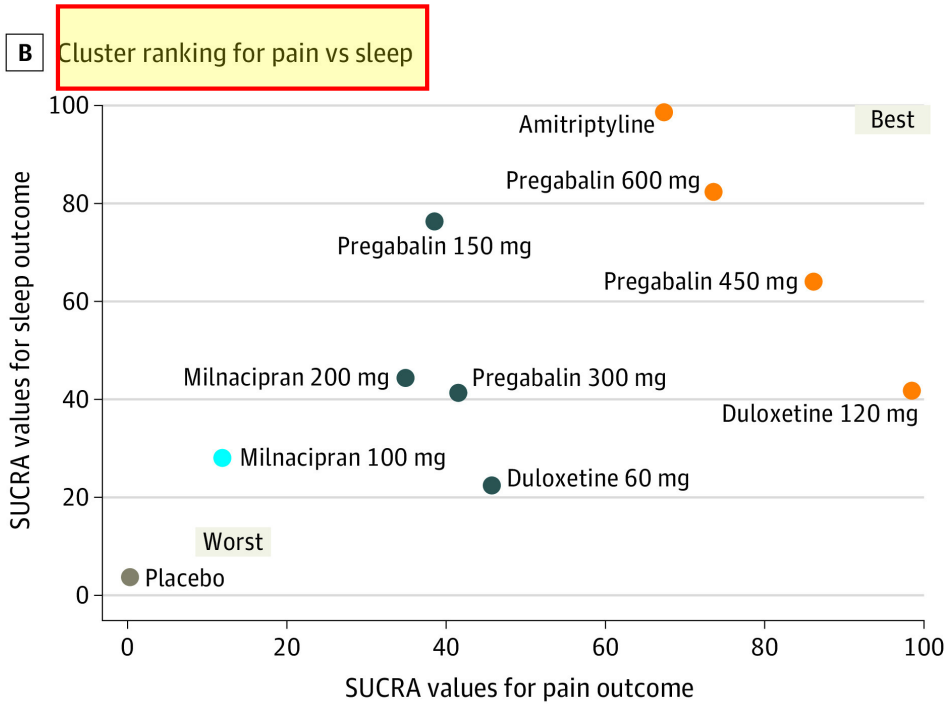
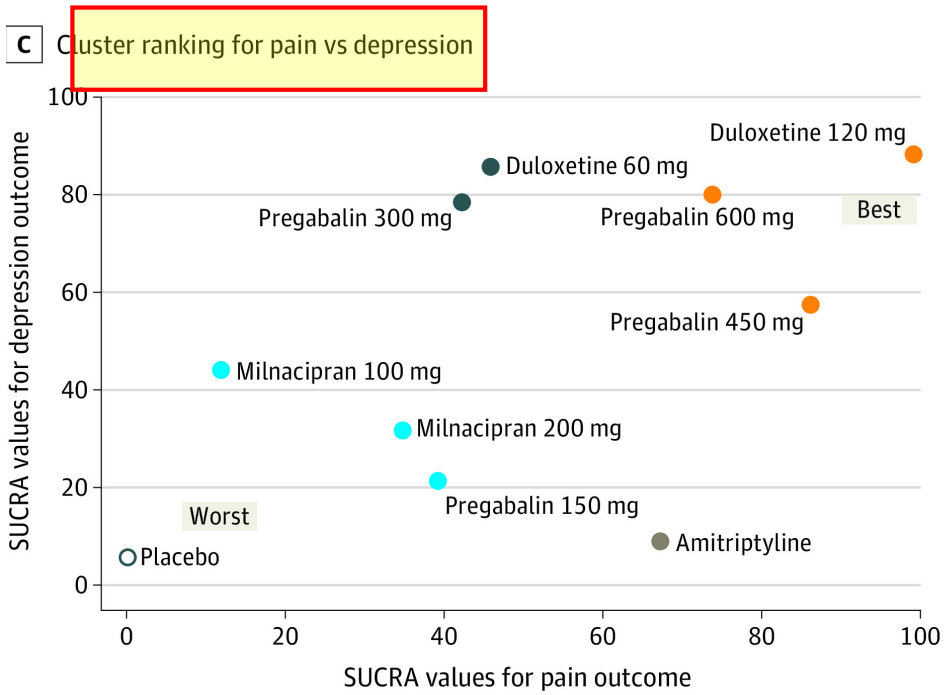
Findings

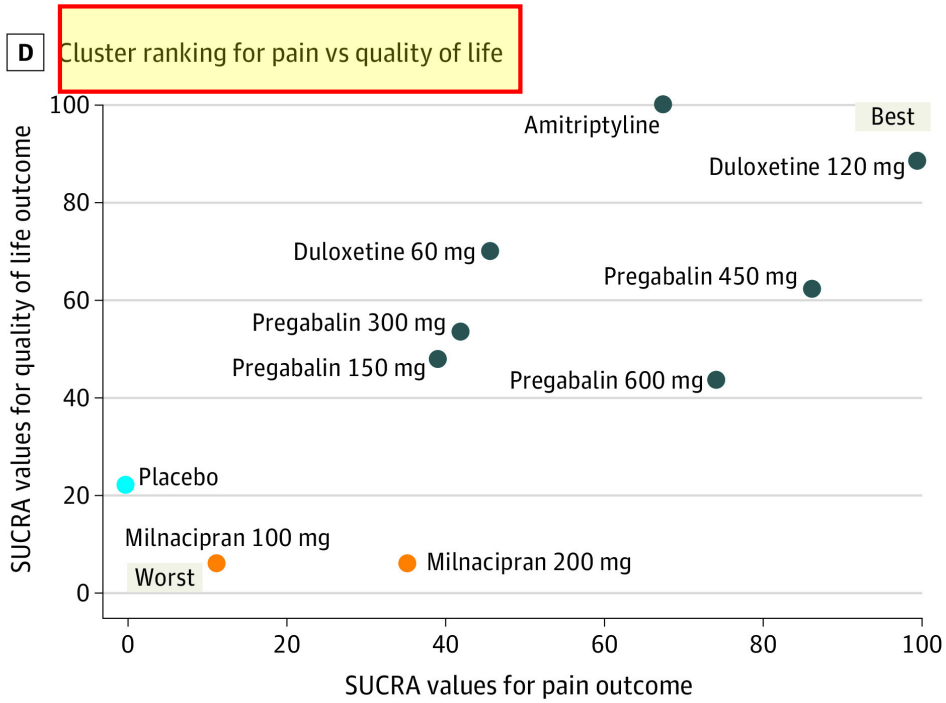
In this systematic review and network meta-analysis of 36 randomized clinical trials (11 930 patients with fibromyalgia), duloxetine (120 mg) was associated with higher efficacy in treating pain and depression, while amitriptyline was associated with higher efficacy and acceptability in improving sleep, fatigue, and health-related quality of life outcomes.

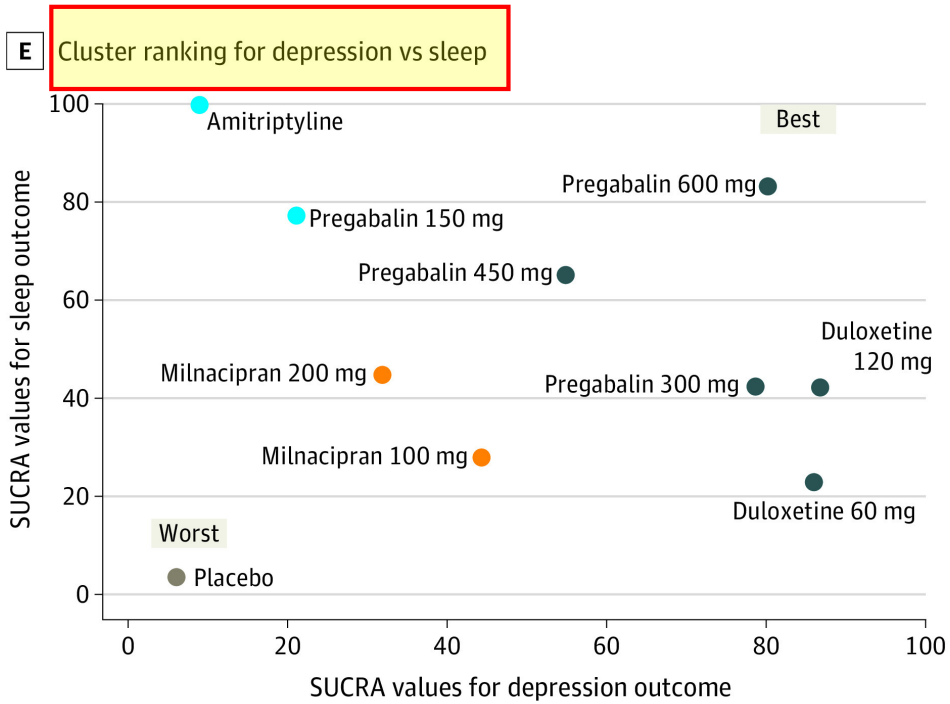
We also found that pregabalin 600 mg, 450 mg, and 150 mg were associated with a moderate improvement in sleep symptoms. Although pregabalin 600 mg was associated with improved QoL, pregabalin generally showed only a small improvements in the other measured symptoms. Milnacipran 100 mg was associated with small improvements in all outcomes except QoL; milnacipran 200 mg was associated with small reductions in pain, depression, and fatigue, but did not improve sleep and QoL outcomes. Pregabalin, duloxetine, and milnacipran were associated with worse acceptability than placebo, while the acceptability outcomes associated with amitriptyline did not significantly differ from placebo.

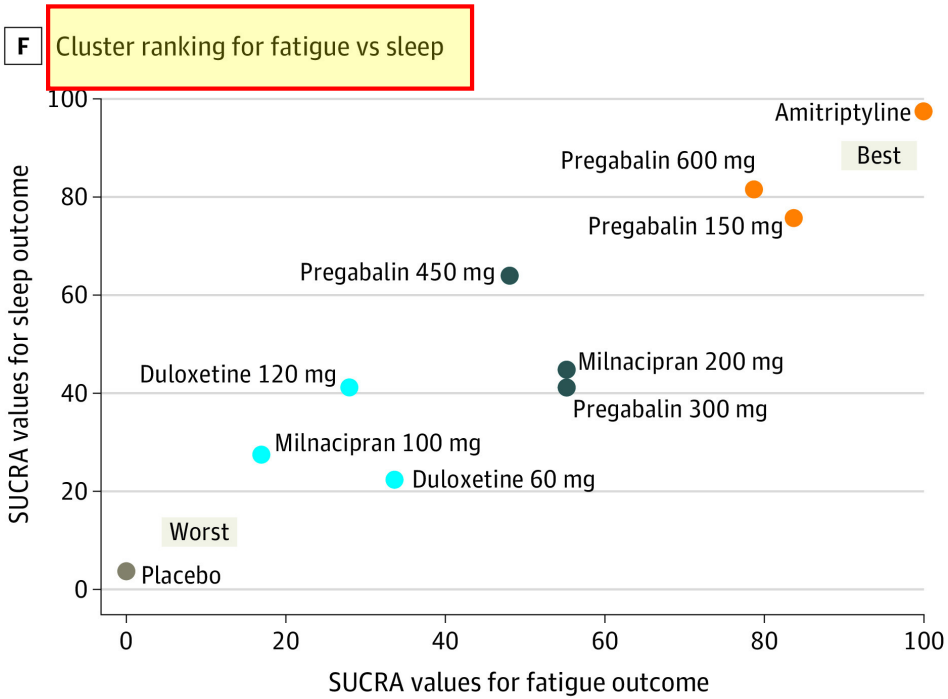

A
Cluster ranking for pain vs acceptability
SUCRA values for acceptability outcome
SUCRA values for pain outcome
Best
Worst
Placebo
Amitriptyline
Pregabalin 300 mg
Duloxetine 60 mg
Pregabalin 450 mg
Duloxetine 120 mg
Milnacipran 100 mg
Pregabalin 600 mg
Milnacipran 200 mg
Pregabalin 150 mg
100
80
60
40
20
0
20
40
60
80
100


B
Cluster ranking for pain vs sleep
SUCRA values for sleep outcome
SUCRA values for pain outcome
Best
Worst
Amitriptyline
Pregabalin 600 mg
Pregabalin 150 mg
Pregabalin 450 mg
Milnacipran 200 mg
Pregabalin 300 mg
Duloxetine 120 mg
Milnacipran 100 mg
Duloxetine 60 mg
Placebo
100
80
60
40
20
0
20
40
60
80
100


C
Cluster ranking for pain vs depression
SUCRA values for depression outcome
SUCRA values for pain outcome
100
80
60
40
20
0
0
20
40
60
80
100
Duloxetine 120 mg
Duloxetine 60 mg
Pregabalin 300 mg
Pregabalin 600 mg
Best
Pregabalin 450 mg
Milnacipran 100 mg
Milnacipran 200 mg
Pregabalin 150 mg
Worst
Amitriptyline
Placebo


D
Cluster ranking for pain vs quality of life
SUCRA values for quality of life outcome
SUCRA values for pain outcome
100
80
60
40
20
0
0
20
40
60
80
100
Amitriptyline
Best
Duloxetine 120 mg
Duloxetine 60 mg
Pregabalin 450 mg
Pregabalin 300 mg
Pregabalin 150 mg
Pregabalin 600 mg
Placebo
Milnacipran 100 mg
Worst
Milnacipran 200 mg


E
Cluster ranking for depression vs sleep
SUCRA values for sleep outcome
SUCRA values for depression outcome
Amitriptyline
Best
Pregabalin 600 mg
Pregabalin 150 mg
Pregabalin 450 mg
Duloxetine 120 mg
Milnacipran 200 mg
Pregabalin 300 mg
Milnacipran 100 mg
Duloxetine 60 mg
Worst
Placebo
0
20
40
60
80
100


F
Cluster ranking for fatigue vs sleep
SUCRA values for sleep outcome
SUCRA values for fatigue outcome
Amitriptyline
Best
Pregabalin 600 mg
Pregabalin 150 mg
Pregabalin 450 mg
Duloxetine 120 mg
Milnacipran 200 mg
Pregabalin 300 mg
Milnacipran 100 mg
Duloxetine 60 mg
Worst
Placebo
0
20
40
60
80
100

Conclusioni

These findings suggest that with the heterogeneity of fibromyalgia symptoms, **pharmacological treatments should be tailored to individual symptoms**, including pain, sleep problems, depressed mood, fatigue, and health-related quality of life.

Table 2 | **Commonly prescribed drugs for fibromyalgia treatment and their adverse effects**

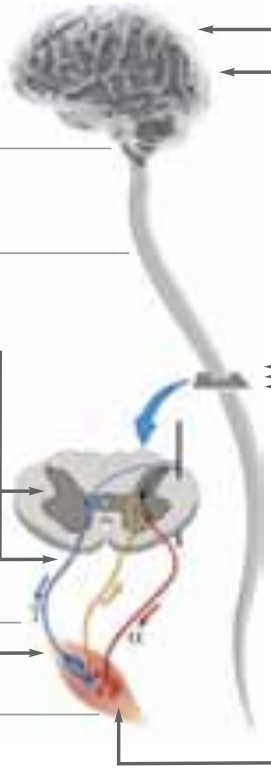
Drug	Class of drug	FDA-approved drugs for fibromyalgia	Adverse effects[169,174,184,187,203,239–242]
Antidepressants			
Duloxetine	SNRI	Yes[243]	Nausea, palpitations, headache, fatigue, tachycardia, insomnia, xerostomia, constipation and serotonin syndrome[a](REFS[244,245])
Milnacipran	SNRI	Yes[246]	
Amitriptyline	Tricyclic antidepressant	No	Xerostomia, constipation, weight gain, urinary retention, sedation and serotonin syndrome[a]
Anticonvulsants			
Pregabalin	GABAergic drug	Yes[247]	Sedation, dizziness, vertigo, asthenia, nausea and weight gain
Gabapentin	GABAergic drug	No	
Muscle relaxants			
Cyclobenzaprine	Serotoninergic muscle relaxant	No	Nausea, palpitations, headache, fatigue, xerostomia, constipation and serotonin syndrome[a]
Tizanidine	α2 receptor agonist	No	Dizziness, asthenia, xerostomia, vomiting, constipation, liver test abnormalities, bradycardia, hypotension and blurred vision
Analgesic drugs			
Tramadol	Weak opioid and SNRI	No	Constipation, nausea, vomiting, dizziness, fatigue, headache, itching and xerostomia
Paracetamol	Analgesic and antipyretic drug	No	Nausea, vomit, constipation and liver disease

Miorilassanti

i miorilassanti s’inseriscono nel percorso terapeutico grazie alla loro capacità di sbloccare il circolo vizioso dolore-contrattura-dolore, per la loro azione favorente il sonno e per la capacità di ridurre la rigidità mattutina.

Principio attivo	Meccanismo d'azione	
Diazepam	Centrale	GABA ergico
Tiocolchicoside	Centrale	
Piridinolo mesilato	Centrale	
Baclofene	Centrale	GABA B presinaptici
Dantrolene	Diretta	
Ciclobenzaprina	Centrale	TCA like
Tizanidina	Centrale	Interneuroni
Eperisone cloridrato	Centrale	Motoneurone gamma Antagonismo sost P

Miorilassanti: meccansimo di azione



EPERISONE CLORIDRATO

1) inibizione della scarica spontanea dei **gamma motoneuroni** spinali;

2) aumento del **flusso ematico** nelle aree che presentano ipertono muscolare mediante un'azione sui canali del calcio voltaggio-dipendente e sulla calmodulina a livello delle cellule muscolari lisce;

3) attività analgesica grazie alla sua azione di **antagonista della Sostanza P** a livello spinale.

DIAZEPAM
Gli effetti terapeutici sono dovuti alla capacità di **incrementare la trasmissione GABAergica**.

TIOCOLCHICOSIDE
Attività selettiva di tipo **agonista** sui recettori **GABA-ergici e glicinergici**.

CICLOBENZAPRINA
Azione TCA-simile

TIZANIDINA
Miorilassante ad azione centrale con azione elettiva sito d'attacco spinale.
Riduce il rilascio degli aminoacidi eccitatori da parte degli interneuroni.

BACLOFENE
Miorilassante ad azione centrale con sito d'attacco spinale. **Inibisce la trasmissione sia monosinaptica che polisinaptica, stimolando preferibilmente i recettori GABA** e di conseguenza **inibendo il rilascio degli aminoacidi eccitatori glutammato e aspartato**.

DANTROLENE
Interferisce con la **liberazione del Ca^{++} sarcoplasmatico** della cellula muscolare inibendo in modo diretto la contrazione muscolare.

Bibliografia
1] Eperisone. Riassunto delle Caratteristiche di Prodotto Expose
2] Diazepam. Martindale. The Complete Drug Reference. "Diazepam", 2009 ed.
3] Tiocolchicoside. Martindale. The Complete Drug Reference. "Tiocolchicoside", 2009 ed.
4] Tizanidina. Riassunto delle Caratteristiche di Prodotto Sirdalud
5] Baclofene. Riassunto delle Caratteristiche di Prodotto Lioresal
6] Dantrolene. Riassunto delle Caratteristiche di Prodotto Dantrium

Description	Spasm	Spasticity	Myofascial Pain
Definition	Involuntary muscle contractions	Velocity-dependent increase in muscle tone caused by CNS dysfunction	Nociceptive pain derived from mechanical injury of soft tissue
Pathophysiology	Peripheral	Central	Peripheral
Etiology	Muscle sprain/injury Nerve compression	Upper motor neuron disorder/injury	Muscle sprain/tears Metabolic/ inflammatory
Symptoms	Jerks Twitch Cramps	Incessant hypertonicity/ stiffness Hyper-reflexia	Tenderness Tightness Limited range of motion
Clinical conditions	Musculoskeletal pain Mechanical dysfunction Spine-related neural impingement (radiculopathy, spinal stenosis) Fibromyalgia	Spinal cord injury Stroke Traumatic brain injury Motor neuron disease Multiple sclerosis Cerebral palsy	Myalgia Myopathic pain syndrome

Chang Phys Med Rehabil Clin N Am 31 (2020) 245–254


Antispasticity Meds
Baclofen
Dantrolene
Dual Property Meds
Tizanidine
Diazepam
Antispasmodic Meds
Ciclobenzaprine

Common skeletal muscle relaxants

	Drug	Onset	Duration	Starting Dose	Therapeutic Dose	Adverse Effects	Note
Centrally Acting	*TCA-like*						
	Cyclobenzaprine	1hr	12–24 hr	5mg TID	10–20 mg TID	Dry mouth, dz, dr	Additive effects with alcohol, TCAs, and CNS depressants, seizures with tramadol and MAO-I

Duration is 8 to 37 hours.
Therapeutic doses are achieved in 3 to 4 days

Received: 7 March 2023 | Accepted: 29 March 2023
DOI: 10.1111/jgs.18372

SPECIAL ARTICLE

Journal of the
American Geriatrics Society

American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults

By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel

Organ system, therapeutic category, drug(s)[a]	Rationale	Recommendation	Quality of evidence[b]	Strength of recommendation
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Muscle relaxants typically used to treat musculoskeletal complaints are poorly tolerated by older adults due to anticholinergic adverse effects, sedation, and increased risk of fractures; effectiveness at dosages tolerated by older adults is questionable. This criterion does not apply to skeletal muscle relaxants typically used for the management of spasticity (i.e., baclofen and tizanidine) although these drugs can also cause substantial adverse effects.	Avoid	Moderate	Strong

Common skeletal muscle relaxants

Drug	Onset	Duration	Starting Dose	Therapeutic Dose	Adverse Effects	Note
Alpha 2 Adrenergic Agonist						
Tizanidine	2wk	variable	2mg TID	4mg TID	Paradoxic spasm/tone, dry mouth, dz, dr	Additive effects with alcohol and CNS depressants, reduced clearance with oral contraceptives Requires slow taper

tizanidine does not share the antihypertensive effects or exert any benefit for treatment of dysautonomia.

Caution in IRC
Inihibition of CYP P450
contraindicated with iv ciprofloxacin

CICLOBENZAPRINA

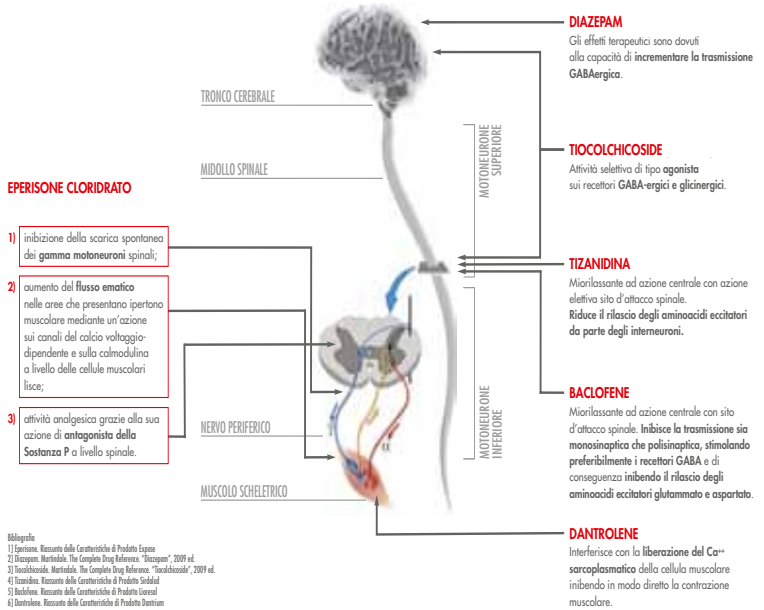
Dosaggio: 10-40 mg/die
NNT e NNH: **non disponibili**
RISULTATI: Modesti su sonno, limitati sul dolore. Non migliora la fatigue
Effetti collaterali: sonnolenza, secchezza delle fauci, vertigini

TIZANIDINA

Agonista a2 receptor: ansiolitiche , analgesiche e sedative
Dosaggio: 2-12 mg/die
NNT e NNH: **non disponibili**
RISULTATI: modesti (pochissimi studi)
Effetti collaterali: sonnolenza, secchezza delle fauci, vertigini, stanchezza

Eperisone relaxes skeletal muscles by reducing muscle spindle sensitivity via γ-motor neurons; furthermore, it antagonizes calcium channels on vascular smooth muscle cells, increasing blood flow in the contracted muscles and improving oxygenation, and has muscular sympatholytic actions. Eperisone also blocks voltage-dependent sodium channels on the nerve fibers, providing an antinociceptive effect. It is associated with a lower incidence of sedation than tizanidine

Pain Ther (2020) 9:S17–S28



Bibliografia
1) Eperisone. Riassunto delle Caratteristiche di Prodotto Exposa
2) Diazepam. Martindale. The Complete Drug Reference. "Diazepam", 2009 ed.
3) Tiocolchicoside. Martindale. The Complete Drug Reference. "Tiocolchicoside", 2009 ed.
4) Tizanidina. Riassunto delle Caratteristiche di Prodotto Sirdalud
5) Baclofene. Riassunto delle Caratteristiche di Prodotto Lioresal
6) Dantrolene. Riassunto delle Caratteristiche di Prodotto Dantrium

Tiocolchicoside

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- It antagonizes GABA and glycine receptor, has anti- inflammatory effects
- teratogenic
- pro-epileptogenic

- Systemic thiocolchicoside is recommended only as adjuvant treatment for acute muscle contractures in spinal pathology, for adults and adolescents from 16 years of age.
- It is not recommended for longer-term treatment of chronic conditions.
- The maximum recommended oral dose is 8 mg every 12 hours; treatment duration should be no more than 7 consecutive days. When given intramuscularly, the maximum dose should be 4 mg every 12 hours, for up to 5 days.
- Medicines containing thiocolchicoside should not be used during pregnancy and lactation, nor in women of childbearing potential who are not taking appropriate contraceptive measures.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 January 2014
EMA/40615/2014

European Medicines Agency recommends restricting use of thiocolchicoside by mouth or injection

Medicine only to be used at low doses for additional short-term relief of painful muscle contractures

Fibromialgia

	Recommendation	LOE
Strength of recommendation A (is recommended)		
General	The approach in patients with fibromyalgia should be multimodal and multidisciplinary.[3,18]	A1
	Control of the disease using specific scoring systems such as the FIQ is adequate for controlling the disease course and adapting the treatment.[15]	A1
Drug therapy	Amitriptyline can be used over short periods of time to relieve pain and improve sleep (10–50 mg/day).[3,17]	A1
Physiotherapy	Patients with fibromyalgia should follow a program of moderate to mild aerobic exercise. They should begin gradually. It is preferable that the exercise be chosen by the patients. Supervision is recommended. The patients should not overexert themselves to avoid making the symptoms worse. This exercise should be performed at least 2–3 times a week for a duration of at least 30 min.[3,18]	A1
	• Muscle strength training is a complement to be added to exercise programs for fibromialgia.[18]	A2
	• Relaxation after performing aerobic exercise helps to improve the symptoms in patients with fibromialgia.[3]	A2
Psychology	Cognitive-behavioral therapy, even over a short period, is useful in reducing fear of pain and of activity.[3,18]	A1
	• Interventions to build up self-efficacy are indicated to help patients to control their symptoms.[18]	A2
Strength of recommendation B (can be recommended)		
General	Educating patients with fibromyalgia helps them to face the disease.	
	• Education is more effective when provided in combination with other therapies.[15]	A2
	• The offer of online resources for patients with fibromyalgia can help them to control the symptoms.[15]	A2
Drug therapy	Cyclobenzaprine at very low doses can be used in patients with fibromyalgia to improve nightly sleep.[3,18]	A1
	Antiepileptic drugs can be used to control the pain in patients with fibromyalgia (principally pregabalin; there is no evidence for gabapentin).[3,18]	A2
	• Pregabalin (50–450 mg/day) can be used for short periods of time, should treatment with amitriptyline not be possible or was not effective.[3,17]	A2
	Serotonin and norepinephrine reuptake inhibitors (SNRI) are indicated for a short period of time in patients with comorbid depression or anxiety, should amitriptyline not be tolerated or not be successful.[3,18]	A2
	• Duloxetine (60 mg/day) is the preferred SNRI for patients with fibromyalgia and comorbid depression or anxiety.[3,17]	A1
	Selective serotonin reuptake inhibitors (SSRI) (fluoxetine, 20–40 mg/day; paroxetine, 20–40 mg/day) can be considered in cases of coexistence of anxiety or depression disorder.[3,18]	A2
Physiotherapy	Stretching is indicated as part of the exercise program.[3]	A2
	Balneotherapy can reduce the symptoms in patients with fibromyalgia.[3,15]	A2
	Aquatic exercise are indicated in patients with fibromyalgia.[17]	A2
	Biofeedback can be used to reduce symptoms in patients with fibromyalgia.[3,15]	A2
	Exercise training can employ kinetics or functional training (in water or on land), twice a week, in groups monitored by a physiotherapist.[3]	B1
Psychology	Hypnosis or guided imagery can be used to reduce the symptoms of fibromialgia.[3,15]	A2

Oppioidi

Patients with fibromyalgia have altered endogenous opioid activity, with little opioid receptor availability but high concentrations of opioid peptides in biological fluids

- Gli **oppioidi** sono gravati da gravi effetti collaterali e non sono realmente efficaci per il dolore FM, quindi il loro uso dovrebbe essere evitato. Il **Tramadolo** è l'unico che può essere efficace nel ridurre il dolore FM, poiché agisce come un agonista degli oppioidi ma anche come inibitore della ricaptazione della serotonina e in parte della noradrenalina.

Cochrane Library

Cochrane Database of Systematic Reviews

Review > Cochrane Database Syst Rev. 2014 Jun 23;(6):CD010692.
doi: 10.1002/14651858.CD010692.pub2.

Oxycodone for neuropathic pain and fibromyalgia in adults

Helen Gaskell [1], R Andrew Moore, Sheena Derry, Cathy Stannard

Affiliations + expand

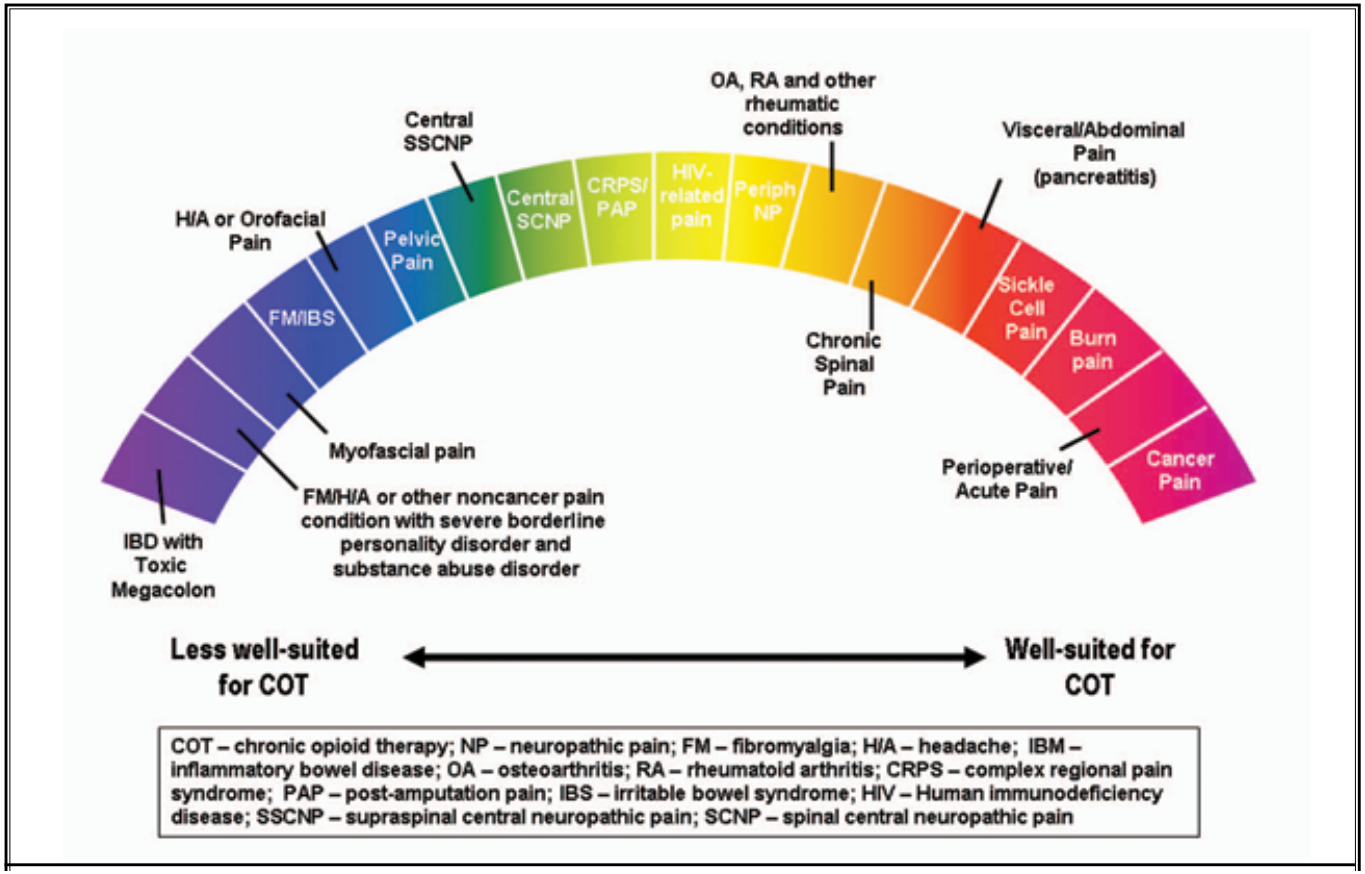
PMID: 24956205 DOI: 10.1002/14651858.CD010692.pub2

We included three studies with 254 participants; 204 had painful diabetic neuropathy and 50 postherpetic neuralgia.

Oxycodone 60 and 120 mg daily;

There is **no evidence** at all for other neuropathic pain conditions, or for fibromyalgia.

Spettro di appropriatezza della COT



Editorial Howard Smith

Pain Physician: Opioid Special Issue July 2012; 15:ES1-ES7

RESEARCH ARTICLE

WILEY

Treatment patterns in fibromyalgia including the use of opioids

Luis F. Valladales-Restrepo[1,2,3] | María C. Oyuela-Gutiérrez[2] | Mariana Alzate-García[2] | Isabella Osorio-Rodas[2] | Valentina Quintero-Flórez[2] | Juan F. Restrepo-Muñoz[2] | Julián A. Suárez-Cardona[2] | Sergio T. Barroso-Fernandes[2] | Jorge E. Machado-Alba[1]

Objective: Opioids (except for tramadol) have not been shown to be effective in patients with fibromyalgia, but they can increase the risk of adverse drug reactions. The aim was to determine the treatment patterns of a group of patients with fibromyalgia and to identify the factors associated with the use of opioids in Colombia.

Variables	Total		Women		Men		
	n = 559	%	*n* = 495	%	*n* = 64	%	*p*
Pharmacological management	-	-	-	-	-	-	-
Non-opioid analgesics	537	96.1	474	95.8	63	98.4	0.299
Acetaminophen	537	96.1	474	95.8	63	98.4	0.299
Non-steroidal anti-inflammatory drugs	10	1.8	10	2.0	0	0.0	0.614**
Opioid analgesics	389	69.6	333	67.3	56	87.5	0.001
Morphine equivalents, median (IQR)	15.0 (10.0–22.5)		15.0 (10.0–22.5)		20.0 (15.0–37.5)		0.001***
Antidepressants	260	46.5	235	47.5	25	39.1	0.204
Serotonin and norepinephrine reuptake inhibitors	191	34.2	173	34.9	18	28.1	0.279

Variables	Total		Women		Men		
	n = 559	%	*n* = 495	%	*n* = 64	%	*p*
Selective serotonin reuptake inhibitors	57	10.2	53	10.7	4	6.3	0.379**
Atypical	25	4.5	22	4.4	3	4.7	1.000**
Tricyclic antidepressants	13	2.3	10	2.0	3	4.7	0.178**
Gabapentinoids	373	66.7	325	65.7	48	75.0	0.135
Muscle relaxants	170	30.4	155	31.3	15	23.4	0.197

Terapaia Farmacologica

In summery

There is no gold standard pharmacological treatment for fibromyalgia.

Maximum doses of a single drug are rarely used because of safety concerns.

Moreover, single drugs tend to have a clinically relevant effect in fewer than half of the treated patients.

Therefore, a combination of drugs is usually preferred using a patient-centred, symptom-based stepwise approach

Cochrane Library

Cochrane Database of Systematic Reviews

Combination pharmacotherapy for the treatment of fibromyalgia in adults (Review)

Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I

Authors' conclusions

There are few, large, high-quality trials comparing combination pharmacotherapy with monotherapy for fibromyalgia, consequently limiting evidence to support or refute the use of combination pharmacotherapy for fibromyalgia.

Table 2 | **Commonly prescribed drugs for fibromyalgia treatment and their adverse effects**

Drug	Class of drug	FDA-approved drugs for fibromyalgia	Adverse effects[169,174,184,187,203,239–242]
Hypnotic drugs			
Zolpidem	GABAergic and non-benzodiazepine hypnotic drug	No	Dizziness, headache, somnolence, confusion, agitation, abdominal pain, constipation and xerostomia
Antipsychotic drugs			
Quetiapine	Atypical antipsychotic drug	No	Somnolence, headache, dizziness, extrapyramidal symptoms, weight gain, dyslipidaemia, hyperglycaemia, xerostomia, vomiting and nausea, and constipation
Cannabis or cannabinoids			
Nabilone	Pure cannabinoid (tetrahydrocannabinol)	No	Drowsiness, dizziness, nausea, xerostomia, confusion, anxiety and tachycardia
Cannabis	Phytopharmaceutical (different concentrations of tetrahydrocannabinol and cannabidiol)	No	Drowsiness, dizziness, nausea, xerostomia, blurred vision, increased/decreased appetite, vertigo, tachycardia and hypotension

CANNABINOIDI

- sono stati recentemente proposti anche come promettente famiglia fitoterapica per la terapia FM, sebbene il suo uso medico sia stato studiato quasi solo con studi osservazionali.
- L'attenzione della comunità medica sui farmaci a base di cannabis è stata attirata sulla base di survey che hanno dato risultati positivi.
- Recentemente, un piccolo studio clinico (17 donne), in doppio cieco, randomizzato controllato con placebo è stato condotto per otto settimane per determinare il beneficio di un olio di cannabis ricco di THC.
- Gli autori hanno concluso che i fitocannabinoidi possono essere una terapia a basso costo e ben tollerata per ridurre i sintomi e aumentare la qualità della vita dei pazienti con fibromialgia. Sono ancora necessari studi per valutare i benefici a lungo termine e studi con diverse varietà di cannabinoidi.

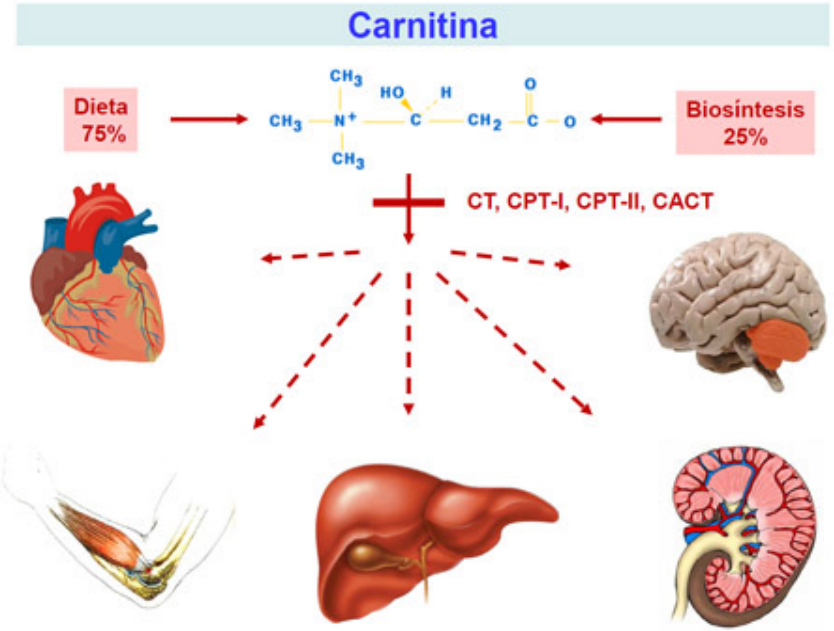
Chaves C, et al. Pain Med 2020; 21: 2212–2218.
assin M, Oron A, Robinson D. Clin Exp Rheumatol 2019; 37 Suppl11:13–20.
Guillouard M, et al. Rheumatology. DOI: 10.1093/rheumatology/keaa534.
Giorgi V, et al Clin Exp Rheumatol 2020; 38: 53–59.

L-ACETIL-CARNITINA

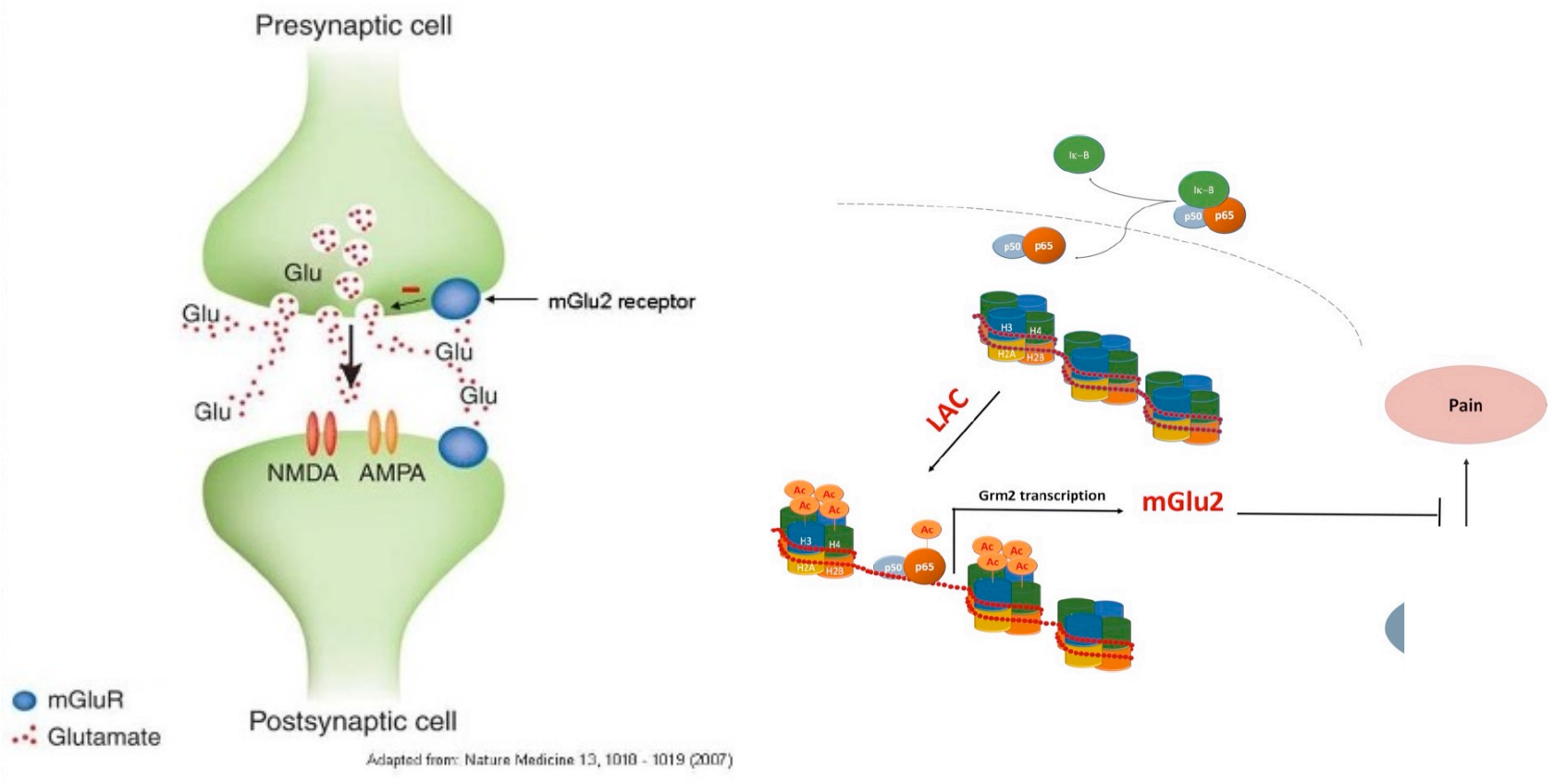
Potrebbe essere utile per:

- Meccanismi di Sensibilizzazione neuro
- Depressione
- Neuropatia delle piccole fibre

Nei pazienti FM.



LA LAC HA UN EFFETTO SULLA DENSITÀ DEI RECETTORI MGLU2, CON UN MECCANISMO EPIGENETICO



L'Azione analgesica di LAC perdura oltre il termine del trattamento

Research Article

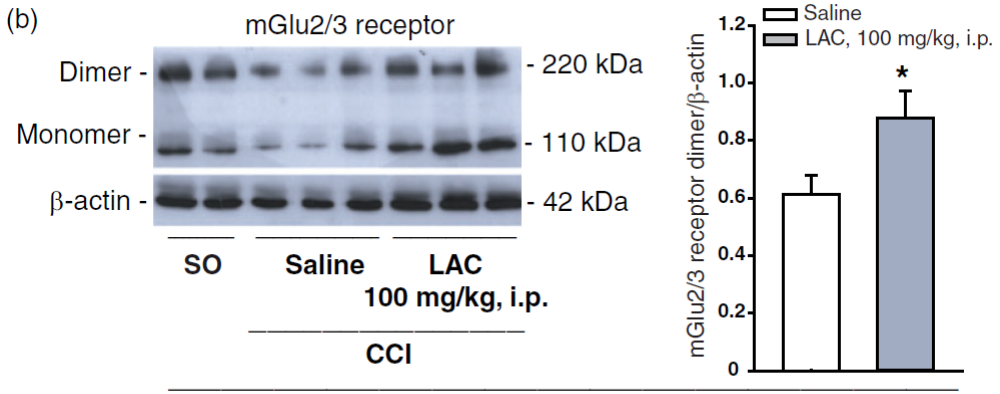
MOLECULAR PAIN

Molecular Pain
Volume 13: 1–12

DOI: 10.1177/1744806917697009
journals.sagepub.com/home/mpx
SAGE

Analgesia induced by the epigenetic drug, L-acetylcarnitine, outlasts the end of treatment in mouse models of chronic inflammatory and neuropathic pain

Serena Notartomaso[1], Giada Mascio[1], Matteo Bernabucci[1], Cristina Zappulla[1], Pamela Scarselli[1], Milena Cannella[1], Tiziana Imbriglio[1], Roberto Gradini[1,2], Giuseppe Battaglia[1], Valeria Bruno[1,3] and Ferdinando Nicoletti[1,3]

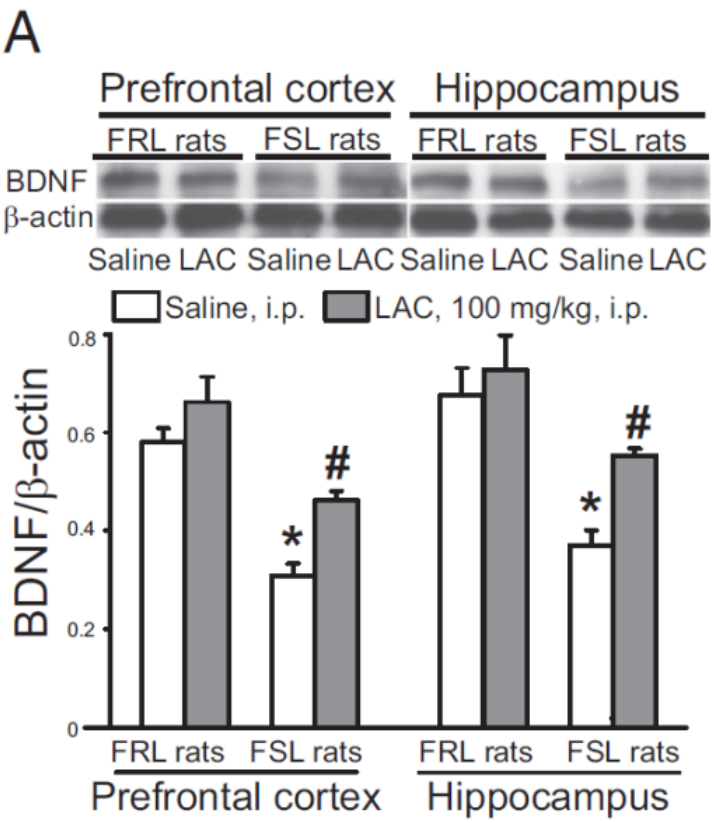


Studio su modello di Dolore Neuropatico da compressione cronica (CCI).

Dopo 37 gg dal termine del trattamento nel gruppo trattato con ALC si osserva ancora una sovra-espressione di mGLU2.

Notartomaso, Molecular Pain 2017

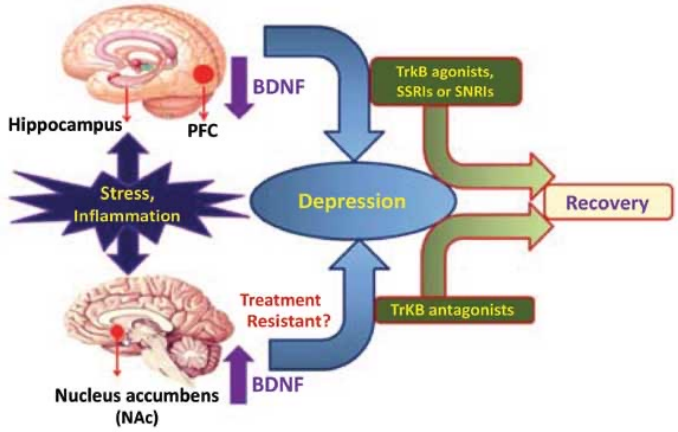
LAC AUMENTA IN MODO SIGNIFICATIVO IL LIVELLI DI BDNF NELLA CORTECCIA PREFRONTALE E NELL'IPPOCAMPO



Livelli cerebrali di BDNF in modello animale di depressione (ratti FSL) rispetto a ratti sani (FRL). I ratti di entrambi i gruppi sono stati trattati con fisiologica i.p. o LAC (100 mg/kg i.p.) per 21 giorni.

* p<0,05 rispetto a tutti gli altri valori; ** p<0,05 rispetto ai ratti FRL trattati con LAC

BDNF: Brain Derivated Neurotrophic Factor



Nasca C et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.

Effetti di L-acetil-carnitina sui sintomi depressivi

Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis

Veronese, Nicola MD; Stubbs, Brendon PhD; Solmi, Marco MD; Ajnakina, Olesya PhD; Carvalho, Andre F. MD; Maggi, Stefania MD

Psychosomatic Medicine: February/March 2018 - Volume 80 - Issue 2 - p 154–159

12 RCTs su un totale di 791 pz con sintomi di depressione hanno dimostrato che il trattamento con **LAC riduce i sintomi depressivi in modo significativo vs placebo.**
Questi dati sono stati ottenuti prevalentemente in studi su **popolazione anziana.**

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bella et al., 1990	-1.542	-2.119	-0.966	0.000
Fulgente et al., 1990	-2.259	-2.907	-1.611	0.000
Garzya et al., 1990	-0.923	-1.703	-0.144	0.020
Gavrilova et al., 2015	-1.211	-1.885	-0.537	0.000
Gecele et al., 1991	-2.734	-3.765	-1.704	0.000
Hagen et al., 2015	-0.123	-0.586	0.339	0.602
Malaguarnera et al., 2011	-0.794	-1.295	-0.293	0.002
Rossini et al., 2007	-0.183	-0.600	0.234	0.391
Tempesta et al., 1987	-0.618	-1.437	0.201	0.139
	-1.104	-1.646	-0.562	0.000

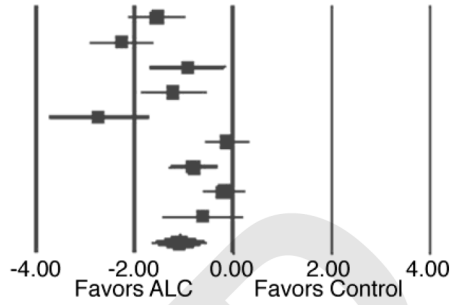
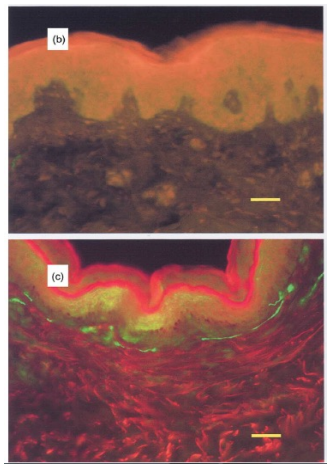
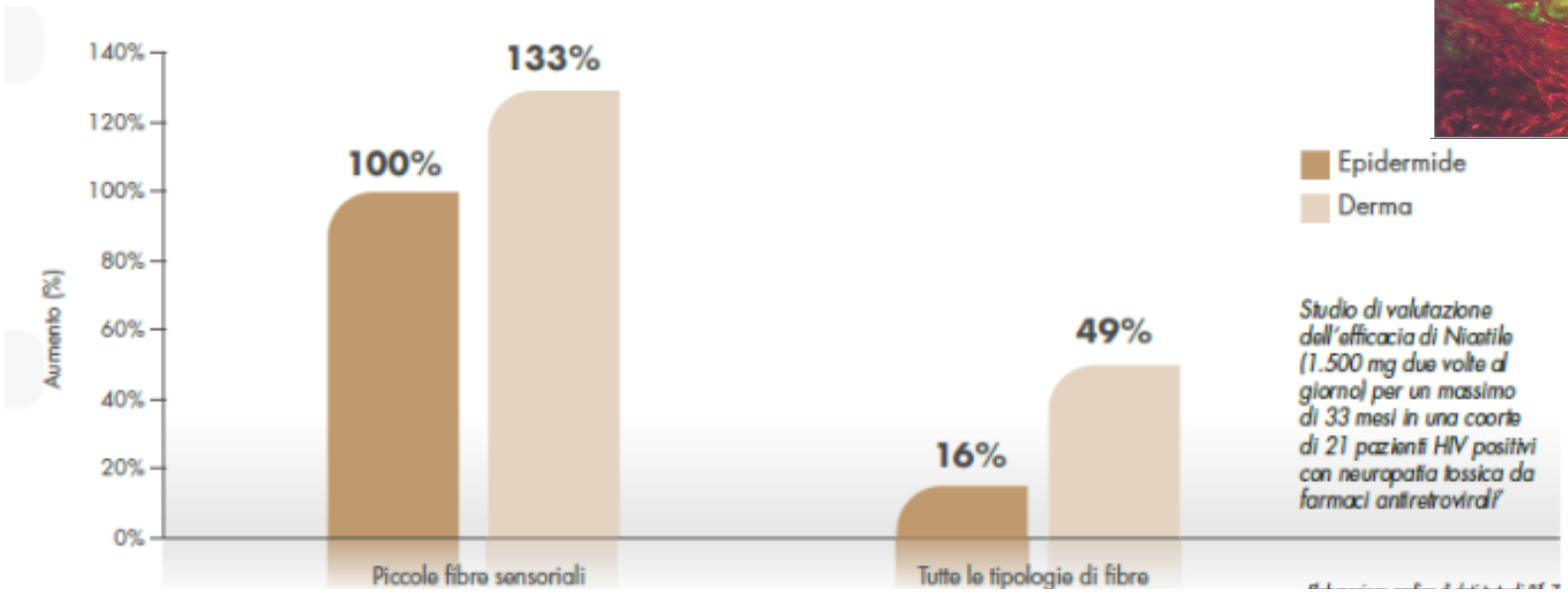


Figure 1. Effect of acetyl-L-carnitine (ALC) on depressive symptoms compared to placebo/no intervention.

L-ACETIL-CARNITINA ha determinato un **incremento significativo** delle **piccole fibre sensitive nel derma e nell'epidermide** (risultati a 6 mesi)





Double-blind, multicenter trial comparing acetyl l-carnitine with placebo in the treatment of fibromyalgia patients

M. Rossini[1], O. Di Munno[2], G. Valentini[3], G. Bianchi[4], G. Biasi[5], E. Cacace[6], D. Malesci[3], G. La Montagna[3], O. Viapiana[1], S. Adami[1]

[1]Rheumatology Unit, University of Verona; [2]Rheumatology Unit, University of Pisa; [3]Rheumatology Unit, University of Naples; [4]Rheumatology Unit, Ospedale "La Colletta", Arenzano; [5]Rheumatology Unit, University of Siena; [6]Rheumatology Unit, University of Cagliari, Italy.

Effetti di L-acetil-carnitina in pazienti con FM

Studio su **102** pazienti con fibromialgia primaria.

Trattamento:

LAC 500 mg per os bid + 500 mg im per 14 gg

LAC 500 mg per os tid per altre 8 settimane

O placebo

LAC ha determinato un **miglioramento significativo** della **depressione** e del **dolore muscolare.**
Si evidenzia anche un effetto positivo sulla **fatigue**

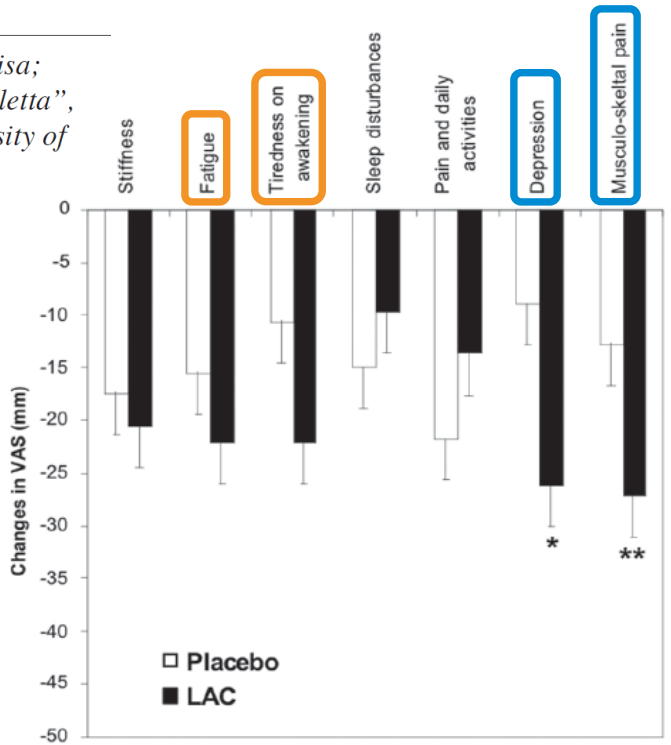


Fig. 3. Changes in VAS score for subjective symptoms from baseline to the end of the treatment.
* $p < 0.05$
** $p < 0.001$

Clinical and Experimental Rheumatology 2007; **25**: 182-188.

Effetti di L-Acetil – Carnitina vs Duloxetina in pazienti con FIBROMIALGIA

A randomised controlled trial comparing duloxetine and acetyl L-carnitine in fibromyalgic patients: preliminary data

P. Leombruni[1], M. Miniotti[1], F. Colonna[1], C. Sica[1], L. Castelli[2], M. Bruzzone[3], S. Parisi[3], E. Fusaro[3], P. Sarzi-Puttini[4], F. Atzeni[5], R.G. Torta[1]

[1]Rita Levi Montalcini Department of Neuroscience, and [2]Department of Psychology, University of Turin, Turin, Italy;
[3]Rheumatology Department, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Turin, Italy;
[4]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy;
[5]IRCCS Galeazzi Orthopaedic Institute, Milan, Italy.

Studio randomizzaro e controllato su **65 pz con fibromialgia primaria.**

Trattamento per **3 mesi** con:

- **Duloxetina 60 mg/die**
- **LAC 1500 mg/die (via orale)**

Le pazienti sono state valutate al basale (T0) e dopo 2 settimane (T1) e 3 mesi (T2) di trattamento.

Leombruni P et al. Clin Exp Rheumatol 2015; 33 (Suppl. 88): S82-S85.

Risultati – efficacia

LAC ha determinato un **miglioramento significativo del tono dell'umore/stato depressivo** (MADRS), **della severità della patologia** (CGI-S) e **del benessere fisico** (componente fisica dell'SF-36).

LAC non ha determinato riduzione significativa dell'intensità del dolore(VAS) (N.B. solo via orale).

Nessuno dei due farmaci ha determinato miglioramento dello stato ansioso.

Table II. Comparison among primary outcomes (pain, depression, clinical improvement) and secondary outcomes (anxiety and well being).

		T0 (SD)	T2 (SD)	*p*-value
VAS				
	Dulo-group	5.70 ± 2.98	3.86 ± 2.68	0.033*
	ALC-group	5.69 ± 2.70	4.51 ± 2.61	0.148
MADRS				
	Dulo-group	19.43 ± 6,27	9.56 ± 4.28	<0.001*
	ALC-group	16.31 ± 6.36)	9.81 ± 3.81	<0.001*
HADS-D				
	Dulo-group	9.17 ± 3.78	7.00 ± 4.03	0.066
	ALC-group	7.45 ± 4.25	8.50 ± 5.00	0.457
CGI-S				
	Dulo-group	4.34 ± 0.57	2.38 ± 1.46	<0.001*
	ALC-group	4.54 ± 0.50	2.36 ± 1.21	<0.001*
HADS-A				
	Dulo-group	9.43 ± 3.97	7.47 ± 4.28	0.115
	ALC-group	7.50 ± 4.27	7.95 ± 5.18	0.755
SF 36 score				
SF 36 Ment	Dulo-group	157.22 ± 81.33	217.48 ± 85.41	0.002*
	ALC-group	201.18 ± 90.41	199.83 ± 108.65	0.939
SF 36 Phys	Dulo-group	129.37 ± 57.02	200.44 ± 80.46	<0.001*
	ALC-group	152.81 ± 88.33	177.10 ± 91.21	0.017*

SD: standard deviation: VAS: Intensity of pain measured by the Visual Analogue Scale; MADRS: Level of Depression measured by Montgomery Asberg Depression Rating Scale; HADS-D: Level of Depression measured by the Depression subscale of the Hospital Anxiety and Depression Scale; CGI-S: Clinical Global Impression- Severity of Illness scale; HADS-A: Level of Anxiety measured by the Anxiety subscale of the Hospital Anxiety and Depression Scale; SF-36 Ment: the mental component summary of the SF-36; SF 36 Physical: the physical component summary of the SF-36. *: $p<0.005$.

Leombruni P et al. Clin Exp Rheumatol 2015; 33 (Suppl. 88): S82-S85.

Effetti di L-Acetil-Carnitina sui sintomi depressivi: Studi di confronto con antidepressivi

LAC è generalmente ben tollerata e può essere associata a tutti gli altri farmaci per la terapia del dolore.

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bersani et al., 2013	-0.238	-0.678	0.202	0.289
Leombruni et at., 2015	0.346	-0.213	0.904	0.225
Zanardi et al., 2006	0.114	-0.168	0.397	0.429
	0.058	-0.224	0.340	0.686

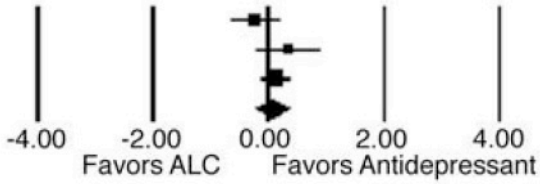


FIGURE 2. Effect of ALC on depressive symptoms compared with antidepressant medications. ALC = acetyl-L-carnitine; CI = confidence interval; Std diff = standardized difference.

3 RCT di **confronto fra LAC e antidepressivi** hanno dimostrato efficacia analoga, ma **migliore tollerabilità di LAC.**

Conclusioni

- Shared decision-making for or against drug therapy
- Tailored selection of drugs according to
  - Key symptoms beyond pain (fatigue, sleep problems)
  - Psychological comorbidities (depressive or anxiety disorder or both)
  - Physical comorbidities (rheumatic disease)
  - Contraindications
  - Individual importance of frequent side effects (for example, weight gain)
- Augment placebo and reduce nocebo response.
- Start low, go slow.
- Monitor for efficacy, tolerability, and safety.
- Progressive treatment reduction in responders
- Consider drug holidays.
- Promote long-term drug-free self-management of the patient.

Programmi interdiscliplinari comprensivi in TEAM

team medico-infermieristico, fisioterapisti, terapisti occupazionali, psicologi……