Atlas
Annual Thinking LAb on Fibromyalgia Syndrome

Come utilizzare le varie classi di farmaci; dall'analgesico al miorilassante e alle nuove prospettive

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Nhow Milano, 30 settembre - 1 ottobre 2022

EULAR revised recommendations for the management of fibromyalgia

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

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

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

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

Working group members

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

Management recommendations flowchart

History and physical exam

↓

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

↓

Patient education and information sheet

↓ ***if insufficient effect***

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

↓ ***if insufficient effect***

Reassessment of patient to tailor individualised treatment

Management recommendations flowchart (continued)

Additional individualised treatment

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

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

Severe pain/ sleep disturbance

→ **Pharmacotherapy**

Severe disability, sick-leave

→ **Multimodal rehabilitation programs**

Severe pain

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

Severe sleep problems

- Low dose Amitriptyline, Cyclobenzaprine or Pregabalin at night

The therapeutic approach

- The therapeutic approach to patients with FM is characterised by **integrated and multidisciplinary interventions**.
- The treatment flowchart should be divided into three pillars:

1) **patient education and fitness**

2) **pharmacological and nonpharmacological treatment**

3) **psychotherapy**

Patient education

- It is important to **ensure that FM patients understand their illness** before they are prescribed any medications.
- It is crucial to **reassure patients that FM is a real pathological condition and to legitimise their suffering**, making it clear that, although invalidating, it is not progressive and is not due to peripheral tissue damage.
- Then, **patients should also be told that they will play a predominant role in FM management**, and should develop their own particular techniques and approaches in order to maximise their quality of life

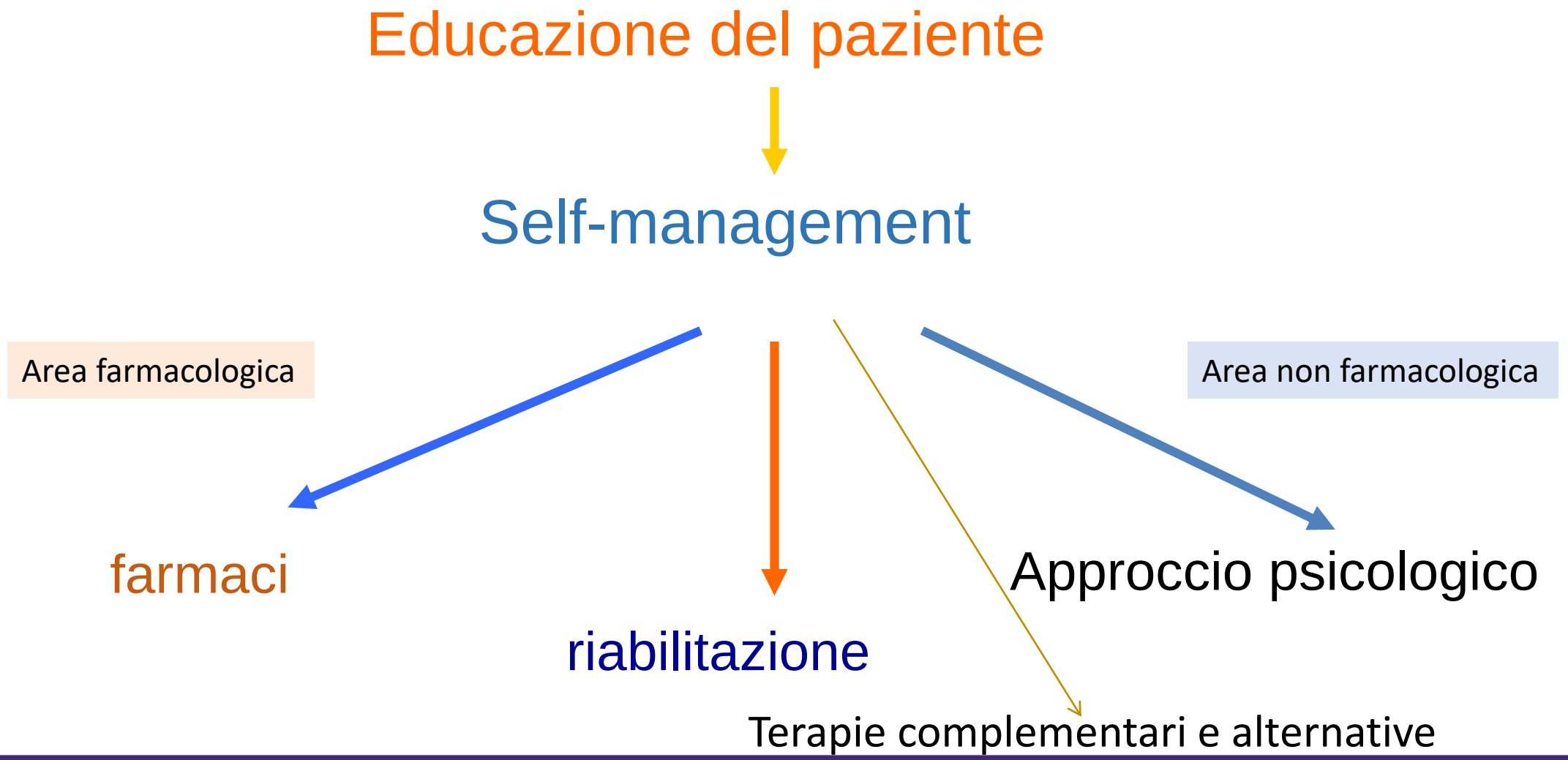
Patient education (2)

- This is paradigmatic of the **“self-management”** that should be used in the case of any chronic condition.
- Moreover, as stress, mood and sleep disturbances play an important role in FM, patients should be encouraged **to learn good sleep hygiene and relaxation techniques, and take part in formal stress reduction programmes, including psychiatric consultations if necessary**

Patient education (3)

- Patients can be encouraged **to continue non-pharmacological measures** on the basis of their individual needs as long as they do not cause any harm.
- **Pharmacological treatment may be helpful in relieving some symptoms**, but patients rarely improve substantially without adopting these core self-management strategies.

Approccio multidisciplinare



La finestra terapeutica

Efficacia clinica

Effetti collaterali

Può essere molto stretta

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

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

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

Inoltre…

Farmaci utilizzati in relazione ai differenti sintomi

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

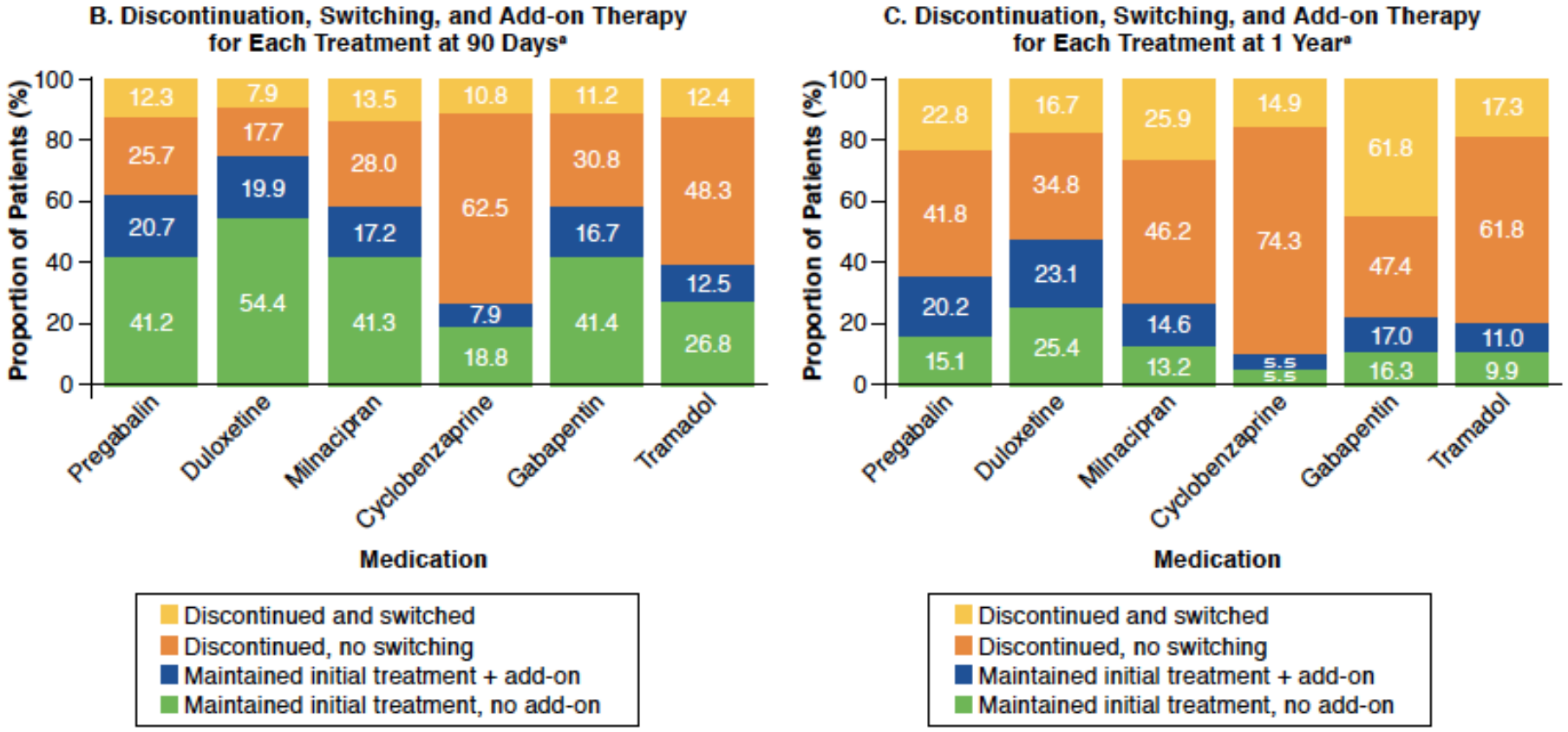
SSRIs = inibitori selettivi della ricaptazione della serotonina; SNRIs = inibitori della ricaptazione della serotonina e della noradrenalina; I-MAO = inibitori delle monamino-ossidasi; FANS = antinfiammatori non steroidei

Manuale pratico per il paziente affetto da sindrome fibromialgica

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

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

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



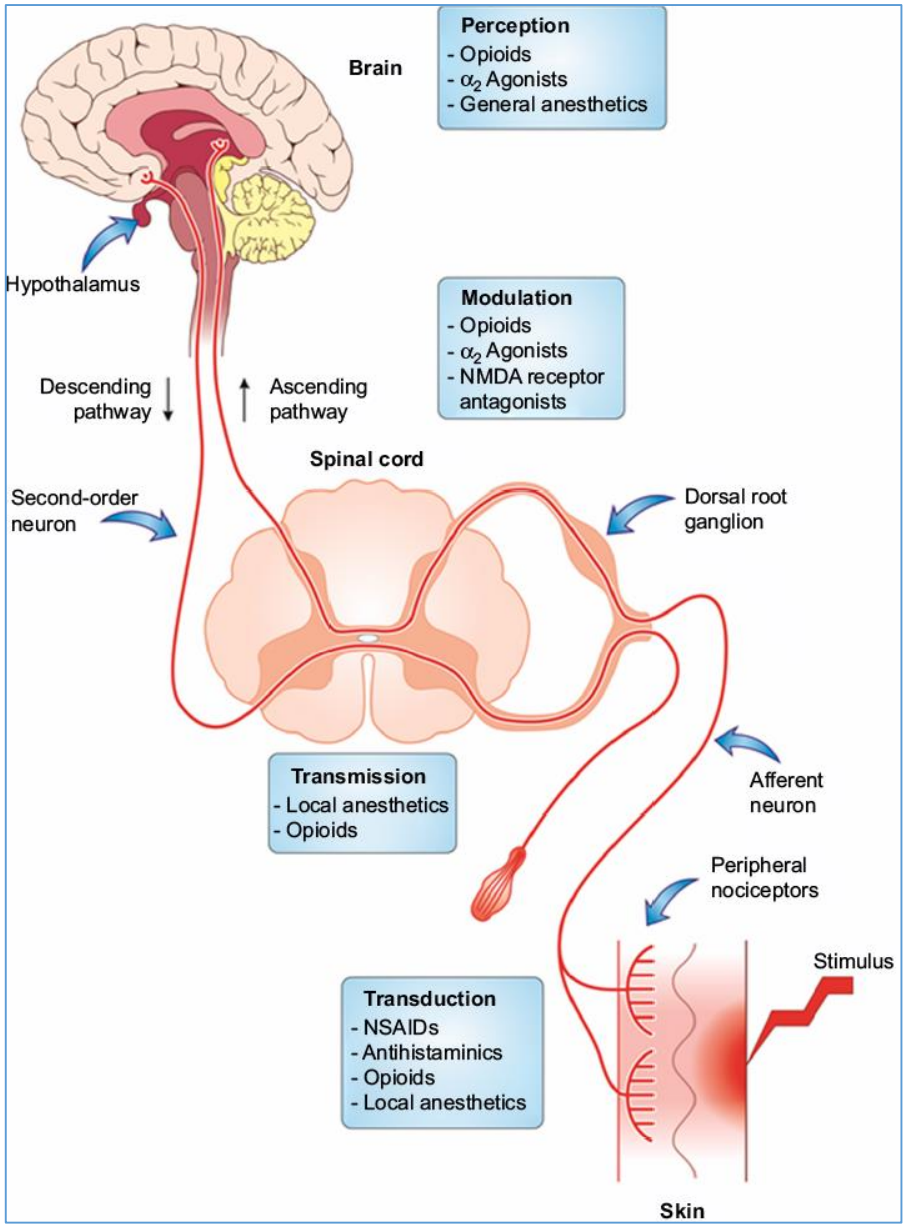
[a]*Switches and add-on therapies were tracked within the 6 medications of interest only.*

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

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

Come utilizzare i farmaci

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



Quali farmaci utilizzare?

Farmaci piu comunemente utilizzati in FM; in rosso quelli approvati dall' FDA

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

Trattamento del dolore cronico: basato sul meccanismo patogenetico

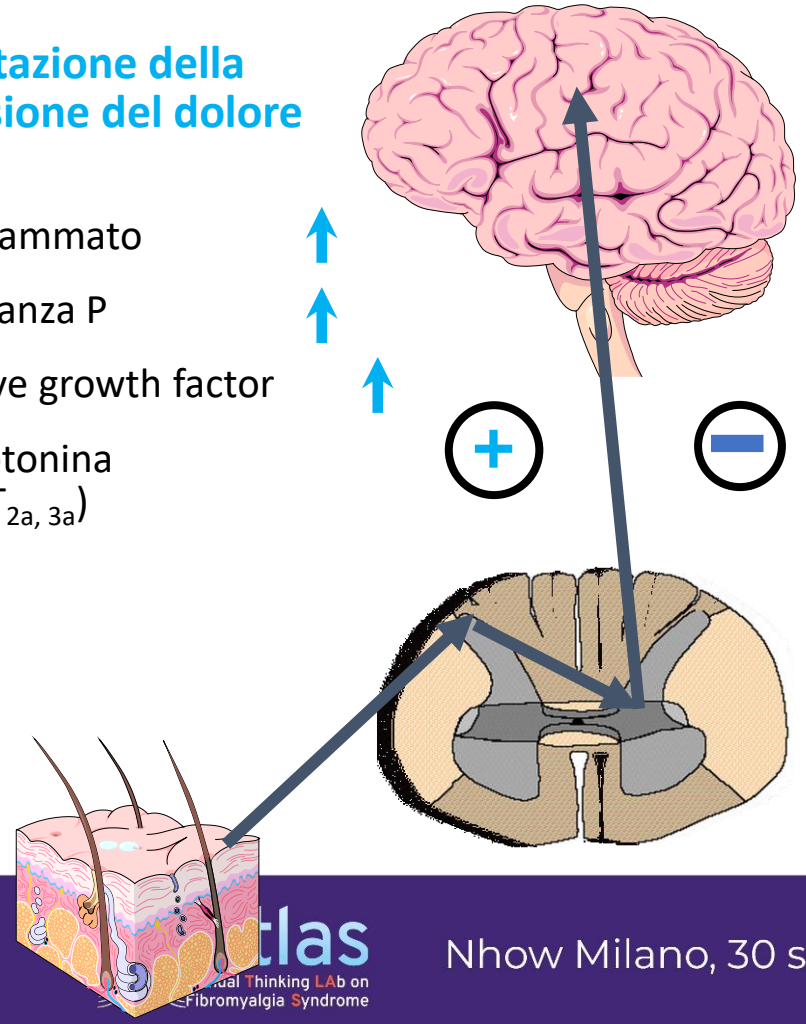
Schmidt-Wilcke T, Clauw DJ. *Nat Rev Rheumatol.* Jul 19 2011.
Clauw DJ. JAMA. 2014.

Facilitazione della Trasmissione del dolore

- Glutammato
- Sostanza P
- Nerve growth factor
- Serotonina ($5HT_{2a,\ 3a}$)

Gabapentinoidi ketamina, memantina

ciclobenzaprina



Inibizione della Trasmissione del dolore

- Vie discendenti antinocicettive
  - Norepinefrina serotonina ($5HT_{1a,b}$), dopamina
  - Oppioidi
- Cannabinoidi
- GABA

Triciclici, SNRIs. tramadolo

Naltrexone a basse dosi

Gammahydroxybutyrate, consumo moderato di alcol

STRATEGIA TERAPEUTICA RACCOMANDATA

Treatment (review reference)	No. of trials (no. of participants) Review quality	Dosages; durations of treatment	Overall trial quality*	Safety and comments
Amitriptyline[12]	10 (767) AMSTAR=6	10–50 mg/day; 8–24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.
Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High	Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies
Growth hormone[16]	2 (74) AMSTA			
MAOIs[26]	3 (241) AMSTA			
NSAIDs[21]	2 (242) AMSTA			
SNRIs—duloxetine[31]	6 (2249 AMSTAR=10			than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no
SSRIs[36]	7 (322) AMSTAR			
Sodium oxybate[16]	5 (1535) AMSTAR			
Tramadol[22]	1 (313) AMSTAR=3	3 months		adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and

Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High
Tramadol[22]	1 (313) AMSTAR=3	37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months	High
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High
SSRIs[36]	7 (322) AMSTAR=8	20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks	Moderate to high

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

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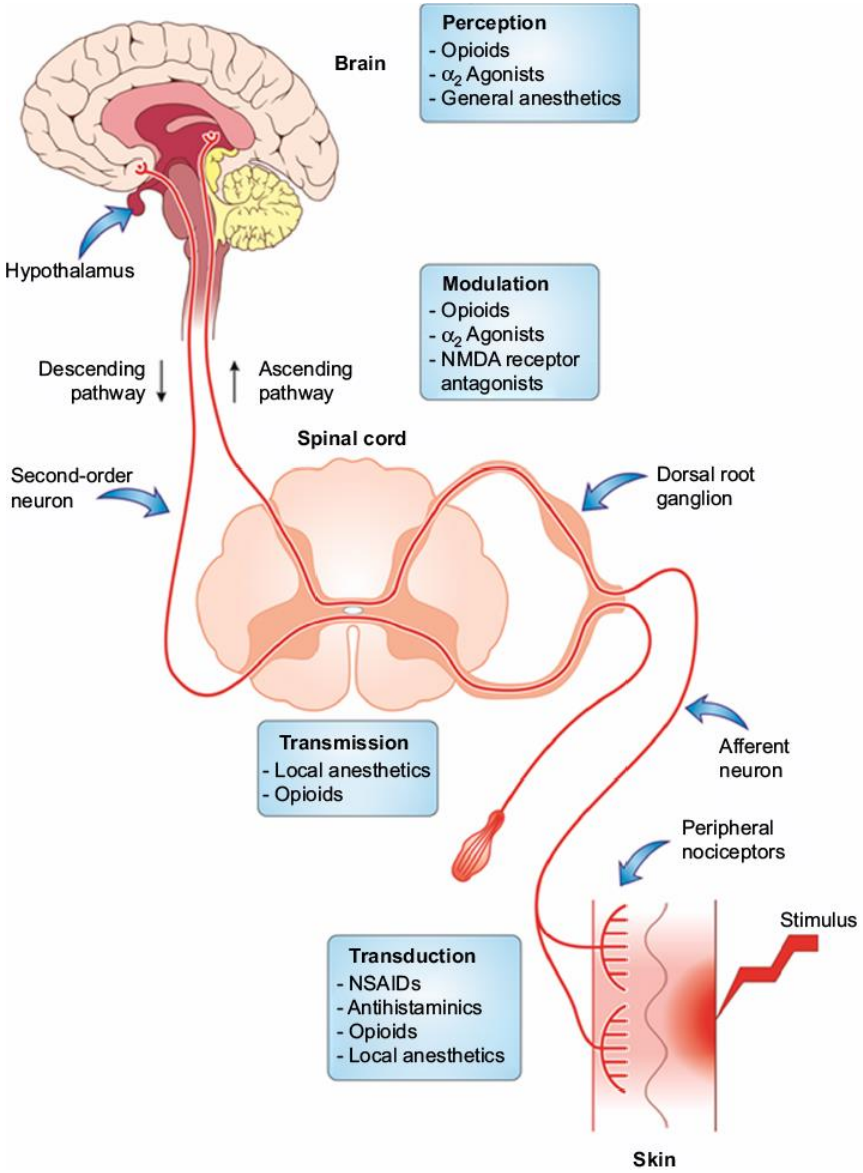
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.
Growth hormone[16]	2 (74) AMSTAR=5	0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year	NE	Safety concerns include sleep apnoea and carpal tunnel syndrome.
MAOIs[26]	3 (241) AMSTAR=9	Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs[21]	2 (242) AMSTAR=7	Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
SNRIs—duloxetine[31]	6 (2249) AMSTAR=10	20–120 mg/day; 12–28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events.
SSRIs[36]	7 (322) AMSTAR=8	20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks	Moderate to high	Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser *et al*[86] showed a small effect of SSRIs in improving depressed mood (SMD −0.37, 95% CI −0.66 to −0.07).
Sodium oxybate[16]				
Tramadol[22]				discontinuation rate in a double-blind phase compared with placebo.[21]

SNRIs—duloxetine[31] 6 (2249) AMSTAR=10 20–120 mg/day; 12–28 weeks Moderate

Cyclobenzaprine[25] 5 (312) AMSTAR=7 10–40 mg; 2–24 weeks Moderate

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



Farmaci Antidepressivi

"Evidence and consensus recommendations for the pharmacological management of pain in India". Journal of Pain Research,

FMS: TERAPIA FARMACOLOGICA

AMITRIPTILINA (Laroxyl®)

- LG: EULAR, Canadian, AWMF
- Dosaggio: 10-75 mg/die (massimo 150 mg/die)
- NNT: 4.6 (3.6-6.6)
- NNH: non disponibile
- RISULTATI: miglioramento FIQ >30%, migliora dolore, stanchezza, sonno

Vantaggi: attivo sulla depressione

Effetti collaterali: sedazione, ritenzione urinaria, stipsi, aritmie, vertigini, ipotensione ortostatica

Tzadok R et al, Pain Res Manage 2020

FMS: TERAPIA FARMACOLOGICA

DULOXETINA (Cymbalta®, Xeristar®)

- LG: FDA approved
- Dosaggio: 30-60 mg/die (massimo 120 mg/die)
- NNT: 8 (5-17)
- NNH: 15 (11-25)
- RISULTATI: miglioramento dolore e depressione

Vantaggi: attivo sulla depressione

Effetti collaterali: nausea, vertigine e sonnolenza

Controindicazioni: mania/disturbo bipolare

Tzadok R et al, Pain Res Manage 2020

FMS: TERAPIA FARMACOLOGICA

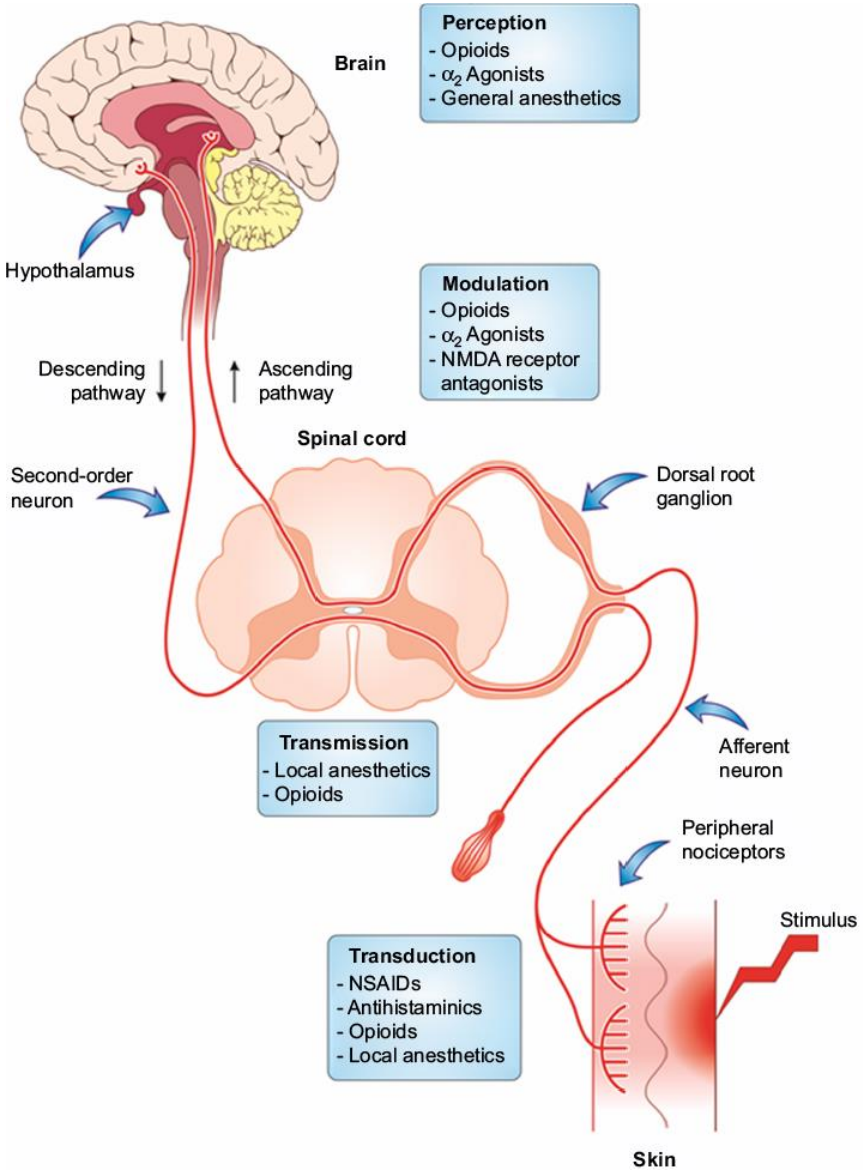
SSRI (Citalopram, escitalopram, fluoxetina, paroxetina, sertralina)

- LG: EULAR, Canadian, AWMF
- Dosaggio: vari a seconda delle molecole
- RISULTATI: migliorano in maniera modesta dolore, depressione e QoL, non risultati sostanziali sul sonno

Antagonisti NMDA (Ketamina, memantina)

- Dosaggio: vari a seconda delle molecole
- RISULTATI: migliorano il dolore ma le evidenze attuali riportano risultati limitati e elevata incidenza di effetti collaterali

Tzadok R et al, Pain Res Manage 2020



Farmaci Anticonvulsivanti

"Evidence and consensus recommendations for the pharmacological management of pain in India". Journal of Pain Research,

FMS: TERAPIA FARMACOLOGICA

GABAPENTINOIDI (PREGABALIN, GABAPENTIN)

- LG: EULAR, Canadian, AWMF, FDA approved
- Dosaggio:
  - Pregabalin 300-450 mg/die (max 600 mg/die)
  - Gabapentin 300-900 mg/die (max 3600 mg/die)
- NNT: 10 (7.4-16)
- NNH: 6
- RISULTATI: miglioramento di dolore, stanchezza, sonno e QoL, nessun effetto su ansia e depressione

Effetti collaterali: vertigini, sonnolenza, edemi periferici

Tzadok R et al, Pain Res Manage 2020

Effetti Collaterali

TCA:

- Associated with an **increased risk of falls** and non- vertebral fracture among geriatric patients due to **increased sedation**
- Fluid and electrolyte disturbances are uncommon
- Strongly associated with **prolonged QT intervals and torsade de pointes** possibly by blocking potassium channels in the myocyte membrane
- Associated with **dementia exacerbation**
- Minimal Bleeding risk
- TCAs are strong antagonists of H1 histamine adrenergic (i.e. alpha and beta) and cholinergic (i.e. muscarinic) receptor

Geriatric Nursing 34 (2013) 53e61

Effetti Collaterali

SNRIs:

- **Hyponatremi**a, especially with increasing patient age or venlafaxine
- May be inappropriate for geriatric patients with heart failure, especially duloxetine, possibly from increased levels of norepinephrine leading **to tachycardia, myocardial ischemia, cardiac failure**
- Minimal extrapyramidal symptoms
- Interference with serotonin receptors **can affect platelet aggregation**
- Relatively low level of sedation
- Mild anticholinergic effect including increased **somnolence and fatigue**

Geriatric Nursing 34 (2013) 53e61

Effetti Collaterali

SSRI:

- With the exception of fluoxetine, **SSRIs are not associated With falls**
- **Hyponatremia,** especially within the first 30 days of therapy, is related to vasopressin release from activation of serotonin-2 and -1C receptors
- **Confusion and fatigue** may be the first indication of an electrolyte imbalance in older adults
- While generally safe for patients with cardiovascular comorbidities, there are reports of **dysrhythmias possibly due to inhibition of cardiovascular ion channels**
- Elderly patients are more likely to develop **dyskiinesia** and tardive dyskinesia as opposed to tremor, akathisia, and dystonia
- **Mild anti-platelet action** that potentiates other antiplatelet drugs, especially within the first month of treatment
- **Minimal Restlessness and sedation** are common adverse effects of SSRIs in elderly patients, especially within the first few days of therapy and the first 3 months of therapy

Geriatric Nursing 34 (2013) 53e61

Effetti Collaterali

SINDROME SEROTONINERGICA:

La sindrome serotoninergica può verificarsi durante un uso terapeutico di farmaci, auto-avvelenamento, o, più comunemente, interazioni farmacologiche involontarie qualora vengano assunti 2 farmaci serotoninergici contemporaneamente

Nella maggior parte dei casi, la sindrome da serotonina si manifesta entro 24 h, in genere entro le 6 h, dalla variazione di un dosaggio o dalla somministrazione iniziale di un farmaco

SINTOMI:

- Alterazioni dello stato mentale: ansia, agitazione psicomotoria e irrequietezza, facilità allo spavento, delirium
- Iperattività autonomica: tachicardia, ipertensione, ipertermia, diaforesi, brividi, vomito, diarrea
- Iperattività neuromuscolare: tremore, ipertonia o rigidità muscolare, mioclono, iperreflessia, clono (incluso il clono oculare), risposte degli estensori plantari

Boyer EW, Shannon M : The serotonin syndrome. N Engl J Med 352(11):1112-20, 2005. doi:

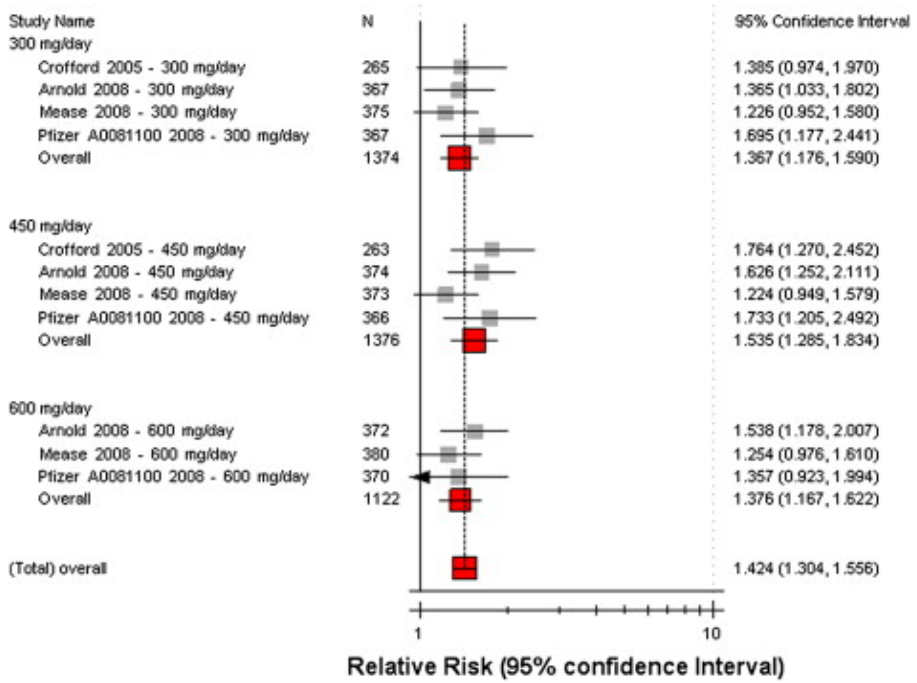
QUALI FARMACI ed POSOLOGIA

Systematic Review of the Comparative Effectiveness of Antiepileptic Drugs for Fibromyalgia

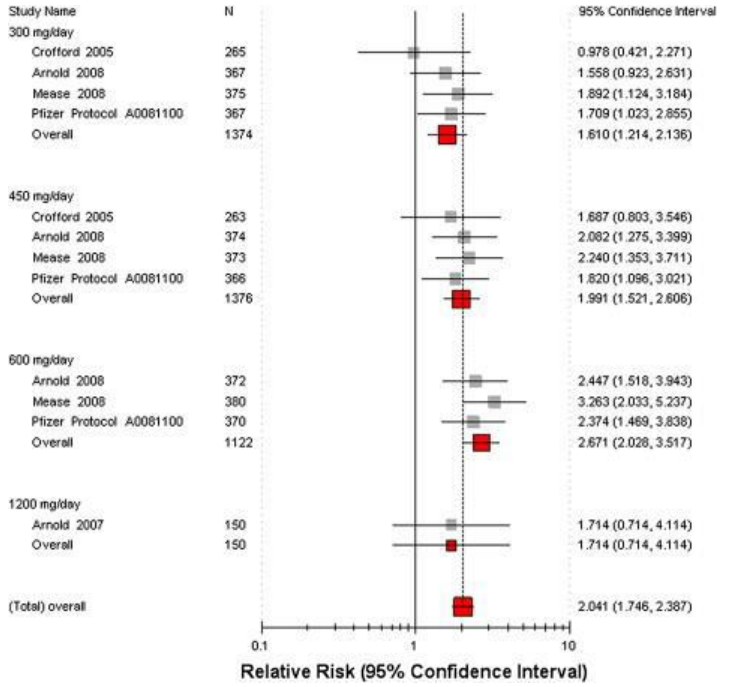
Anne Chamberlin Siler, Hallie Gardner, Keenan Yanit, Tera Cushman, and Marian McDonagh

Oregon Health & Science University, School of Medicine, Portland, Oregon.

PREGABALIN
Fino a 450mg/die suddiviso in 2-3 somministrazioni



GABAPENTIN
Da 300 a 1200mg/die suddiviso in 2-3 somministrazioni



Effetti Collaterali

Sonnolenza (30-45%)
dose-correlato, insorgenza 1-2 giorni, durata 18-88 giorni
meccanismo responsabile non chiarito

Vertigini (40-50%) dose-relato, insorgenza 1-2 giorni, durata 4-44 giorni meccanismo responsabile non chiarito

Altri sintomi SNC: visione offuscata, cefalea, disturbi dell'equilibrio, disturbi cognitivi

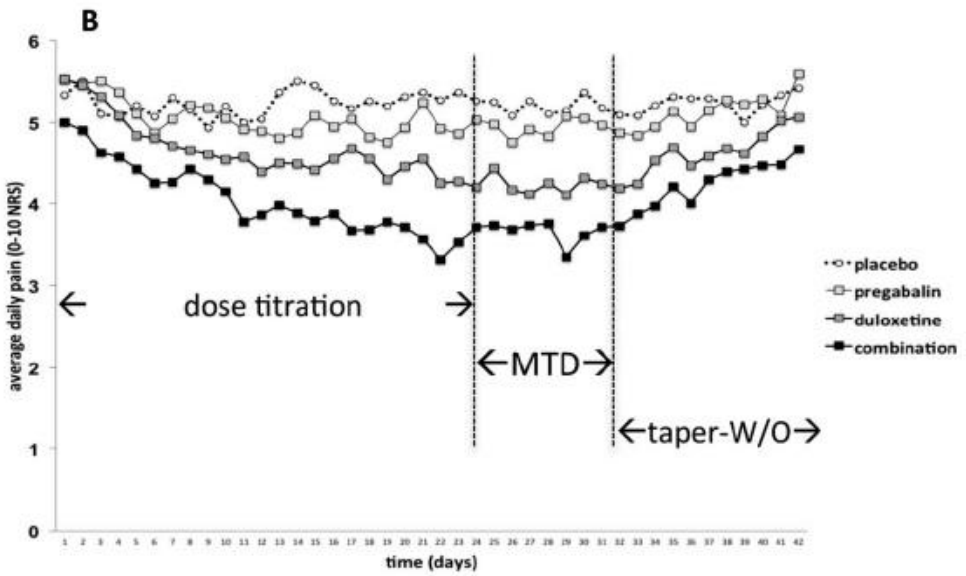
Edema periferico (8-11%)
meccanismo responsabile non chiarito
nessuna associazione con disturbi cardiaci o renali

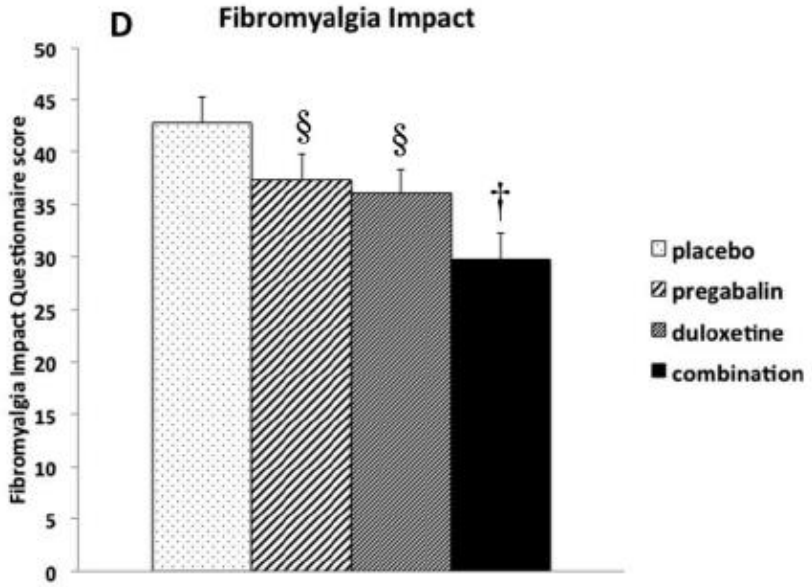
Aumento ponderale (14%)

Gravidanza: Classe C (farmaci che causano, o si ha il sospetto che causino, effetti dannosi al feto o al neonato, potenzialmente reversibili, non malformativi)

FMS: TERAPIA FARMACOLOGICA

Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial





Gilron I et al, Pain 2016

FMS: TERAPIA FARMACOLOGICA

CICLOBENZAPRINA (Flexiban®)

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

TIZANIDINA (Sirdalud®)

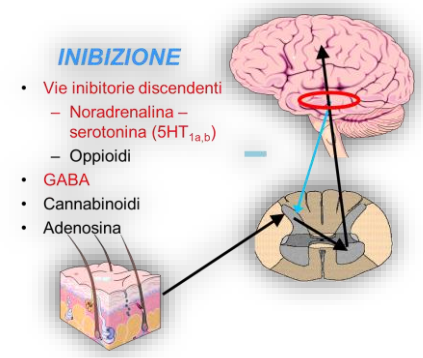
- Dosaggio: 2-12 mg/die
- NNT e NNH: **non disponibili**
- **RISULTATI**: <u>modesti</u> (pochissimi studi)
- **Effetti collaterali**: sonnolenza, secchezza delle fauci, vertigini, stanchezza

Tzadok R et al, Pain Res Manage 2020

Ciclobenzaprina

Strutturalmente correlato agli antidepressivi triciclici, dotato sia di un azione decontratturante che analgesica diretta.

Potenzia l'attività delle **vie sovraspinali discendenti** coinvolte nell'inibizione dello stimolo doloroso, dall'altro espleta la propria attività **decontratturante** riducendo a monte l'attivazione dei motoneuroni alfa e gamma, probabilmente attraverso un meccanismo di potenziamento dell'attività GABAergica dei recettori centrali, che si concretizza nella riduzione locale dei neurotrasmettitori eccitatori.



Ciclobenzaprina

Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate

E’ presente nella raccomandazioni EULAR 2016 con evidenza IA e grado A

Effetti Collaterali più frequenti:
sonnolenza, secchezza delle fauci e vertigini

FMS: TERAPIA FARMACOLOGICA

Oppiacei deboli (tramadolo)

- LG: EULAR
- Dosaggio: non determinato (riportato da 37.5 a 400 mg/die)
- NNT e NNH: non disponibili
- RISULTATI: migliora il dolore >30%

Oppiacei forti

- LG: against or strong against
- Dosaggio: vari
- NNT e NNH: non disponibili
- RISULTATI: non evidenze di efficacia dai trials clinici, RISCHIO ADDICTION

Tzadok R et al, Pain Res Manage 2020

FMS: TERAPIA FARMACOLOGICA

CANNABINOIDI (preparazioni varie)

- LG: Canadian
- Dosaggio e preparazioni: varie
- NNT e NNH: non disponibili
- RISULTATI: riduzione significativa nel dolore, miglioramento del sonno e depressione in uno studio prospettico su 367 pazienti (Sagy I et al, 2019). Ulteriori studi necessari

ENDOCANNABINOIDI (PEA)

- Dosaggio e preparazioni: um-PEA 900 mg per 2/die
- NNT e NNH: non ancora disponibili
- RISULTATI: miglioramento significativo nel dolore e nella QoI in uno studio prospettico su 359 pazienti (Schweiger V et al, 2019). In corso RCT verso placebo

Tzadok R et al, Pain Res Manage 2020

Cannabinoids

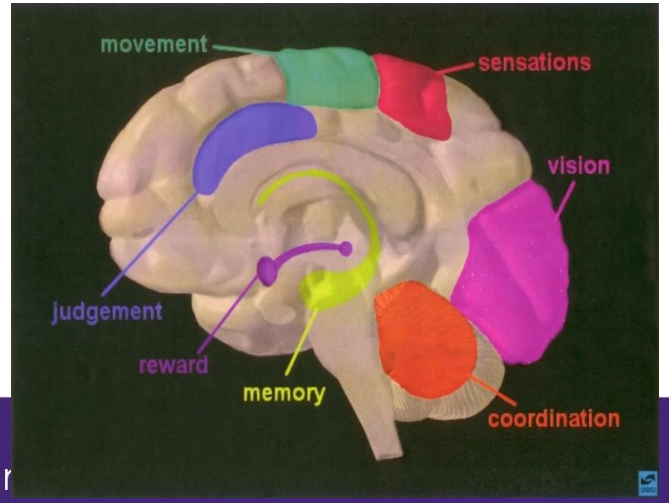
- PhytoCanabinoids → Herbal Cannabis → More than 120 active ingredients

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

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

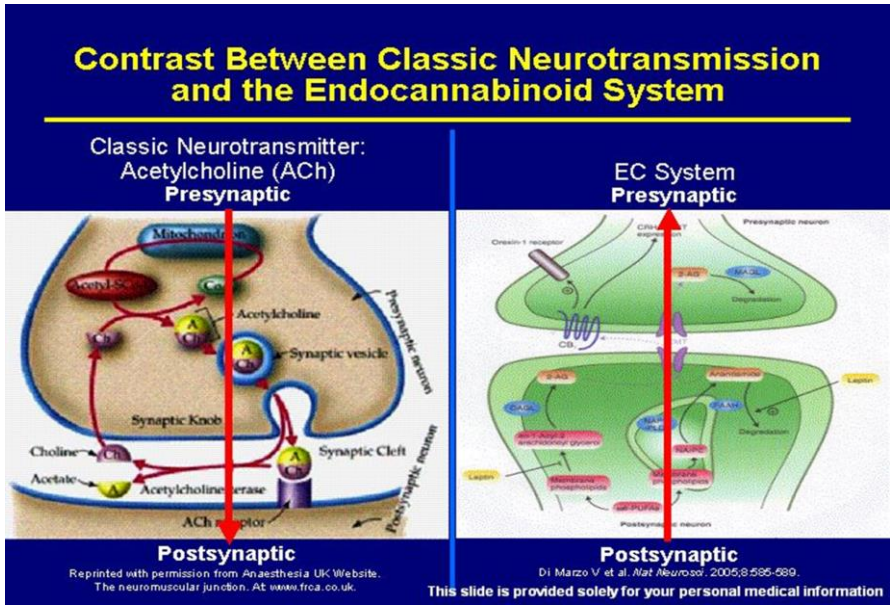
Pharmacological actions of THC

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



Pharmacological Effects of CBD

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



Adding medical cannabis to standard analgesic treatment for fibromyalgia: a prospective observational study

V. Giorgi[1], S. Bongiovanni[1], F. Atzeni[2], D. Marotto[3], F. Salaffi[4], P. Sarzi-Puttini[1]

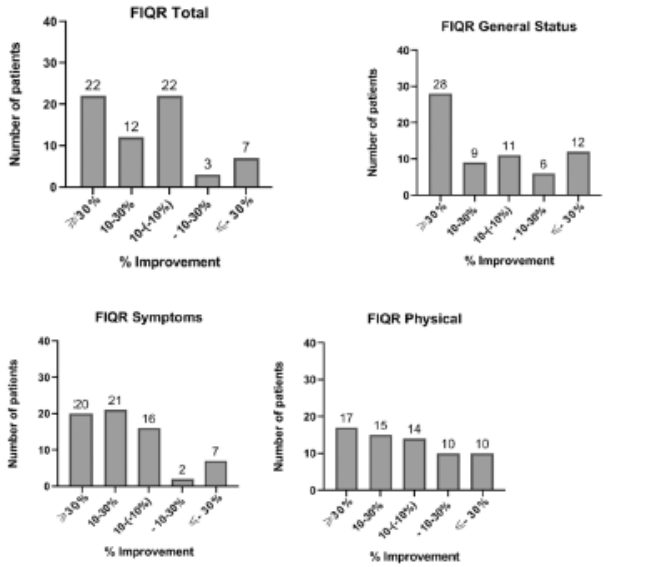


Fig. 4. The number of patients in each FIQR outcome group. A ≥30% improvement was considered significant.

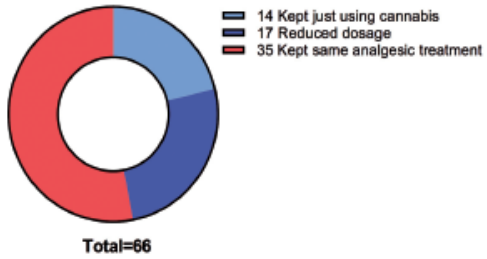


Fig. 5. Changes in the concomitant analgesic treatment of the patients completing the study.

The 6-month retention rate was 64%.

A significant improvement in the PSQI and FIQR was observed in respectively 44% and 33% of patients.

50% showed a moderate improvement in the anxiety and depression scales.

Multiple regression analysis showed a correlation between the body mass index (BMI) and FIQR improvement (p=0.017).

Concomitant analgesic treatment was reduced or suspended in 47% of the patients.

One-third experienced mild adverse events, which did not cause any significant treatment modifications

Clin Exp Rheumatol 2020; 38 (Suppl. 123): S53-S59.

A Systematic Review of Atypical Antipsychotics in Chronic Pain Management

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

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

AAs are second-generation antipsychotic agents used in the treatment of psychotic and affective (mood) disorders. On the basis of pharmacological properties, AAs are classified into:

(1) **serotonin-dopamine antagonists**, which show high affinity for 5-HT2A and D2 receptors as well as affinity for alpha-1 adrenoreceptors (ie, risperidone, paliperidone, ziprasidone, iloperidone, lurasidone);

(2) **multiacting receptor–targeted antipsychotics which act on multiple receptors** such as 5-HT2A, D2, 5HT1A, 5HT1C, cholinergic, histaminergic, and other receptors (eg, clozapine, olanzapine, quetiapine, asenapine);

(3) **combined D2/D3 receptor antagonists which preferentially block D2 and D3 receptors** (ie, amisulpride);

(4) **partial dopamine receptor agonists** (ie, aripiprazole and cariprazine).

Clin J Pain 2018;34:585–591

Antipsychotics for Fibromyalgia in Adults

The NNT Group rating system:

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

Antipsychotics for Fibromyalgia in Adults

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

Naltrexone

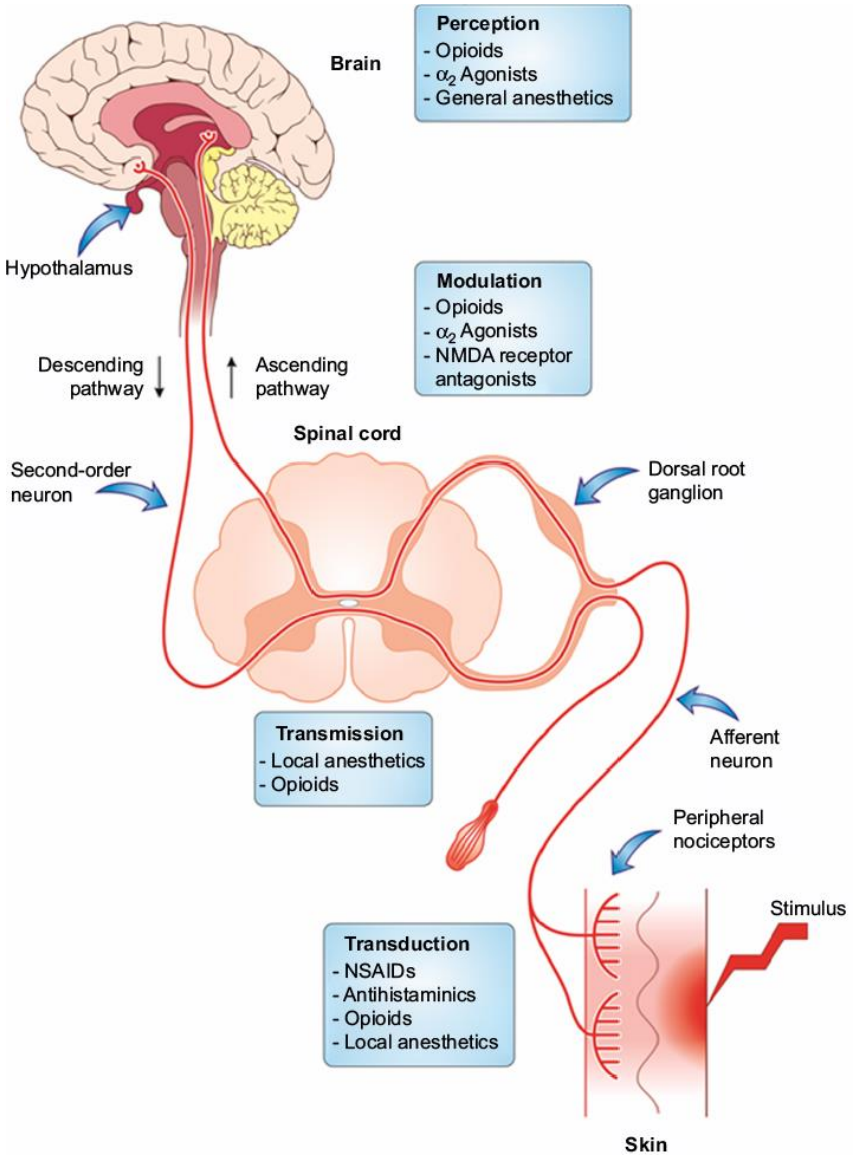
- **Naltrexone, an opioid antagonist**, has achieved promising results in Fm related pain due to the increase in the endorphinergic tone related to the transient blockade of opioid receptors in the central nervous system.
- Naltrexone simultaneously has an antagonist effect on nonopioid receptors (Toll-like receptor 4 or TLR4) that are found on macrophages such as microglia (**new class of therapeutic agents called glial cell modulators**)
- some pilot studies evidenced **a good profile of efficacy and safety of this drug in the FM setting**

Metyas S, Chen CL, Yeter K, Solyman J, Arkfeld DG. Low Dose Naltrexone in the Treatment of Fibromyalgia. Curr Rheumatol Rev. 2018;14(2):177-180

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

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

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



Analgesici e FANS

" Evidence and consensus recommendations for the pharmacological management of pain in India". Journal of Pain Research,

FANS

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults

Sheena Derry[1], Philip J Wiffen[2], Winfried Häuser[3], Martin Mücke[4], Thomas Rudolf Tölle[5], Rae Frances Bell[6], R Andrew Moore[7]

[1]Oxford, UK. [2]Thame, UK. [3]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, München, Germany. [4]Department of Palliative Medicine, University Hospital of Bonn, Bonn, Germany. [5]Department of Neurology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany. [6]Regional Centre of Excellence in Palliative Care, Haukeland University Hospital, Bergen, Norway. [7]Plymouth, UK

Contact address: R Andrew Moore, Plymouth, UK. andrew.moore@omkltd.org.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 2, 2020.

- The latest search was in January 2017. Six studies satisfied the inclusion criteria, randomising 292 participants to treatment with NSAID or placebo. NSAIDs tested were etoricoxib 90 mg daily, ibuprofen 2400 mg daily, naproxen 1000 mg daily, and tenoxicam 20 mg daily; 146 participants received NSAID and 146 placebo. Study duration was between three and eight weeks.
- We found no difference between NSAID or placebo for a range of outcomes.
- The very low-quality evidence and the lack of any obvious benefit mean that NSAIDs cannot be regarded as useful for the management of fibromyalgia.

OPPIODI

REVIEW

MAYO CLINIC

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Opioid Use in Fibromyalgia: A Cautionary Tale

Don L. Goldenberg, MD; Daniel J. Clauw, MD; Roy E. Palmer, DPhil; and Andrew G. Clair, PhD

TABLE 2. Outcome Data on the Use of Opioid Analgesics in Fibromyalgia

Study design	Sample (No.)	Regimen, type of opioid(s), and number of patients	Study duration (y)	Main outcomes	Reference, year
Single center, prospective, longitudinal	131	43 opioid users and 88 nonopioid users	2	Pain severity scores at 2 y were significantly better in nonopioid vs opioid users, as measured by VAS ($P<.05$) and MPQ ($P<.01$) Scores for measures of patient function, including PGA, FIQ, and HAQ, were all significantly better ($P<.05$) in nonopioid vs opioid users at 2 y	Fitzcharles et al,[56] 2013
Multicenter, prospective, observational	1700	412 opioid users (including concurrent tramadol) and 1056 nonopioid users	1	Improvements in BPI-S scores not significantly different between cohorts Significant improvements in scores for BPI-I, FIQ, ISI, SDS, and PHQ-8 (all $P<.05$) for nonopioid vs opioid cohorts	Peng et al,[57] 2015

BPI-I = Brief Pain Inventory-Interference; BPI-S = Brief Pain Inventory-Severity; FIQ = Fibromyalgia Impact Questionnaire; HAQ = Health Assessment Questionnaire; ISI = Insomnia Sleep Index; MPQ = McGill Pain Questionnaire; PGA = patient global assessment; PHQ-8 = 8-item Patient Health Questionnaire; SDS = Sheehan Disability Scale; VAS = visual analog scale.

- The mechanism of action of traditional opioids predicts their lack of efficacy in FM, and there is no evidence from clinical trials that opioids are effective for the treatment of FM.

OPPIODI


REVIEW

MAYO CLINIC

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Opioid Use in Fibromyalgia: A Cautionary Tale

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- FM guidelines recommend against the use of opioid analgesics.

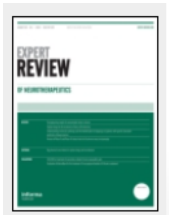
TRAMADOLO

Treatment (review reference)	No. of trials (no. of participants) Review quality	Dosages; durations of treatment	Overall trial quality*	Safety and comments
Amitriptyline[12]	10 (767) AMSTAR=6	10–50 mg/day; 8–24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.
Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High	Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.
Growth hormone[16]	2 (74) AMSTAR=5	0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year	NE	Safety concerns include sleep apnoea and carpal tunnel syndrome.
MAOIs[26]	3 (241) AMSTAR=9	Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs[21]	2 (242) AMSTAR=7	Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
SNRIs—duloxetine[31]	6 (2249) AMSTAR=10	20–120 mg/day; 12–28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no
SSRIs[36]	7 (322) AMSTAR			
Sodium oxybate[16]	5 (1535) AMSTAR			
Tramadol[22]	1 (313) AMSTAR=3	3 months		adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo.[21]

Tramadol[22]	1 (313) AMSTAR=3	37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months	High

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

TRAMADOLO



Drug Profile

Tramadol for the treatment of fibromyalgia

Ashley JB MacLean & Thomas L Schwartz

Pages 469-475 | Published online: 20 Apr 2015

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

SYSTEMATIC REVIEW

Tramadol for management of fibromyalgia pain and symptoms: Systematic review

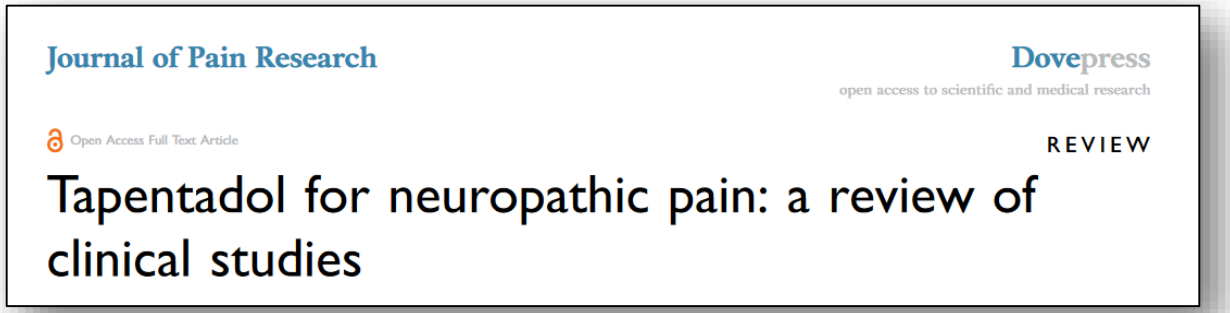
Aline Pereira da Rocha, Carolina Christianini Mizzaci, Ana Carolina Pereira Nunes Pinto, Alexia Gabriela da Silva Vieira, Vinicius Civile, Virgínia Fernandes Moça Trevisani,

First published: 04 December 2019 | https://doi.org/10.1111/ijcp.13455 | Citations: 6

Tramadol has a fair evidence base to support its off-label use in treating fibromyalgia.

Its application should be considered in more treatment-resistant or refractory cases of fibromyalgia.

TAPENTADOLO



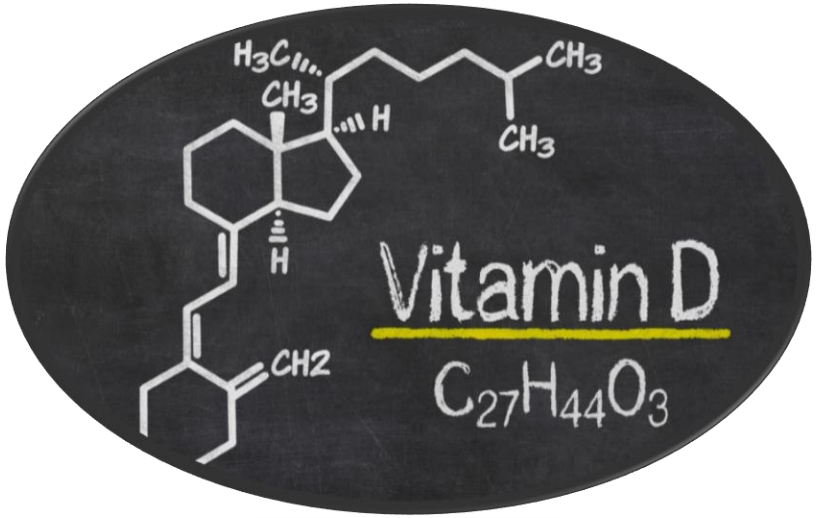
In randomized controlled trials, tapentadol has proved to be effective in relieving NP in diabetic peripheral neuropathy and in chronic low back pain.

In observational studies, tapentadol reduced NP in chemotherapy-induced peripheral neuropathies, blood and solid cancers, and the NP component in neck pain and Parkinson's disease.

No RCT up to know specific for Fibromyalgia

Vitamina D e fibromialgia

- Non c'è attualmente consenso riguardo l'associazione tra vitamina D e fibromialgia sebbene una recente metanalisi evidenzi come i **livelli sierici di vitamina D siano significativamente inferiori nei soggetti fibromialgici rispetto al controllo (Makran A. H., 2017)**



Nutraceutici nella FM

Diversi nutraceutici possono essere interessanti nel trattamento del paziente fibromialgico:

- **Acetyl L carnitina per os** (1000-1500 mg/day) (*)
- Pea (palmitoiletanolamide) (600-1200)
- Acido alfa lipoico (1200-1800 mg/day)
- **Coenzima Q** (200-300 mg/day)
- Vitamina D
- **Creatina** (dose di carico a seguire dose di mantenimento)
- Probiotici
- Magnesio
- **Gingko Biloba** (240 mg /day; titolo 24% gingko flavoni; 6% terpeni)

L'impiego dei nutraceutici in questi pazienti in genere è molto compliante (non sono farmaci né tantomeno psicofarmaci) ed è in linea con l'approccio soft alla fibromialgia previsto dalla linee guida EULAR

* In Italia l'acetyl l carnitina è considerata integratore alimentare fino ad un dosaggio di 1 gr gg oltre il quale è dosaggio farmacologico

Problemi Attuali…

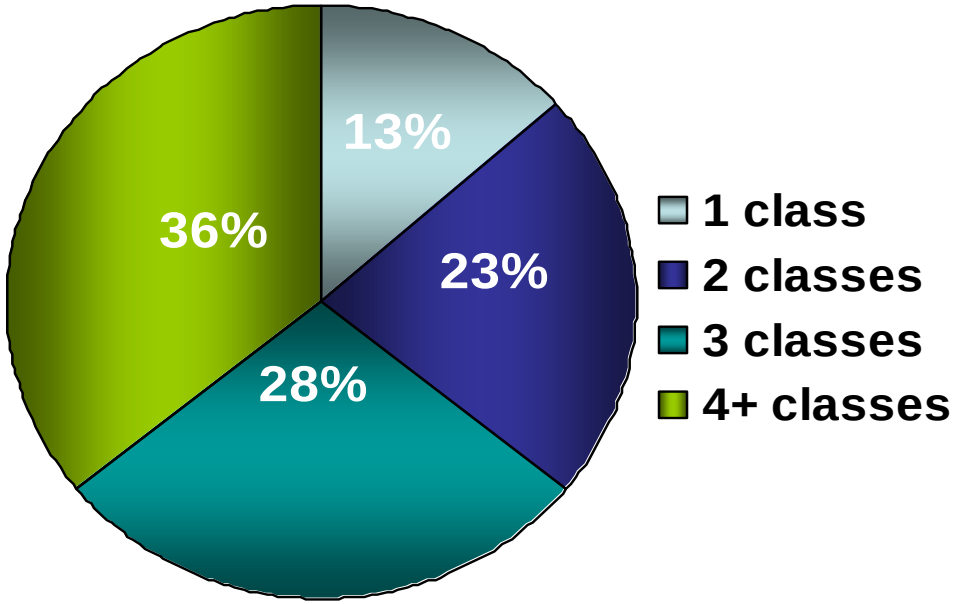
- Attualmente non vi sono protocolli standardizzati per indicazione
- Standardizzazione del medicinale
- Carenza cronica di Cannabis e Scarsità di laboratori galenici
- Costi

CONTROINDICAZIONI:

Disturbi psichiatrici anche solo sospetti
Grande cautela nei soggetti di età inferiore ai 21 anni e anziani
Attività lavorativa che implica guida di veicoli o controlli antidoping
Cautela nei soggetti con patologie cardiovascolari (pregresse aritmie e infarto del miocardio)

Terapie combinate:

Percentuale di pazienti in relazione al numero di classi di combinazione farmacologica



I pazienti fibromialgici assumono in media 2.5 farmaci
36% dei pazienti sono con 4+ classi di farmaci

IMS Health, 2006 data US market.

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

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REVIEW

Check for updates

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

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

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

ABSTRACT

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

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

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

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

ARTICLE HISTORY
Received 31 March 2019
Accepted 6 September 2019

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

1. Introduction

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

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

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

2. Legality of cannabis

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

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

3. The endocannabinoid system

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

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Cannabinoids in the treatment of rheumatic diseases: Pros and cons

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

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ABSTRACT

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

1. Introduction

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

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

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

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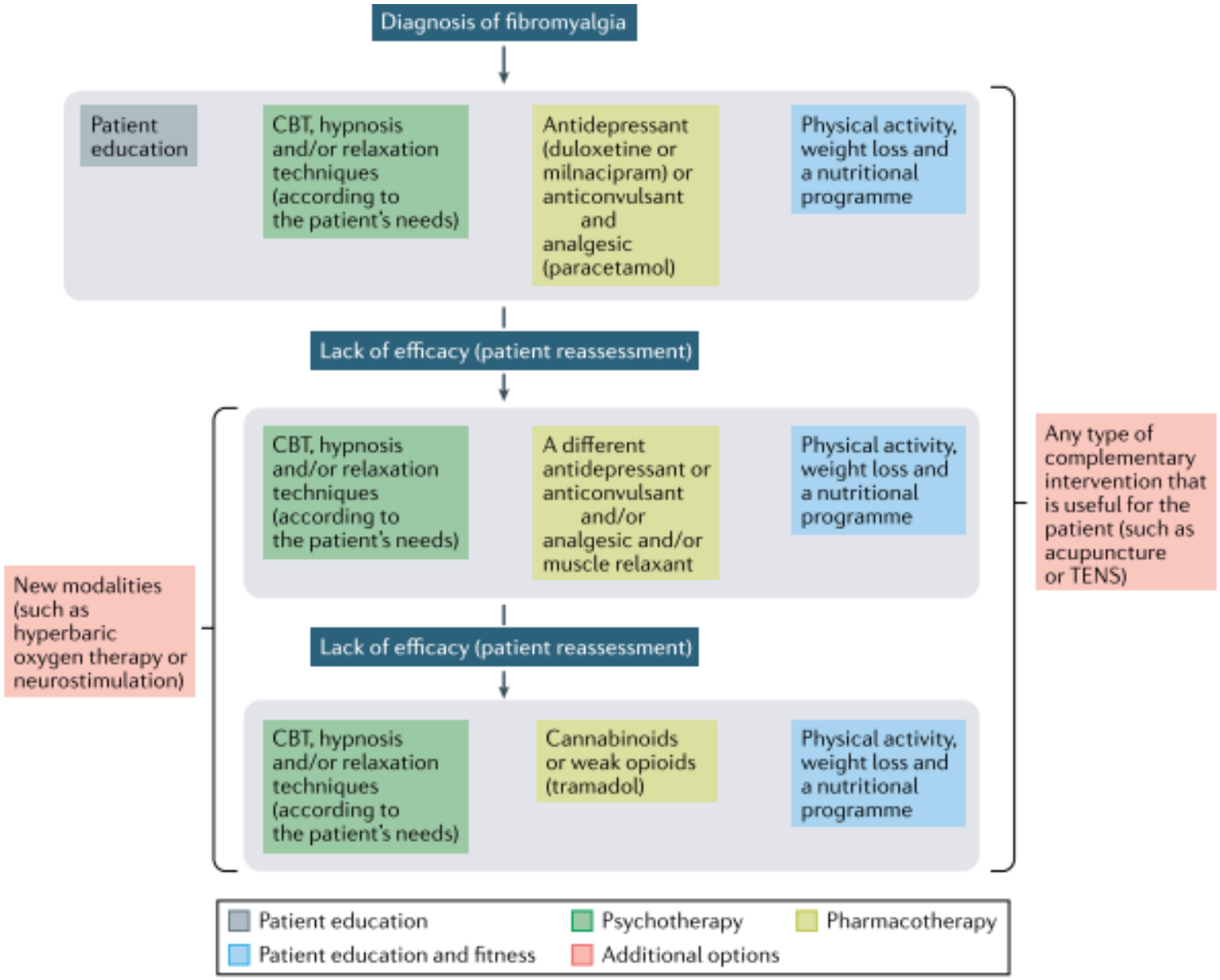

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Conclusioni:

- Il trattamento della FM è **multimodale e multidisciplinare**
- La terapia farmacologica da sola può **ridurre il dolore in media del 30%**
- **Stretta finestra terapeutica** per cui iniziare farmaci sempre con dosaggi bassi ed incrementarli gradualmente in relazione ai sintomi e alla tollerabilità (anche insegnando al paziente come gestire il farmaco prescritto)
- **Orientare il trattamento ed adattarlo al singolo paziente** ed ai sintomi più severi in quel momento (anche utilizzando combinazioni di farmaci)
- **Utilizzare la clinimetria** per «misurare» i miglioramenti dei nostri pazienti