



YEDİTEPE ÜNİVERSİTESİ

Fibromiyalji Sendromu Tedavisinde Neredeyiz?

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Yeditepe Üniversitesi Tıp Fakültesi

FTR ABD

Tanım

- Fibromiyalji Sendromu (FMS) yaygın vücut ağrısı ve belirli anatomik bölgelerde hassas noktaların varlığı ile karakterize, etiyolojisi tam olarak bilinmeyen kronik bir kas-iskelet sistemi sorunu
- Yıllık prevalansı %2-4
- 25-55 yaşları arasında ve kadınlarda daha sık

Yeni tanımlama

- Ağrının anormal santral işlenmesi bozukluğu (hastalığı) olup,
- Ağrının yanı sıra yorgunluk, duygudurum ve bilişsel fonksiyonlarda değişiklik gibi nöropatik karakterde farklı semptomlarla karakterizedir
- FMS'deki ağrı tanımı:
 - Allodini, hiperpati ve hiperaljezinin eşlik ettiği (sinovitin olmadığı) generalize hassasiyet

1990 ACR Tanı Kriterleri

- En az 3 ay süreli yaygın ağrı
 - Vücudun sağ veya sol yarısında,
 - Aksiyel iskeleti de kapsayan belin alt veya üst yarısında ağrı
- Ve
 - Tanımlanmış 18 noktanın en az 11'inde 4 kg basınç uygulayacak bir palpasyonla ağrı
- Dışlama Kriterleri
 - Başka hastalıkların varlığı fibromiyalji tanısını ekarte ettirmez

ACR TANI KRİTERLERİ YETERLİ Mİ?

- Hassas nokta kavramı???



Harden RN et al. A critical analysis of the tender points in fibromyalgia. Pain Med 2007

- Eşlik eden semptomlar??

- Yorgunluk, halsizlik
- Uyku bozuklukları
- Tutukluk,
- Subjektif yumuşak doku şişliği,
- Uyuşma, karıncalanma, güçsüzlük
- Baş ağrısı
- Depresyon, anksiyete
- Hafıza ve bilişsel bozukluklar
- Reynaud fenomeni
- Kuru ağız-kuru göz
- İrritabl barsak sendromu
- Üretral Sendrom
- Çarpıntı, göğüs ağrısı
- Çene ağrısı
- Vestibüler yakınmalar

FMS alt grupları??

- Grup 1: Ağrıya karşı artmış duyarlılık, psikolojik bozukluk yok
- Grup 2: Kronik ağrıya bağlı depresyon ve FMS
- Grup 3: Depresyon ve FMS
- Grup4: Somatizasyon bozukluđuna bađlı FMS

Giesecke T et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain threshold and psychological factors. Arthritis Rheum 2004

Müler W, et al. The classification of fibromyalgia syndrome. Rheumatol Int 2007.

FMS alt grupları

- 1. düşük hassasiyet, orta derecede depresyon/anksiyete, sorun büyütme eğilimi, ağrı kontrolü
- 2. yüksek hassasiyet, yüksek derecede depresyon/anksiyete, sorun büyütme eğilimi, düşük derecede ağrı kontrolü
- 3. yüksek hassasiyet, düşük derecede depresyon/anksiyete, sorun büyütme eğilimi, yüksek derecede ağrı kontrolü

Yeni tanı kriterleri

- Yeni kriterler, yaygın ağrının yanısıra yorgunluk, uyku bozukluğu, bilişsel disfonksiyon ve somatik semptomların şiddetini de değerlendirmekte
- Hassas nokta sayısı kullanılmamakta FMS tanımını ağrıdan başka semptomları da ekleyerek genişletmekte
- Semptom ilişkili FMS şiddetini ölçme imkanı sunmakta

Fibromyalgia Moldofsky Questionnaire

- 6 madde
 - Yaygın ağrı
 - Duyarlılık
 - Enerji
 - Dinlendirmeyen uyku
 - Psikolojik stres
 - Bozulmuş fonksiyonellik

Değerlendirme Ölçekleri

FIQ

	Her zaman	Çoğu zaman	Nadiren	Hiçbir zaman
1-) Bunları yapabiliyor musunuz ?				
a) Alışveriş yapmak	0	1	2	3
b) Çamaşır yıkamak (çamaşır makinesi ile)	0	1	2	3
c) Yemek pişirmek	0	1	2	3
d) Elde bulaşık yıkamak	0	1	2	3
e) Halı süpürmek	0	1	2	3
f) Yatakları yapmak	0	1	2	3
g) Birkaç sokak yürümek	0	1	2	3
h) Arkadaş/akraba ziyaretleri	0	1	2	3
i) Bahçe işleri	0	1	2	3
j) Araba kullanmak	0	1	2	3

2-) Geçen hafta içinde kaç gün kendinizi iyi hissettiniz ?

1 2 3 4 5 6 7

3-) Geçen hafta içinde hastalığınız nedeni ile kaç gün işe gitmediniz ? (Ev hanımı iseniz boş bırakınız.)

1 2 3 4 5

4-) İşe gittiğinizde ağrınız ya da hastalığınızla ilgili diğer sorunlarınız işinizi yapmanızı ne kadar etkiliyor ?

Hiç etkilemiyor

Çok etkiliyor

5-) Ne derece ağrınız var ?

Ağrı yok

Dayanılmaz ağrı var

6-) Ne derece yorgunluk hissediyorsunuz ?

Yorgunluğum yok

Çok yorgunum

7-) Sabahları nasıl uyanıyorsunuz ?

İyi dinlenmiş olarak

Çok yorgun olarak

8-) Ne derece sabah tutukluğunuz var ?

Tutukluğum yok

Çok tutukluğum var

9-) Kendinizi ne derece gergin, sinirli veya endişeli hissediyorsunuz ?

Gergin hissetmiyorum

Çok gerginim

10-) Kendinizi ne derece üzüntülü veya sıkın hissediyorsunuz ?

Üzüntülü hissetmiyorum

Çok üzüntülüymüm

ARTICLE

The Reliability and Validity of the Turkish Version of the Fibrofatigue Scale

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Berfu Akbas
Muge Bıkoçgil
Gulcin Gulsen
Gunes Yavuzer

ABSTRACT. Objective: To validate translated Turkish version of the Fibrofatigue Scale [FFS].

Methods: The Turkish version of FFS was administered to a consecutive sample of 82 patients with fibromyalgia syndrome [FMS; 78 women]; mean age was 37 years and mean symptom duration was 2.3 years. The Turkish version of the Fibromyalgia Impact Questionnaire, the Beck Depression Inventory [BDI], and the Medical Outcome Survey Short Form-36 [SF-36] were documented. Reliability was tested by the test-to-test reliability [intraclass correlation coefficient] and internal consistency [Cronbach's alpha coefficients]. Construct validity was assessed by association with BDI and SF-36 [Spearman's correlation coefficient]. Paired *t*-test was used to determine the statistical significance of change score [responsiveness].

Results: The test-retest reliability and internal consistency of the FFS were excellent with intraclass correlation coefficient of 0.98 [0.97-0.99] and Cronbach's alpha of 0.74. The correlations between the FFS and the Fibromyalgia Impact Questionnaire items [$\rho = 0.56$], BDI [$\rho = 0.52$], and subscales of SF-36 [ρ value ranging from -0.333 to -0.553] were adequate. The FFS score improved significantly after a four-week physical therapy program [$P < 0.001$].

Conclusions: The Turkish FFS is a reliable and valid instrument for detecting and measuring functional disability and symptom severity in Turkish patients with FMS.

FİBROMİYALJİ-KRONİK YORGUNLUK SKALASI

Ağrı:

- 0 yok veya geçici
1
2 zaman zaman belirgin ağrı ve acı
3
4 uzamış ve rahatsız edici ağrı/acı, etkili ağrı kesici alma ihtiyacı
5
6 Aşırı derecede rahatsız edici, dayanılmaz ağrı

Kas gerginliği:

- 0 yok
1
2 zaman zaman kullanmakla/hareketle artıyor
3
4 belirgin rahatsız edici, otururken veya yatarken rahat pozisyon bulmada güçlüğe sebep olan kas gerginliği
5
6 fiziksel gevşemeyi imkansız kılan acılı/ağrılı kas gerginliği

Yorgunluk:

- 0 genelde gücüm yerinde, yorgunluk hissetmiyorum
1
2 çabuk yorulurum ama dinlenmemi (işime ara vermeme) gerektirmez
3
4 belirgin yorgunluk ve enerji kaybı, sık sık ara verme ve dinlenme ihtiyacı
5
6 hemen hemen her aktivitede aşırı yorgunluk/tükenmişlik hissi

Konsantrasyon kaybı:

- 0 yok
- 1
- 2 düşüncelerimi zaman zaman toplamada güçlük
- 3
- 4 okumayı ve konuşmayı engelleyecek derecede konsantrasyon kaybı ve düşünceyi toparlamada zorluk
- 5
- 6 Ciddi düzeyde kısıtlayıcı konsantre olamamak

Hafıza:

- 0 normal (her zamanki gibi)
- 1
- 2 zaman zaman hatırlayamama
- 3
- 4 rahatsız edici veya sosyal yaşamı etkileyen unutkanlık
- 5
- 6 ciddi hafıza kaybı

Sinirlilik-huzursuzluk:

- 0 Kolay sinirlenmem
- 1
- 2 Kolay sinirlenirim ama sinirlilik halim çabuk geçer
- 3
- 4 Genelde huzursuzum veya öfkeliyim, patlamalarım olur
- 5
- 6 Kontrol etmesi zor veya imkansız olacak kadar sürekli sinirlilik/huzursuzluk/öfke içindeyim

Üzüntü:

- 0 Üzülmem gerektiği durumlarda üzülürüm
1
2 Çoğu zaman üzüntülüymüm, ama iyi hissettiğim de olur
3
4 Beni hiçbir şey mutlu edemez, genelde üzgünüm
5
6 Sürekli üzüntülü ve kederliyim

Uyku bozukluğu:

- 0 yok
1
2 Uykuya geçmekte hafif zorluk, az uyuma, hafif uyku, veya normalden derin ve uzun uyuma
3
4 Uyku saatim az, en az 2 saate 1 uyanıyorum, veya normalden fazla uyuyorum
5
6 Ciddi uyku bozukluğu, 2-3 saaten az uyku veya bütün günü uykuda geçiriyorum

Otonom bozukluk (çarpıntı, nefes darlığı, baş dönmesi, artmış terleme, el ve ayaklarda soğukluk, ağız kuruluğu):

- 0 yok
1
2 ara sıra duygusal stres altındayken var
3
4 rahatsız edici ve sosyal yaşamı engelleyecek kadar sık ve yaygın bozukluklar (yukarıdakilerden 2 veya daha fazlası)
5
6 günlük yaşam aktivitelerimi engelleyecek kadar çok

İrritabl barsak (karında ağrı veya rahatsızlık hissi, gaz, gerginlik, sık tuvalete çıkma, ishal/kabızlık):

- 0 yok
- 1
- 2 zaman zaman duygusal stres altındayken var
- 3
- 4 rahatsız edici ve sosyal yaşamı engelleyecek kadar sık
- 5
- 6 günlük yaşam aktivitelerimi engelleyecek kadar çok sık

Baş ağrısı (başta rahatsızlık, ağrı veya acı hissi):

- 0 yok veya geçici
- 1
- 2 zaman zaman belirgin
- 3
- 4 uzun süreli, rahatsız edici, etkili, ilaç almayı gerektiren
- 5
- 6 ciddi baş ağrısı

Enfeksiyon:(hafif ateş, boğaz ağrısı, grip gibi):

- 0 yok
- 1
- 2 zaman zaman belirgin
- 3
- 4 tedavi gerektirecek kadar sık
- 5
- 6 ciddi, yaşamı engelleyecek boyutta bulgularla birlikte

Tedavi

Tedavi Stratejisi

- Etiyopatogeneze göre
- Kliniđe göre

Etiyopatogenez-1

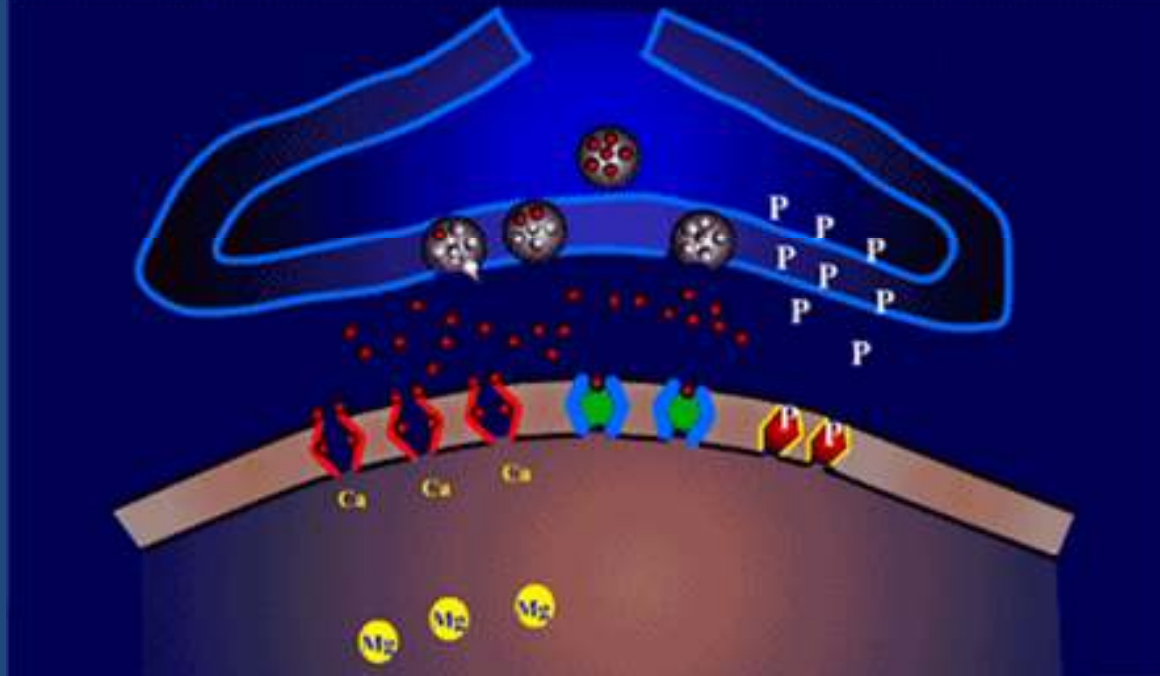
- Genetik faktörler:
 - 5HT2A, D4, COMT reseptör polimorfizmi
- İmmünolojik mekanizmalar:
 - ANA pozitifliği
 - Dermal-epidermal bileşkede IgG depolanması
 - NK hücre aktivitesinde azalma, Thelper/Tsupressor oranında bozulma
 - Sitokin artışı
 - Enfeksiyon ve aı ile immün sistemde deęişiklik
- Periferik teoriler:
 - Fokal kas kontraksiyonu, lokal hipoksi, ATP azlığı
 - Sempatik sinir sistemi aşırı aktivitesi
 - Kas ve deri nosiseptörlerinin sensitizasyonu

Etiyopatogenez-2

- Santral teoriler:
 - Otonomik ve nöroendokrin disfonksiyon
 - Ağrının işlenmesi
 - Nöroplastisite
 - **Santral sensitizasyon**
 - Ağrının modülasyonu:
 - Serotonin ve norepinefrin düzeyinin BOS'da azalması

Santral sensitizasyon

Pathophysiology: Peripheral and Central Sensitization



Imamura M et al. Fibromyalgia: from treatment to rehabilitation. Eur J Pain 2009

- Ağrının devamlılığı ve ek nöroplastik değişiklikler devam eden kısır döngüye ve sonuç olarak kronik ve dirençli hastalığa neden olur.
- Daha uzun süreli hastalık daha çok ve daha dirençli ağrıya yol açar.
- Tedavi santral sensitizasyonda rol alan SSS yapılarını hedef almalıdır
- Pronosiseptif girdiyi inhibe eden ve modülasyon sinyalini arttıran ilaçlar tedavide kullanılmalıdır

Farmakolojik Tedaviler

- Etkinlik için güçlü kanıt
 - Amitriptyline, 10-50 mg (yatarken)
 - Cyclobenzaprine, 10-30 mg (yatarken)
 - Pregabalin, 300-450 mg/gün
 - Gabapentin, 1600-2400 mg/gün
 - Duloxetine, 60-120 mg/gün
 - Milnacipran, 100-200 mg7gün
- Orta düzeyde kanıt
 - Tramadol, 200-300 mg/gün
 - SSRIs (fluoxetine, sertraline)
- Zayıf düzeyde kanıt
 - pramipexole, gamma hydroxybutyrate, growth hormone, 5-hydroxytryptamine, tropisetron, s-adenosyl-methionine
- Kanıt yok
 - opioids, NSAIDS, benzodiazepene and nonbenzodiazepene hypnotics, melatonin, magnesium, DHEA, thyroid hormone, guaifenesin

ABD'de FMS Klinik Çalışmalar websitesi listesinde yer alan yeni ilaçlar:

rotigotine,
sodium oxybate,
eszopicone,
reboxetine,
quetiapine,
nabilone,
dronabinol,
naltrexone,
esreboxitine,
armodafinil,
Neurotropin
etoricoxib.

Farmakolojik Tedavi

- FDA onaylı ilaçlar:
 - Duloksetin
 - Pregabalin
 - Milnasipran

Pregabalin

- İkinci jenerasyon GABA yapısal analogu
- Voltaja duyarlı kalsiyum kanallarının” alfa 2 delta alt ünitesine bağlandıktan sonra depolarizasyonla indüklenmiş Ca girişini ve glutamat, noradrenalin ve substans P gibi eksitatuar nörotransmitterlerin salınımını azaltır.
- FDA onayı 300 ve 450 mg içindir

Pregabalin avantajları

- Diğer ilaçlarla etkileşim minimal
- KCFT.lerini bozmaz ama kreatinin klirensi tedaviye başlamadan önce ölçmek gerekir, bu değere göre doz ayarı yapılır.
- Dispepsisi ve irritabl barsak hastalığı olanlarda tercih et.
- RKÇ'da sağlıklı gönüllülerde yavaş-dalga uykuyu belirgin şekilde arttırmış (Hindmarch, Sleep 2005)

Pregabalin dezavantajları

- Fibrofog olanlarda nörokognitif deęişiklikler nedeniyle (dikkat bozukluğu, konfüzyon gibi) kullanımı kısıtlıdır (Katz RS et al. J Clin Rheumatol 2004))
- İntihar eğilimi
- Yoksunluk sendromu olabileceğinden yavaş yavaş kesilmeli

Pregabalin yan etkiler

- Anjiyoödem
- Hipersensitivite reaksiyonları
- Periferel ödem
- Baş dönmesi, sersemlik
- Yüz, cilt, boyunda şişme
- Rabdomiyoliz
- Kardiyak PR intervalinde uzama
- Trombositopeni
- Libido azalması
- İntihar eğiliminde artış

FMS'da Pregabalin kullanımını için anahtar noktalar

- 450 mg/gün ikiye bölünmüş doz en iyi dozdur
- Çoğu yan etki doz bağımlıdır
- İlacın tolere edilebilirliği uzun titrasyon perioduna bağlıdır
- FMS'de uyku bozukluğunda da etkindir
- Bu öneriler sadece primer FMS için geçerlidir.

Duloksetin

- FDA onayı aldığı diğer durumlar:
 - Diabetik polinöropati
 - Major depresyon
 - Jeneralize anksiyete bozuklukları
- 5-HT ve NE geri alım inhibitörüdür (5/1 oranında)
- Yani endojen ağrı inhibitör mekanizmaları üzerinden etkili
- 60-120 mg/gün etkin dozudur.

Duloksetin yan etkiler

- Baş ağrısı, somnolans, baş dönmesi, uykusuzluk
- GİS: diyare, bulantı, karın ağrısı
- KVS: Kan basıncı artışı, ortostatik hipotansiyon, senkop, çarpıntı

Duloksetin avantaj-dezavantajlar

- Anksiyete/depresyon olsun olmasın ağrıda etkilidir
- Yaşlı, hipovolemik hastalarda hiponatremi ve sADH sendromu açısından dikkat edilmeli
- Kesilirken azaltarak kesilmeli
- Gerilim tipi baş ağrısı/migreni olanları yakından takip et

Milnasipran

- 5-HT ve NE geri alım inhibitörü (oran 1/3)
- Endojen ağrı inhibitör mekanizması üzerinden etkili
- Önerilen doz 50 mgx2/gün
- Maksimum doz 200 mg/gün (2'ye bölünmüş dozda)
- CYP450 üzerinde etkili değil
- Renal yolla atılımı var. Renal yetmezlikte doz ayarı gerekmekte (%50 daha düşük doz ile) ve titrasyonu daha uzun sürede yapılmalı
- Yan etkiler: Paroksizmal hipertansiyon ve aritmi
- Ağrının yanısıra yorgunluk ve fiziksel performans üzerinde de olumlu etkileri var
- Gerilim tipi baş ağrısı/migreni olanları yakından takip et

Critical Review

Comparative Efficacy and Harms of Duloxetine, Milnacipran, and Pregabalin in Fibromyalgia Syndrome

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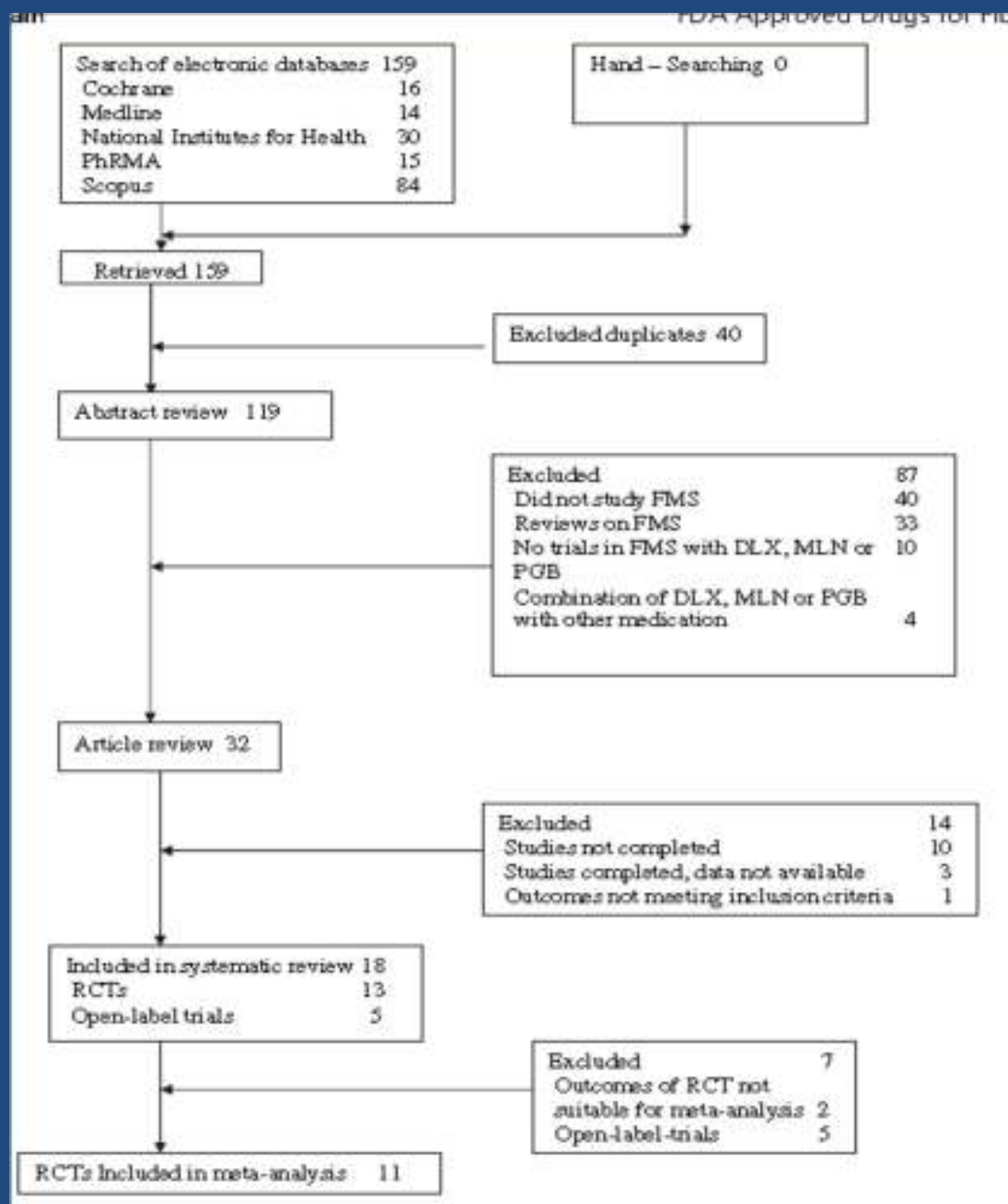
[§]Department of Psychosomatic Medicine, Technische Universität München, D-81675 München, Germany.

Abstract: Duloxetine (DLX), milnacipran (MLN), and pregabalin (PGB) are the only drugs licensed by the US Food and Drug Administration (FDA) for fibromyalgia syndrome (FMS). Evidence on the comparative benefits and harms is still accruing. The authors searched MEDLINE, SCOPUS, Cochrane Central Register of Controlled Trials, and sought unpublished data from the databases of FDA, US National Institutes for Health, and Industry through May 2009 for randomized controlled trials. Outcomes of interest were symptom reduction (pain, fatigue, sleep disturbance, depressed mood, reduced health-related quality of life), and adverse events. 17 studies with 7,739 patients met the inclusion criteria. The 3 drugs were superior to placebo except DLX for fatigue, MLN for sleep disturbance, and PGB for depressed mood. Adjusted indirect comparisons indicated no significant differences for 30% pain relief and dropout rates due to adverse events between the 3 drugs. Significant differences in average symptom reduction were found: DLX and PGB were superior to MLN in reduction of pain and sleep disturbances. DLX was superior to MLN and PGB in reducing depressed mood. MLN and PGB were superior to DLX in reducing fatigue. The risk of headache and nausea with DLX and MLN was higher compared with PGB. The risk of diarrhea was higher with DLX compared to MLN and PGB. There is evidence for the short-term (up to 6 months) efficacy of DLX, MLN, and PGB. Differences with regard to the occurrence of the key symptoms of FMS and to drug-specific adverse events may be relevant for the choice of medication.

Perspective: This article presents comparative data on the efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. The results can help clinicians in choosing medication since the 3 drugs have different effects on the key symptoms of fibromyalgia syndrome and differences in side effects, contraindications, and warnings.

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Key words: Fibromyalgia syndrome, duloxetine, milnacipran, pregabalin, systematic review.



- Anlamlı fayda: en az %30 ağrı azalması
- cevabın olmaması: yan etkiye bağlı ilacın bırakılması veya %30'dan daha az ağrı azalması
- %30 ağrı azalması için NNT değerleri:
 - DLX: 7,2
 - MLN:19
 - PGB: 8,6

Table 3. Most Frequent Side Effects in Randomized Controlled Trials (Parallel Design) with Duloxetine, Milnacipran and Pregabalin (All Dosages Pooled Together)

<i>DULOXETINE</i>				
<i>SIDE EFFECT</i>	<i>SUM RCTs N = 876 (%)</i>	<i>PLACEBO N = 535 (%)</i>	<i>NNH (95% CI)</i>	<i>RR (95% CI) I²; P VALUE</i>
Nausea	257 (29.3)	61 (11.4)	5.6 (4.5,7.2)	2.54 (1.92,3.37) 0%; <.0001
Headache	175 (20.0)	64 (12.0)	12.5 (8.4,23.8)	1.61 (1.20,2.17) 0%; .001
Dry mouth	159 (18.1)	29 (5.4)	7.9 (6.3,10.5)	3.16 (2.11,4.72) 0%; <.0001
Insomnia	127 (14.5)	49 (9.2)	18.7 (11.5,51.0)	2.47 (0.57,10.71) 40%; .23
Constipation	118 (13.5)	19 (3.6)	10.1 (7.9,13.9)	3.50 (2.23,5.79) 0%; <.0001
Hyperhidrosis	84 (9.6)	6 (1.1)	11.8 (9.4,15.8)	5.71 (2.34,13.95) 0%; .0001
Dizziness	96 (10.9)	36 (6.7)	23.6 (13.9,79.0)	2.62 (1.53,4.50) 27%; .0004
Diarrhea	102 (11.6)	42 (7.8)	26.6 (14.5,147)	1.59 (1.11,2.29) 8%; 0.01
Fatigue	127 (14.5)	38 (7.1)	13.5 (9.4,23.8)	2.07 (1.47,2.91) 0%; <.0001
Somnolence	84 (9.6)	15 (2.8)	14.7 (10.9,22.8)	2.66 (1.78,3.96) 0%; <.0001

MILNACIPRAN

<i>SIDE EFFECT</i>	<i>SUM RCT'S N = 1,460 (%)</i>	<i>PLACEBO N = 624 (%)</i>	<i>NNH (95% CI)</i>	<i>RR (95% CI) I²; P VALUE</i>
Nausea	536 (36.7)	124 (19.9)	5.1 (4.3,6.3)	1.84 (1.55, 2.18) 0%, <0001
Headache	255 (17.5)	84 (13.5)	25.0 (19.7,144)	1.30 (1.04,1.64) 0%; .02
Dry mouth	44/665 (6.6)	6/223 (2.7)	25.5 (14.8, 92.3)	2.46 (1.06,5.69) 0%; .04
Insomnia	171 (11.7)	57 (9.1)	38.8 (18.8,45.3)	1.35 (1.01,1.79) 0%; .04
Constipation	232 (15.9)	22 (3.5)	8.1 (6.8,10.0)	4.47 (2.91,6.86) 0%, <0001
Hyperhidrosis	125 (8.6)	10 (1.6)	14.4 (11.5,19.2)	5.00 (2.64,9.47) 0%, <0001
Dizziness	150 (10.3)	32 (3.2)	19.4 (13.4,35.5)	1.94 (1.34,2.81) 0%; .0004;
Diarrhea	68 (4.6)	40 (6.4)	-5.7 (-25.3,29.1)	.72 (.49,1.05) 0%; .09
Fatigue	NR	NR		
Somnolence	NR	NR		

PREGABALIN

<i>SIDE EFFECT</i>	<i>SUM RCT'S N = 2,064 (%)</i>	<i>PLACEBO N = 683 (%)</i>	<i>NNH (95% CI)</i>	<i>RR (95% CI) I²; P VALUE</i>
Dizziness	793 (38.4)	67 (9.8)	3.5 (3.2,3.9)	3.87 (3.06,4.89) 0%, <0001
Somnolence	424 (20.5)	33 (.05)	6.4 (5.5,7.5)	4.21 (2.96,5.94) 0%, <0001
Fatigue/asthenia	158 (7.7)	31 (.04)	32.1 (19.8,84.8)	1.67 (1.15,2.43) 0%, .0007
Weight gain	231 (11.1)	17 (.02)	11.5 (9.9,14.5)	4.58 (2.44,6.82) 0%, <0001

PREGABALIN

<i>SIDE EFFECT</i>	<i>SUM RCT'S N = 2,064 (%)</i>	<i>PLACEBO N = 683 (%)</i>	<i>NNH (95% CI)</i>	<i>RR (95% CI) I²; P VALUE</i>
Peripheral edema	146 (7.1)	15 (.2)	20.5 (15.5,30.1)	3.52 (2.01,6.18) 0%, <.0001
Headache	145 (7.0)	88 (12.9)	-17.1 (-32.1,11.6)	.72 (.57,.91) 0%, .007
Dry mouth	168 (8.1)	11 (.02)	15.3 (12.4,19.9)	4.98 (2.72,9.10) 0%, <.0001
Nausea	44/741 (.06)	27/387 (.07)	-96.3 (-24.4,49.6)	.97 (.64,1.48) 0%, .89
Diarrhea	68/1517 (.04)	30/505 (.06)	-64.6 (-117,26.9)	.79 (.42,1.48) 40%, .46
Constipation	65/741 (.09)	18/387 (.05)	24.3 (14.1,83.6)	3.94 (.50,30.74) 74%, .19

Sonuçlar-1

- DLX ve PGB MLN'a göre uyku bozuklukları ve ağrıyı azaltmada daha etkin
- DLX, PGB ve MLN'a göre depresif duygudurumu azaltmada daha etkin
- MLN ve PGB, DLX'e göre yorgunluğu azaltmada daha etkin
- Baş ağrısı ve bulantı DLX ve MLN'da daha fazla
- Diyare DLX'de daha fazla.

Sonuçlar-2

- Yoksunluk sendromu her 3 ilaçta da var
- Kısa vadede yani 6 aylık izlemde her üç ilaç da plaseboya üstün
- DLX yorgunluk, MLN uyku bozukluğu, PGB ise depresif duygudurum için iyi seçenek değil
- Ağrı üzerindeki etkinlik açısından aralarında fark yok
- DLX ve MLN en sık yan etkisi GIS ve baş ağrısı
- PGB en sık yan etkisi nörobilişsel yan etkiler, kilo alımı ve periferik ödem

Table 5. Summary of Prescribing Information of Duloxetine, Milnacipran, and Pregabalin Given by the FDA

<i>DRUG</i>	<i>DOSAGE RECOMMENDED IN FMS</i>	<i>CONTRAINDICATIONS</i>	<i>WARNINGS AND PRECAUTIONS</i>	<i>DRUG INTERACTIONS PREGNANCY AND NURSING PEDIATRIC PATIENTS</i>	<i>LAST UPDATE</i>
Duloxetine	60 mg/d once a day	<ol style="list-style-type: none"> 1. Concomitant use of monoaminoxidase inhibitors 2. Uncontrolled narrow-angle glaucoma 3. Substantial alcohol use or evidence of chronic liver damage 4. Severe renal impairment 	<ol style="list-style-type: none"> 1. Suicidality 2. Hepatotoxicity 3. Orthostatic hypotension and syncope 4. Serotonin- or neuroleptic syndrome-like reactions 5. Abnormal bleeding 6. Discontinuation syndrome 7. Activation of mania 8. Blood pressure control 9. Hyponatremia 10. Glucose control in diabetes 11. Slow gastric emptying 12. Urinary hesitation and retention 	<ol style="list-style-type: none"> 1. Inhibitors of CYP1A2 or Thioridazine should be avoided 2. Potent inhibitors of CYP2D6 may increase duloxetine concentration 3. Duloxetine is a moderate inhibitor of CYP2D6 Use only if potential benefits justifies the potential risks Not approved 	01/30/2009
Milnacipran	100 mg/d two divided dosages, may increased to 200 mg/d	<ol style="list-style-type: none"> 1. Concomitant use of monoaminoxidase inhibitors 2. Uncontrolled narrow-angle glaucoma 3. Substantial alcohol use or evidence of chronic liver damage 	<ol style="list-style-type: none"> 1. Suicidality 2. Hepatotoxicity 3. Serotonin syndrome 5. Abnormal bleeding 6. Discontinuation syndrome 7. Elevated blood pressure 8. Urinary hesitation and retention 9. Seizures 	<p>No clinically significant pharmacokinetic drug interactions Use only if potential benefits justifies the potential risks Not approved</p>	08/01/2009
Pregabalin	150 mg up to 300 mg/d in two divided dosages	Known hypersensitivity against pregabalin	<ol style="list-style-type: none"> 1. Angioedema 2. Hypersensitivity reactions 3. Increased seizure frequency in patients with seizure disorders in case of rapid discontinuation. 4. Dizziness and somnolence and impair patients' ability to drive or operate machinery 	<p>No clinically significant pharmacokinetic drug interactions Use only if potential benefits justifies the potential risks Not approved</p>	07/2007

Pregabalin in fibromyalgia - responder analysis from individual patient data

Sebastian Straube¹, Sheena Derry², R Andrew Moore^{*2}, Jocelyn Paine³ and Henry J McQuay²

Abstract

Background: Population mean changes are difficult to use in clinical practice. Responder analysis may be better, but needs validating for level of response and treatment duration. A consensus group has defined what constitutes minimal, moderate, and substantial benefit based on pain intensity and Patient Global Impression of Change scores.

Methods: We obtained individual patient data from four randomised double blind trials of pregabalin in fibromyalgia lasting eight to 14 weeks. We calculated response for all efficacy outcomes using any improvement ($\geq 0\%$), minimal improvement ($\geq 15\%$), moderate improvement ($\geq 30\%$), substantial improvement ($\geq 50\%$), and extensive improvement ($\geq 70\%$), with numbers needed to treat (NNT) for pregabalin 300 mg, 450 mg, and 600 mg daily compared with placebo.

Results: Information from 2,757 patients was available. Pain intensity and sleep interference showed reductions with increasing level of response, a significant difference between pregabalin and placebo, and a trend towards lower (better) NNTs at higher doses. Maximum response rates occurred at 4-6 weeks for higher levels of response, and were constant thereafter. NNTs (with 95% confidence intervals) for $\geq 50\%$ improvement in pain intensity compared with placebo after 12 weeks were 22 (11 to 870) for pregabalin 300 mg, 16 (9.3 to 59) for pregabalin 450 mg, and 13 (8.1 to 31) for pregabalin 600 mg daily. NNTs for $\geq 50\%$ improvement in sleep interference compared with placebo after 12 weeks were 13 (8.2 to 30) for pregabalin 300 mg, 8.4 (6.0 to 14) for pregabalin 450 mg, and 8.4 (6.1 to 14) for pregabalin 600 mg. Other outcomes had fewer respondents at higher response levels, but generally did not discriminate between pregabalin and placebo, or show any dose response. Shorter duration and use of 'any improvement' over-estimated treatment effect compared with longer duration and higher levels of response.

Conclusions: Responder analysis is useful in fibromyalgia, particularly for pain and sleep outcomes. Some fibromyalgia patients treated with pregabalin experience a moderate or substantial pain response that is consistent over time. Short trials using 'any improvement' as an outcome overestimate treatment effects.

Sonuçlar

- Daha yüksek doz PGB'de daha düşük NNT değeri saptanmış
- Maksimum yarar 4-6 hafta arasında çıkmış sonra sabit devam etmiş
- 12. haftadan sonra orta ve yüksek oranda ağrı azalması olan hastaların bu oranları azalmaya başlamış. Bu dönemde nonfarmakolojik tedavilerin eklenmesi önerilmiş
- Zaman uzadıkça ağrı ve uyku bozukluğu için NNT değeri artıyor (her 3 dozda da)
 - İlacı bırakma
 - Yan etki
 - Daha yüksek doza ihtiyaç
- PGIC'de iyileşme 600 mg'da 450 mg'a göre daha düşük
- 450 mg optimal doz

FMS'de farmakolojik tedavi seçimi

- Anahtar semptomlara
- Yan etki profiline
- Eşlik eden hastalıklara
- Hastanın tercihinine göre yapılmalı

- Kullanılan ilacın etkisi görülür ve yan etkisi ortaya çıkmaz ise en az 6 ay devam edilmeli
- FMS heterojen klinik antiteler grubu
- Nöral mekanizmalardaki kompleks yolaklar hastalar arasında değişiyor olabilir
- Farklı yolaklar farklı ağrı paternleriyle direkt uyumlu değil
- Kronik ağrı beyinde fonksiyonel, yapısal, kimyasal değişiklikler ile karakterize
- İlaçlara fizyolojik cevaplarda kişisel farklılıklar olabilir
- Genetik, nörobiyolojik çalışmalar FMS'de hedef tedaviyi belirlemede faydalı olabilir

FMS alt gruplarına göre tedavi

- Grup 1: Ağrıya karşı artmış duyarlılık, psikolojik bozukluk yok---SSRI
- Grup 2: Kronik ağrıya bağlı depresyon ve FMS-SNRI, TAD
- Grup 3: Depresyon ve FMS-düşük-tam doz TAD, SNRI
- Grup4: Somatizasyon bozukluđuna bađlı FMS- psikoterapi ve psikoaktif ilaçlar

FIBRO Metodu (mVASFIQ)

- Fatigue---modafinil¹ (50-400 mg/gün),
 - Sabah dozu ile başla, gerekirse öğle dozu ekle
 - KCFT ve BFT bozuk olan hastalarda dikkatli takip
 - Alkol ve ilaç bağımlılığı olanlara önerilmez
- Insomnia---Pregabalin², Ketiapin (25-100 mg)³
 - PGB uzun süredede etkili olamayabilir
- Blues---SNRI, TAD
 - MLN öncelikle tercih edilebilir.
- Rigidity---Siklobenzaprin (10 mgx4-5)⁴, Tizanidin?
- Ow---(pain)

1Schwartz TL et al. Modafinil treatment for fatigue associated with fibromyalgia. J Clin Rheumatol 2007

2Hindmarch I et al. A doubleblind study in healthy volunteers to ases the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005

3 Hidalgo J et al. An open-label study of quetiapine in the treatment of fibromyalgia. Biol Psychiatry 2007

4 Tofferi JK et al. Treatment of fibromyalgia with cyclobenzaprin Arthritis Rheum 2000.

Tedavi Kılavuzları

Kanıt Dayalı Tıp

Düzy

Kanıt Tipi

- | | |
|-----|---|
| I | Kanıtlar, iyi dizayn edilmiş çok sayıda meta analizden ve kontrollü çalışmadan elde edilmiştir. |
| II | Kanıtlar, en az iyi dizayn edilmiş bir deneysel çalışmadan elde edilmiştir. |
| III | Kanıtlar iyi dizayn edilmiş non-randomize, kontrollü, tek-grup, pre-post, kohort, zaman, eşleştirilmiş vaka kontrollü deneysel çalışmalardan elde edilmiştir. |
| IV | Kanıtlar iyi dizayn edilmiş karşılaştırmalı ve korrelasyon tanımlı çalışmalar gibi deneysel olmayan çalışmalardan ve olgu çalışmalarından elde edilmiştir. |
| V | Kanıtlar olgu sunumlarından ve klinik deneyimlerden elde edilmiştir. |

Kanıta Dayalı Tıp

ÖNERİ DERECELERİ

- A Kanıtlar düzey I' e dayalıdır veya II, III, IV düzeyde kanıt sağlayan pek çok çalışma mevcuttur.
- B Kanıtlar düzey II, III, IV' e dayalıdır ve bulguları genellikle tutarlıdır.
- C Kanıtlar II, III, IV' e dayalıdır ancak bulgular tutarlı olmayabilir
- D Çok düşük düzeyde veya hemen hiç olmayan ampirik kanıtlar mevcuttur.

EULAR 2008

Recommendation	Level of Evidence	Strength
General		
Full understanding of fibromyalgia requires <u>comprehensive assessment of pain, function, and psychosocial context</u> . Fibromyalgia should be recognised as a complex and heterogeneous condition where there is <u>abnormal pain processing and other secondary features</u> .	IV	D
Optimal treatment requires a <u>multidisciplinary approach</u> with a combination of <u>non-pharmacological and pharmacological treatment modalities</u> tailored according to pain intensity, function, associated features such as depression, fatigue and sleep disturbance in discussion with the patient.	IV	D
Non-Pharmacological Management		
<u>Heated pool treatment</u> with or without exercise is effective in fibromyalgia.	IIa	B
Individually tailored exercise programmes including <u>aerobic exercise and strength training</u> can be beneficial to <u>some patients with fibromyalgia</u> .	IIb	C
<u>Cognitive behavioural therapy</u> may be of benefit to some patients with fibromyalgia.	IV	D
Other therapies such as <u>relaxation, rehabilitation, physiotherapy and psychological support</u> may be used depending on the <u>needs of the individual patient</u> .	IIb	C
Pharmacological Management		
<u>Tramadol</u> is recommended for the management of pain in fibromyalgia.	Ib	A
<u>Simple analgesics such as paracetamol and other weak opioids</u> can also be considered in the treatment of fibromyalgia. <u>Corticosteroids and strong opioids are not recommended</u> .	IV	D
<u>Antidepressants: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole</u> , reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia.	Ib	A
<u>Tropisetron, pramipexole and pregabalin</u> reduce pain and are recommended for the treatment of fibromyalgia.	Ib	A

APS-2005
(American Pain Society)

Interventions

7. Begin treatment of FMS by confirming the diagnosis of FMS and explaining what the condition is and what it is not. **(Panel consensus)** Patient education is critical to optimal management of FMS. **(B)**

8. Use multiple strategies and include both pharmacologic and nonpharmacologic therapies in the management of FMS. **(A)**

Pharmacologic Therapies

9. For initial treatment of FMS, prescribe a tricyclic antidepressant for sleep, in particular 10 to 30 mg amitriptyline or cyclobenzaprine at bedtime. **(A)**

10. Use selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, alone or in combination with tricyclics, for pain relief. **(B)** The doses of all antidepressants should be individualized and any concurrent mood disturbances treated. **(Panel consensus)**

11. Do not use non-steroidal anti-inflammatory drugs (NSAIDs) as the primary pain medication for people with FMS. **(A)** There is no evidence that NSAIDs are effective when used alone to treat FMS patients. NSAIDs, including COX-2 selective agents and acetaminophen, may provide some analgesia when used with other medications. **(C)**

12. Use tramadol (50 to 100 mg two or three times daily) for pain relief in people with FMS. The dose of tramadol should be increased slowly over time and should be tapered gradually when discontinued. Tramadol can be used alone or in combination with acetaminophen. **(B)**

13. Use opioids for management of FMS pain only after all other pharmacologic and nonpharmacologic therapies have been exhausted. **(Panel consensus)**

14. Use sleep and anti-anxiety medications such as trazodone, benzodiazepines, nonbenzodiazepine sedatives, or

L-dopa and carbidopa in FMS, especially if sleep disturbances such as restless leg syndrome are prominent. **(A)**

15. Do not use corticosteroids in the treatment of FMS unless there is concurrent joint, bursa, or tendon inflammation. **(A)**

16. Ask patients about their use of complementary products and practices and have sufficient knowledge of them to be able to answer questions concerning efficacy and identify possible negative interactions with prescribed treatment. **(C)**

Nonpharmacologic Therapies

17. Provide all patients with basic information on FMS and treatment options, and educate them about pain management and self-management programs as an initial part of treatment. **(A)**
18. Incorporate cognitive-behavioral therapy into a multimodality treatment approach to reduce pain, enhance self-efficacy, and improve function. **(A)**
19. Encourage and support people with FMS to perform moderately intense aerobic exercise (60-75% of age-adjusted maximum heart rate [210 minus the person's age]) two to three times per week. **(A)** In individuals who are deconditioned, this rate can be achieved with very low levels of exercise.
20. Advise people with FMS to avoid exercise-induced pain by stretching to the point of slight resistance, not to the point of pain. This is especially important in a subgroup of individuals who have joint hypermobility. **(B)**
21. Begin exercise programs for people with FMS at a level just below their capacity, and progress in frequency, duration, or intensity as their levels of fitness and strength increase. Exercise progression should be slow and gradual, or participants will experience a marked, exercise-induced exacerbation of pain that may lead to discontinuation of the exercise program. **(Panel consensus)**
22. Encourage people with FMS to perform muscle-strengthening exercise two times per week. **(B)**
23. Encourage ongoing exercise to maintain exercise-induced gains. **(B)**
24. Offer clinician-assisted treatments such as clinical hypnosis and biofeedback **(B)**, acupuncture **(C)**, chiropractic manipulation, therapeutic massage **(B)**, and balneotherapy **(A)**, which may be helpful for pain relief.
25. Use multidisciplinary approaches that incorporate two or more strategies to decrease pain and improve function in FMS, especially in people who have not responded to simpler approaches. **(A)**

AWMF-2009
(Association of Scientific Medical Societies in
Germany)

TABLE 1

General diagnostic principles

Structured assessment of pain (pain sketch)

Thorough history:

- ◆ General symptoms (fatigue, weakness), further physical complaints (e.g., irregular bowel habits, abdominal pain, dyspepsia, urinary symptoms, sicca symptoms, general irritability) and mental-health complaints (e.g., disturbances of sleep or concentration, lack of drive)

 - ◆ Accompanying illnesses

 - ◆ Current medications

 - ◆ Impaired activities of daily living

 - ◆ Subjective notions of causation and fears relating to illness

 - ◆ Psychosocial stressors
-

Physical examination of the entire body

Planned ancillary diagnostic testing for the rapid exclusion of other conditions

TABLE 2

Obligatory laboratory testing in the initial evaluation of chronic widespread pain

- ◆ Erythrocyte sedimentation rate, C-reactive protein, complete blood count (provides evidence of polymyalgia rheumatica or rheumatoid arthritis)
- ◆ Creatine kinase (evidence of muscle disease)
- ◆ Serum calcium (evidence of hypercalcemia)
- ◆ Basal thyroid-stimulating hormone (evidence of hypothyroidism)

TABLE 3

Indications for specialized psychotherapeutic evaluation in patients diagnosed with RMS (1)

- ◆ The patient reports current, severe psychosocial stressors
- ◆ The patient reports current or earlier psychiatric treatment and/or use of psychotropic drugs
- ◆ The patient reports severe biographical stress factors (including traumatic stress factors)
- ◆ Evidence of maladaptive response to disease (e.g., catastrophizing, inappropriate self-protective or coping strategies)
- ◆ Patient's beliefs about psychosomatic illness

TABLE 4

Important things to tell the patient when FMS is initially diagnosed

The symptoms are permanent in most patients.

The symptoms do not lead to invalidism or shorten life expectancy.

Total relief of symptoms is not possible in most cases.

The goals of treatment are improvement and maintenance of the quality of life (functional ability in everyday situations) and reduction of symptoms.

Regular physical activity, such as cardiovascular exercise, contributes to symptom reduction and to improved adaptation to the symptoms.

BOX 3

Recommendations for the stratified treatment of fibromyalgia syndrome

(The level of treatment and the therapeutic options should be chosen by shared decision-making of the patient and treating physician, in the light of the patient's preferences and accompanying illnesses, if any.)

Level 1

- Cognitive behavioral therapy and operant therapy for pain, including patient education (grade 1a evidence, grade A recommendation, strong consensus)
- Aerobic endurance training adapted to the patient's individual performance level (grade 1a evidence, grade A recommendation, strong consensus)
- Pool-based exercise / aquatic jogging (grade 1a evidence, grade A recommendation, consensus)
- Spa therapy (bathing in thermal springs) (grade 1a evidence, grade A recommendation, strong consensus)
- Amitriptyline 25-50 mg/d (grade 1a evidence, grade A recommendation, strong consensus)
- Diagnosis and treatment of comorbid physical and mental illnesses (grade 5 evidence, open recommendation, strong consensus)

Level 2

- Multimodal treatment (requirement for medical training therapy or other type of activating movement therapy coordinated with psychotherapeutic methods) (grade 1a evidence, grade A recommendation, strong consensus)
 - Mainly outpatient; (partly) inpatient, when outpatient treatment is inadequate or impossible
 - (Pain therapy or psychosomatic medicine ward in an acute hospital, or else a rheumatological or psychosomatic rehabilitation center)

Level 3

- Short-term: duloxetine 60–120 mg/d or fluoxetine 20–40 mg/d or milnacipran 100–200 mg/d or paroxetine 20–40 mg/d or pregabalin 150–300 mg/d (grade 1a evidence, grade B recommendation, majority opinion)
- Short-term: hypnotherapy/directed imagery (grade 2b evidence, grade B recommendation, consensus) or therapeutic writing (grade 2b evidence, grade B recommendation, strong consensus)
- Multimodal interval/booster therapy (grade 5 evidence, open recommendation, strong consensus)
- Short-term: complementary therapeutic techniques (homeopathy, vegetarian diet) (grade 2b evidence, open recommendation, consensus)

Karşılaştırma

- APS ve AWMF sistemik derleme ve meta-analizleri, EULAR RKÇ.ları baz almış
- EULAR farmakolojik, APS ve AWMF nonfarmakolojik tedavilere daha fazla yer veriyor.
- AWMF ilk defa tabakalı tedavi öneriyor. Diğer kılavuzlardan farklı olarak alternatif ve tamamlayıcı tedavileri son aşamada öneriyor.
- AWMF'de uzun dönem tedavi için de öneriler var
(aerobik egzersiz, psikoterapi ve muldimodal tedavi)

Nonfarmakolojik tedavi stratejileri: Etkinlik Düzeyleri

Güçlü Kanıt

Egzersiz

Fiziksel ve Psikolojik faydalar

Aerobik performansı ve ağrı eşiğini yükseltebilir
ve ağrıyı rahatlatılabilir

Egzersiz sürekli olmalı bırakılınca etkinlik kaybolur

Bilişsel terapi

Ağrı, yorgunluk, fiziksel fonksiyonlar ve ruhsal
durumda düzelme

Genellikle aylarca süren uzun süreli düzelme

Hasta eğitimi

Ağrı, uyku, yorgunluk ve yaşam kalitesinde düzelme

Kombinasyon (multidisipliner terapi)

Orta Düzeyde kanıt

Güçlendirme ve germe eğitimi

Akupunktur, lazer

Hipnoterapi

EMG biofeedback

Balneoterapi

Transkraniyal elektrik stimülasyonu

Zayıf düzeyde Kanıt

Manuel terapi

Masaj tedavisi

Ultrason

Kanıt yok

Hassas nokta enjeksiyonu

Fleksibilite egzersizleri

RESEARCH ARTICLE

Open Access

Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials

Winfried Häuser^{*1,2}, Petra Klose³, Jost Langhorst³, Babak Moradi⁴, Mario Steinbach⁴, Marcus Schiltenswolf⁴ and Angela Busch⁵

Abstract

Introduction: The efficacy and the optimal type and volume of aerobic exercise (AE) in fibromyalgia syndrome (FMS) are not established. We therefore assessed the efficacy of different types and volumes of AE in FMS.

Methods: The Cochrane Library, EMBASE, MEDLINE, PsychInfo and SPORTDISCUS (through April 2009) and the reference sections of original studies and systematic reviews on AE in FMS were systematically reviewed. Randomised controlled trials (RCTs) of AE compared with controls (treatment as usual, attention placebo, active therapy) and head-to-head comparisons of different types of AE were included. Two authors independently extracted articles using predefined data fields, including study quality indicators.

Results: Twenty-eight RCTs comparing AE with controls and seven RCTs comparing different types of AE with a total of 2,494 patients were reviewed. Effects were summarised using standardised mean differences (95% confidence intervals) by random effect models. AE reduced pain (-0.31 (-0.46, -0.17); $P < 0.001$), fatigue (-0.22 (-0.38, -0.05); $P = 0.009$), depressed mood (-0.32 (-0.53, -0.12); $P = 0.002$) and limitations of health-related quality of life (HRQOL) (-0.40 (-0.60, -0.20); $P < 0.001$), and improved physical fitness (0.65 (0.38, 0.95); $P < 0.001$), post treatment. Pain was significantly reduced post treatment by land-based and water-based AE, exercises with slight to moderate intensity and frequency of two or three times per week. Positive effects on depressed mood, HRQOL and physical fitness could be maintained at follow-up. Continuing exercise was associated with positive outcomes at follow-up. Risks of bias analyses did not change the robustness of the results. Few studies reported a detailed exercise protocol, thus limiting subgroup analyses of different types of exercise.

Conclusions: An aerobic exercise programme for FMS patients should consist of land-based or water-based exercises with slight to moderate intensity two or three times per week for at least 4 weeks. The patient should be motivated to continue exercise after participating in an exercise programme.

Aerobik Egzersiz

- Kanıtlar:
 - Ağrı, yorgunluk, depresif ruh halini azaltmakta ve HRQOL ve fiziksel performansı arttırmakta
 - Uyku üzerinde pozitif etki saptanmamış (medikasyon eklenmeli)
 - Uzun dönem takipte ağrı ve yorgunluk üzerine etkisi geçmiş
 - Su içi egzersizlerin karada yapılan egzersizlere üstünlüğü yok
 - Hafif-orta düzeyde aerobik egzersiz etkin (MHR<%50 etkin değil)
 - Haftada 2-3 kez ve en az 4-6 hafta sürmeli
 - Germe ve kuvvetlendirme egzersizleri eklemenin ek yararı görülmemiş

Aerobic exercise in fibromyalgia: a practical review

Eric N. Thomas · Francis Blotman

Table 1 Randomized controlled trials of land-based aerobic-only exercise versus other exercise programs

References	Number of subjects	Program duration exercise modalities	Aerobic group/control improvement
McCain et al. [17]	42	20 weeks cycle ergometry vs. flexibility	Fitness, pain threshold
Richards and Scott [18]	136	12 weeks aerobic (walking, cycling) vs. relaxation and flexibility	General health
Valim et al. [19]	76	20 weeks aerobic/stretching function vs. flexibility	VO ₂ max, depression, pain
Bircan et al. [20]	30	8 weeks vs. muscle strengthening	No significant change

Table 2 Randomized controlled trials of land-based aerobic-only exercise versus no exercise for patients with fibromyalgia

References	Number of subjects	Program duration exercise modalities	Aerobic group/control improvement
Mengshoel et al. [21]	35	20 weeks aerobic dance/no treatment	Upper extremity endurance
Wigers et al. [22]	60	14 weeks aerobic/stress management/no treatment	Aerobic capacity pain distribution tender point score
Verstappen et al. [23]	72	24 weeks aerobic running, cycling, swimming/no treatment	No significant change between groups
Gowans et al. [24]	30	23 weeks aerobic pool and land based vs. controls	6-min walk test depression, self-efficacy
van Santen et al. [25]	143	24 weeks aerobic/biofeedback/controls	No significant change
King et al. [26]	132	12 weeks aerobic/education/combined/written information	6-min walk test self-efficacy
Schachter et al. [27]	143	16 weeks aerobic long/short sessions/controls	Disease severity, well-being
Da Costa et al. [28]	79	12 weeks home-based moderate intensity exercise/usual care	Functional capacity upper-body pain FIQ total score
Etnier et al. [9]	16	18 weeks	Psychological aspects cognitive performances

Table 3 Randomized controlled trials of pool-based aerobic-only exercise for patients with fibromyalgia

References	Number of subjects	Program duration exercise modalities	Aerobic group/control improvement
Jentoft et al. [29]	34	20 weeks aerobic pool/land based	Grip strength (land based) pain, anxiety, depression self-reported physical impairment days of feeling good (pool based)
Altan et al. [30]	50	12 weeks pool-based aerobic/balneotherapy	Sleep, stiffness, depression
Cedraschi et al. [31]	164	6 weeks pool-based aerobic/waiting list	Quality of life, FIQ
Thomas-Carus et al. [32]	34	12 weeks aquatic training/leisure activities	Physical function, body pain, mental and general health balance, stair climbing
Thomas-Carus et al. [33]	30	8 months exercise in warm water/control group (inactive)	Physical function, pain anxiety, depression
de Andrade et al. [34]	46	12 weeks	Thalassotherapy > pool for depression

Klinisyen için öneriler

- Hastanın bazal fiziksel fonksiyon ve ağrı şiddetine göre egzersizi bireyselleştir
- Düşük yoğunlukta başla ve dereceli olarak hasta toleransına göre arttır
- Egzersiz en azından başlangıçta gözetim altında olmalı ki egzersiz sonrası ağrıyı artışı varsa egzersizler modifiye edilsin
- FMS semptomlarında artış olursa egzersiz yoğunluğu azaltılmalı ama sıklık aynı kalmalı
- Düşük-orta şiddette haftada 2-3 kez egzersiz yoğunluğu semptomlar, psikolojik stres ve fiziksel performans üzerinde etkilidir.
- Son nokta MHR %60-70'inde 20-30 dk süreyi başarmak olmalıdır

Physical Therapy Modalities in Management of Fibromyalgia

Ali Gür*

- Fizik tedavi uygulamaları,
 - Ağrı
 - Yorgunluk
 - Kondüsyon
 - Kas kuvveti
 - Uyku problemleri

- Kesikli US ve interferansiyel akım kombinasyonu ağrı ve uyku bozukluğunda etkin (Almedia et al, Pain 2003)
- FMS, jeneralize kas-iskelet sistemi ağrısı olduğu için TENS kullanımı limitli. Kullanım yerine göre etkin bulan yayınlar var (Offanbacher et al Scand J Rheumatol 2000, Minor MA et al, Rheum Dis Clin N AM, 1999)
- Laser: doz ve süre ile ilgili bir standart yok. FMS semptomlarının çoğu üzerinde etkin bulan çalışmalar var (Gür A, Laser Med SC 2002, Rheumatol Int 2002)
- Magnetoterapi: RKÇ'da tüm vücut PEMF uygulamasının 3 aylık takibinde ağrı ve yaşam kalitesi düzeyinde artış saptanmışken depresyon düzeyinde etkinlik görülmemiş (Sutbeyaz ST et al. Clin J Pain 2009)

The use of electrothermal and phototherapeutic methods for the treatment of fibromyalgia syndrome: a systematic review

A utilização dos recursos eletrotermofototerapêuticos no tratamento da síndrome da fibromialgia: uma revisão sistemática

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Abstract

Objective: To systematically investigate the scientific evidence relating to electrothermal and phototherapeutic methods for the treatment of fibromyalgia syndrome (FMS). **Methods:** The search for reports on interventions using electrothermal and phototherapy for FMS was carried out in the Pubmed, Medline, Lilacs, Scielo, ISI Web of Knowledge, PEDro and Cochrane Collaboration databases. Randomized controlled clinical trials published over the past 10 years in English, Portuguese and Spanish were selected. The methodological quality of the studies was assessed using the Jadad scale. The analysis on the study results was done by means of critical review of the content. **Results:** Seven studies were reviewed in full, and these identified interventions using laser (n=4), transcutaneous electrical nerve stimulation (TENS; n=1), interferential current (IFC) alone (n=1) and IFC combined with ultrasound (US; n=1). Only two studies showed good methodological quality according to the Jadad scale. Most of the studies (n=6) used the criteria of the American College of Rheumatology for the clinical diagnosis of FMS. Pain was the most frequently evaluated FMS symptom. The intervention methods and their duration varied widely, and there was no mention of the parameters used in the electrothermal and phototherapeutic methods. Pain levels reduced significantly in all of the studies. **Conclusion:** There are still limitations on the generalization of the results, adverse reactions and doses of the FMS treatment. Further studies are needed to establish the effectiveness of electrothermal and phototherapy in treating FMS.

Table 1. Data summary of the randomized clinical trials using electrothermal and phototherapy methods for the treatment of fibromyalgia.

Study	Subjects	Assessment	Study design	Intervention	Outcomes
Gür et al. ¹⁷	<p>Diagnosis: ACR.</p> <p>Inclusion: no medication for at least one month.</p> <p>Age: not mentioned</p> <p>Groups:</p> <p>EG=Laser (n=20 ♀).</p> <p>CG=Placebo (n=20 ♀).</p>	<p>Likert Scale for Symptoms (0=none; 1=mild; 2=moderate; 3=severe; 4=extreme):</p> <ul style="list-style-type: none"> - pain. - number of tender points. - morning stiffness. - sleep disturbance. - skinfold tenderness. - muscle spasms. - fatigue. 	<p>Prospective, controlled, randomized, pre/post-intervention assessment.</p>	<p>EG: Low power laser (Ga-As).</p> <p>CG: Placebo. Same procedure without the emission of rays.</p> <p>Intervention EG:</p> <ul style="list-style-type: none"> - Laser Ga-As, 904 nm, power 11.2 mw. - Application: patient seated with $2\text{J}/\text{cm}^2$ emission for 3 minutes in each tender point. - Individual treatment. - 5x/week. - Total: 2 weeks (10 sessions). - Sessions in the afternoon at a room temperature of 20°C. 	<ul style="list-style-type: none"> - Significant improvement in <u>all parameters</u> evaluated in the EG. - Significant improvement in all parameters evaluated in the CG, except for skinfold tenderness, sleep disturbance and fatigue. - With respect to pain, muscle spasms, morning stiffness and number of tender points, the EG had greater improvement than the CG.
Gür et al. ¹⁸	<p>Diagnosis: ACR.</p> <p>Inclusion: no medication for at least one month.</p> <p>Age: mean of 30 years.</p> <p>Groups:</p> <p>EG=Laser (n=20 ♀ 5 ♂).</p> <p>CG1=Placebo (n=19 ♀ 6 ♂).</p> <p>CG2=Medication (n=21 ♀ 4 ♂).</p>	<p>Likert Scale for Symptoms (0=none; 1=mild; 2=moderate; 3=severe; 4=extreme):</p> <ul style="list-style-type: none"> - pain. - number of tender points. - morning stiffness. - sleep disturbance. - skinfold tenderness. - muscle spasms. - fatigue. <p>Quality of life: FIQ</p> <p>Depression: Hamilton Depression Scale</p>	<p>Prospective, controlled, randomized, pre/post-intervention assessment.</p>	<p>EG: Low power Laser (Ga-As).</p> <p>CG1: Placebo. Same procedure without the emission of rays.</p> <p>Intervention EG:</p> <ul style="list-style-type: none"> - Laser Ga-As, 904 nm, power 11.2 mw. - Application: patient seated with $2\text{J}/\text{cm}^2$ emission for 3 minutes in each tender point. - Individual treatment. - 5x/week. - Total: 2 weeks (10 sessions). - Sessions in the afternoon with the room temperature of 20 °C. <p>CG2: Medication - 10 mg amitriptyline before bed, daily for 8 weeks.</p>	<ul style="list-style-type: none"> - Significant improvement in all parameters evaluated in the EG. - Significant improvement in all parameters evaluated in the CG, except for skinfold tenderness, sleep disturbance, depression and fatigue. - Significant improvement in all parameters evaluated in CG2, except for fatigue. - With respect to pain, muscle spasms, morning stiffness and number of tender points, the EG had greater improvement than CG1.
Matsutani et al. ¹⁹	<p>Diagnosis: clinical</p> <p>Inclusion: cognition to follow commands.</p> <p>Age: 25-60 years (mean of 45 years)</p> <p>Groups:</p> <p>EG=Stretching/Laser (n=10 ♀)</p> <p>CG=Stretching (n=10 ♀)</p>	<p>Pain:</p> <ul style="list-style-type: none"> - Pain threshold by dolorimetry at tender points. - VAS of pain <p>Quality of life:</p> <ul style="list-style-type: none"> - FIQ - SF-36 	<p>Prospective, randomized, pre/post-intervention assessment.</p>	<p>EG and CG: Education (booklet and lecture)</p> <p>Intervention EG:</p> <ul style="list-style-type: none"> - Laser GaAlAs, 830nm, power 30 mw - Application: $3\text{J}/\text{cm}^2$ continuous emission at each tender point. - general stretching exercises. - 1 hour session, individual treatment. - 2x/week. - total: 5 weeks (10 sessions) <p>Intervention EG:</p> <ul style="list-style-type: none"> - general stretching exercises. - 1 hour session, individual treatment. - 2x/week. - total: 5 weeks (10 sessions). 	<ul style="list-style-type: none"> - Significant improvement in pain as evaluated by VAS in both groups. - Significant <u>worsening in the pain threshold at tender points</u> in both groups. - FIQ and SF-36 – improvement in both groups after intervention. No difference between groups after the interventions.

Table 2. (Continued)

Amagan et al. ²⁸	<p>Diagnosis: ACR.</p> <p>Inclusion: no medication.</p> <p>Age: 26–47 years (mean 38 years).</p> <p>Groups:</p> <p>EG= Laser (n=16 ♀).</p> <p>CG= Placebo (n=16 ♀).</p>	<p>Likert Scale:</p> <ul style="list-style-type: none"> - morning stiffness (0=none, 1=mild, 2=moderate, 3=severe, 4=extreme). - subjective wellbeing (1=great improvement, 2=moderate improvement, 3=mild improvement, 4=without improvement, 5= worsening). <p>Pain score (0–54 points)</p> <p>Quality of life: FIQ.</p> <ul style="list-style-type: none"> - number of pain tender points by the digital pressure. 	<p>Prospective, controlled, randomized, pre/post-intervention assessment and 6 months of follow-up.</p>	<p>EG: Laser GaAlAs, 830 nm, power 50 mW.</p> <ul style="list-style-type: none"> - Application: 2J emission for 1 minute at each tender point. - Individual treatment. - 5x/week. - Total: 2 weeks (10 sessions). <p>CG: Placebo. Same procedure as EG without emission of rays.</p>	<ul style="list-style-type: none"> - Significant improvement in all parameters evaluated in the EG after intervention and in the follow-up compared to baseline. - Significant improvement in number of tender points and stiffness in the CG after intervention. - Significant improvement in the FIQ, subjective wellbeing and pain in the EG compared to the CG after intervention. - Significant improve in all parameters evaluated in the EG compared to the CG during follow-up.
Falman-do et al. ²⁹	<p>Diagnosis: ACR.</p> <p>Inclusion: positive tender points of the trapezius muscle.</p> <p>Age: 27–50 years.</p> <p>Groups:</p> <p>EG= IFC 150Hz (n=6 ♀).</p> <p>CG= IFC 20Hz (n=4 ♀).</p>	<p>Pain:</p> <ul style="list-style-type: none"> - pain points: digital pressure grading (0–5 points). - intensity VAS. <p>Quality of life: FIQ.</p>	<p>Prospective, randomized, pre/post-intervention assessments.</p>	<p>EG: IFC application at 150 Hz.</p> <p>CG: IFC application at 20 Hz.</p> <p>Intervention in both groups:</p> <ul style="list-style-type: none"> - individual sessions. - 2x/week. - total: 5 weeks (10 sessions). - Application: 30 minutes with tetrapolar 5x9 cm electrodes, tetrapolar sweep mode. 	<ul style="list-style-type: none"> - VAS: significant improvement in the CG (IFC 20 Hz). - Tender points: significant improvement in the CG (IFC 20 Hz) and the EG (150Hz). - FIQ: improvement in both groups after intervention, but without statistical analysis.
Almeida et al. ³⁰	<p>Diagnosis: ACR.</p> <p>Inclusion: women, >50 years; pain and sleep disorder in the last 6 months.</p> <p>Age: >50 years.</p> <p>Groups:</p> <p>EG= IFC and US (n= 9 ♀).</p> <p>CG= placebo (n= 8 ♀).</p>	<p>Pain:</p> <ul style="list-style-type: none"> - VAS body map. - pain points: digital and pressure algometry. <p>Sleep assessment:</p> <ul style="list-style-type: none"> - Brazilian list of sleep disorders. - Polysomnography. 	<p>Prospective, randomized, pre/post-intervention assessment.</p>	<p>EG: Combination therapy</p> <p>CG: Placebo, inactive current in different parts of the body</p> <p>Intervention in both groups:</p> <p>Pain electrodiagnosis:</p> <ul style="list-style-type: none"> - continuous US – 1 MHz; 0.5 W/cm² - IFC – 400Hz, AMF: 100 Hz <p>Treatment:</p> <ul style="list-style-type: none"> - pulsed US (1MHz; 2.5 W/cm²) - IFC - individual treatment. - 3x/week. - total: 4 weeks (12 sessions). 	<ul style="list-style-type: none"> - Greater improvement in the pain parameters of the EG than the CG. - Greater improvement in the sleep parameters of the EG than the CG. - Improvement in all parameters of the EG before and after intervention.
Silva et al. ³¹	<p>Diagnosis: ACR.</p> <p>Inclusion: no disability.</p> <p>Age: mean between 47 and 50 years.</p> <p>Groups:</p> <p>EG= TENS (n=5 ♀).</p> <p>CG= hydrotherapy (n=5 ♀).</p>	<p>Flexibility: finger-to-finger distance</p> <p>Pain: VAS</p> <p>Quality of life:</p> <ul style="list-style-type: none"> - SF-36. - Nottingham Health Profile (NHP). <p>Depression: Beck Inventory.</p>	<p>Prospective, randomized, pre/post-intervention assessment.</p>	<p>EG: TENS</p> <ul style="list-style-type: none"> - Application of TENS using surface electrodes and conductive gel placed at the tender points of the trapezius, supraspinous, gluteus and medial jointline of the knee, bilaterally. - Parameters: pulse frequency of 15 Hz, pulse time of 150 µs and the intensity of tingling sensation. - Total time of application: 40 minutes. - 3x/week (total of 10 sessions). <p>CG: Hydrotherapy.</p> <ul style="list-style-type: none"> - Therapy consisting of warm-up (5 min), stretching (20 min) and aerobic exercise (15 min). 	<ul style="list-style-type: none"> - In the EG, improvement in pain and depressive symptoms evaluated by the Beck inventory and improvement in quality of life evaluated by SF-36. - In the CG, improvement in quality of life evaluated by SF-36 and NHP (Emotional Reaction dimension). - After intervention, the EG had lower VAS than the CG.

Hasta eğitimi

- Sendromun tipik semptomlarını tanımlamak,
- Sebepleri, süreci ve tedaviyi anlatmak
- Ağır kaldırma, kötü postür gibi alışkanlıkları düzeltmek
- Günlük yaşam aktivitelerini düzenlemek, iş yoğunluğunu derecelendirmek, molaları planlanamak, egzersiz için zaman ayırmak

Bilişsel-Davranışsal Tedavi

- SSS ve PSS, farklı seviyelerde ağrının işlenmesi hakkında eğitim
- Psikolojik ve mental stresle başa çıkma yolları
- Uyku kalitesini arttırıcı davranışsal teknikler
- Amaçların başarılması, kendine güven ve mental sağlık için tatmin edici aktiviteler önermek
- Psikososyal destek

SON SÖZ

- Hastaya vakit ayrılmalı,
- Semptomlar detaylı bir şekilde irdelenmeli
- Kişiyeye göre özelleştirilmiş farmakolojik ve nonfarmakolojik tedaviler kombine edilmeli
- Hastaya hastalığı ve tedavisi konusunda eğitim verilmeli
- Farmakolojik ve nonfarmakolojik tedaviler yakından takip edilip, doğru zamanda doğru müdahaleler yapılmalı
- Hasta sahiplenilmeli

Teşekkürler

