Des médicaments sont-ils efficaces dans la fibromyalgie?

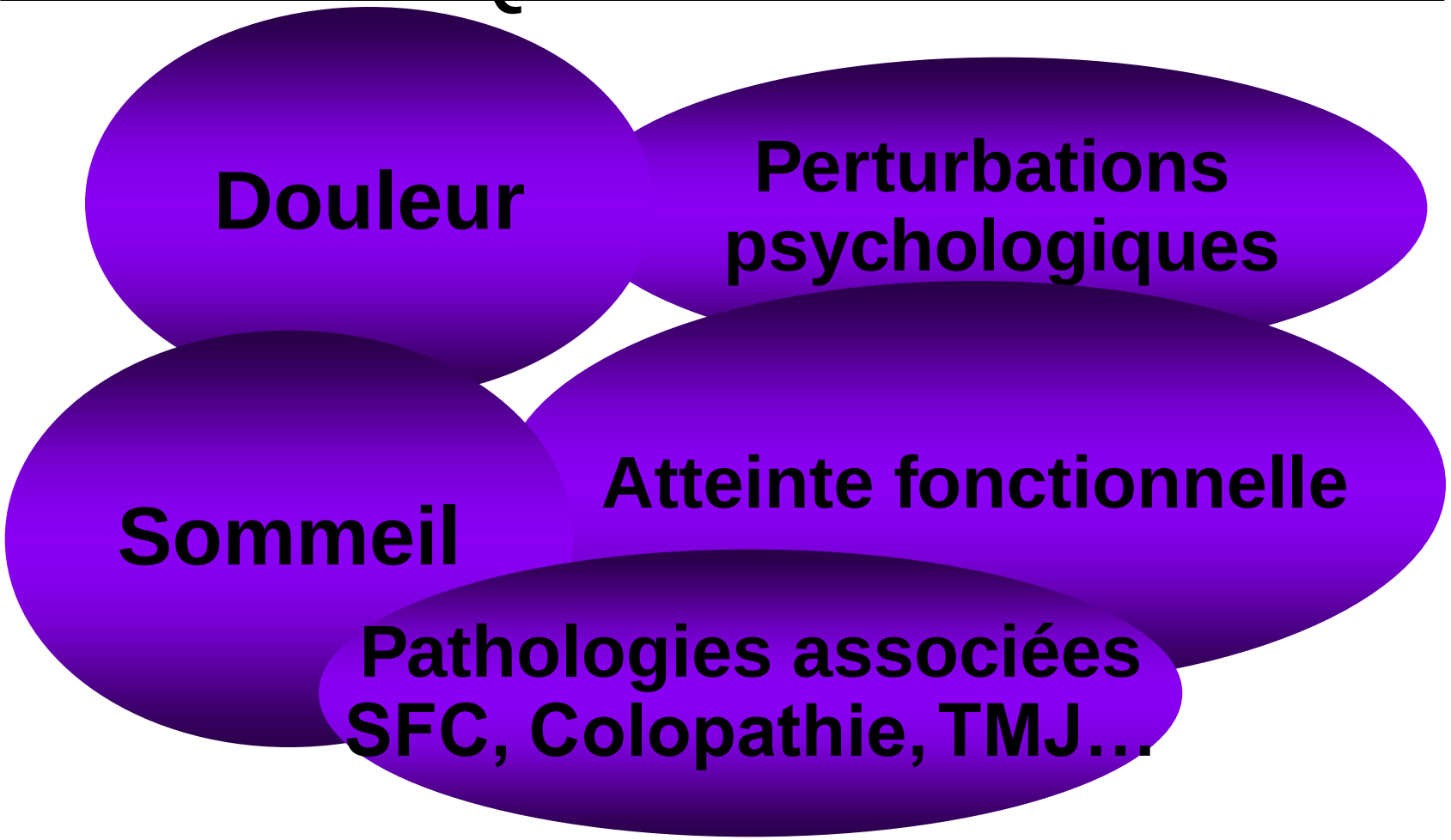
« La seule façon d'être heureux c'est d'aimer souffrir »
W Allen

Serge Perrot

Hotel Dieu, Paris

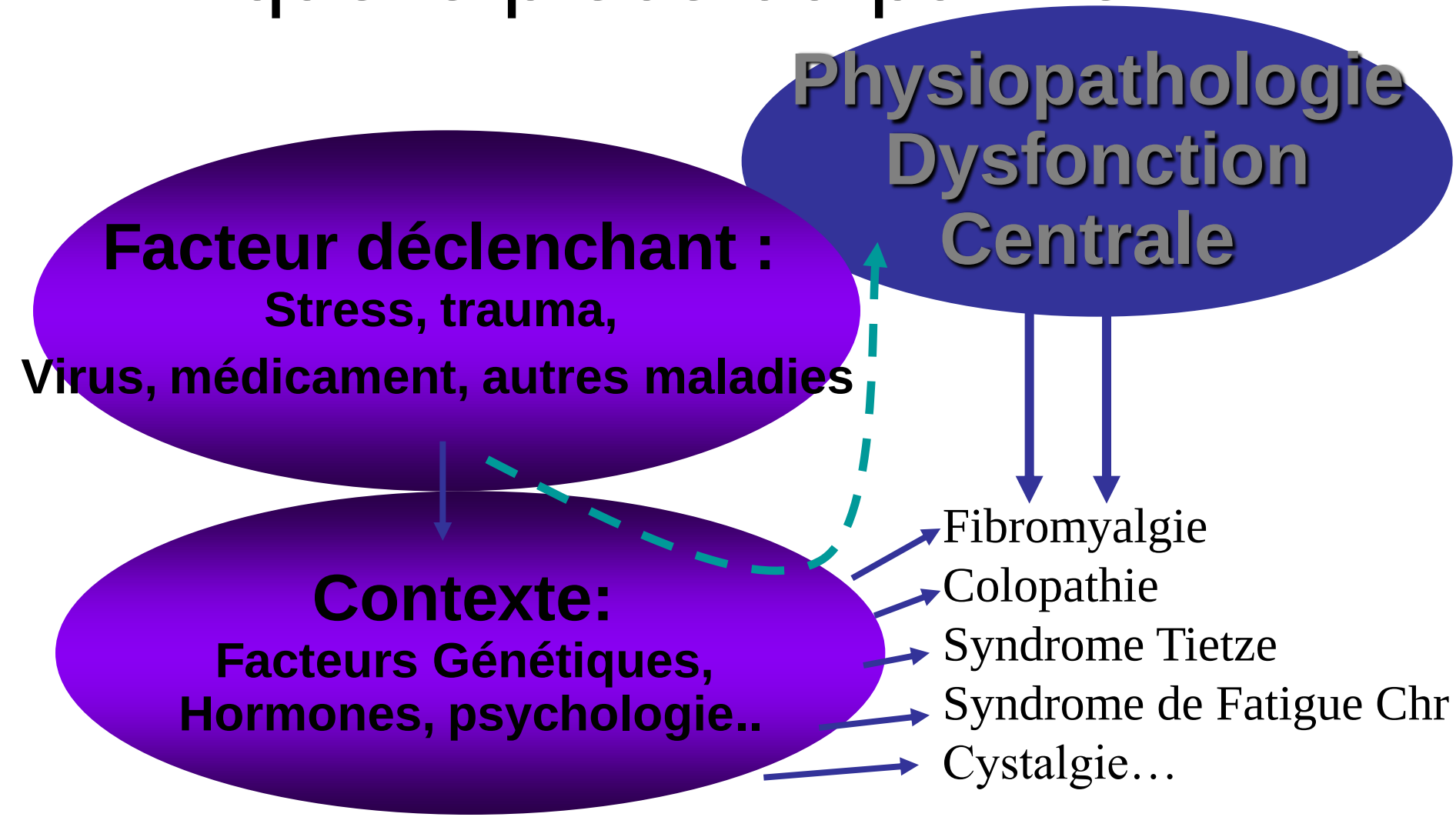
UNIVERSITÉ René Descartes PARIS 5

FIBROMYALGIE
Que traiter?



« Le traitement de la fibromyalgie est autant un art qu'une science », Clauw 200

FIBROMYALGIE: agir sur quelle pièce du puzzle ?



Kop, Arthritis Rheum. 2005; 52:296-303.

TRAITEMENTS: classement selon les modes d'action

- SYMPTOMES
- PHYSIOPATHOLOGIE
- ADJUVANTS
- THERAPEUTIQUES ALTERNATIVES

FIBROMYALGIA IS REAL

TRAITEMENTS: classement selon les objectifs

- DOULEUR
- FATIGUE
- TROUBLES DU SOMMEIL
- FONCTION
- STRESS
- QUALITE DE VIE
- DEMANDE DES PATIENTS
- AUTRES...

EST CE QUE NOUS « MESURONS » LE PROBLEME ?

- Patient ou médecin: demande? Le pourcentage d'amélioration?
- Altérations cognitives (mémoire)
- Annonce du diagnostic avec le traitement
- Suivi: court ou long terme?
- Quel délai d'évaluation?

Traitements de la fibromyalgie Recherche bibliographique EULAR

- Recherche préliminaire: 478 études
- Total de 146 articles identifiés comme éligibles
  - 59 Pharmacologiques
  - 87 Non-pharmacologiques

Approches pharmacologiques publiées

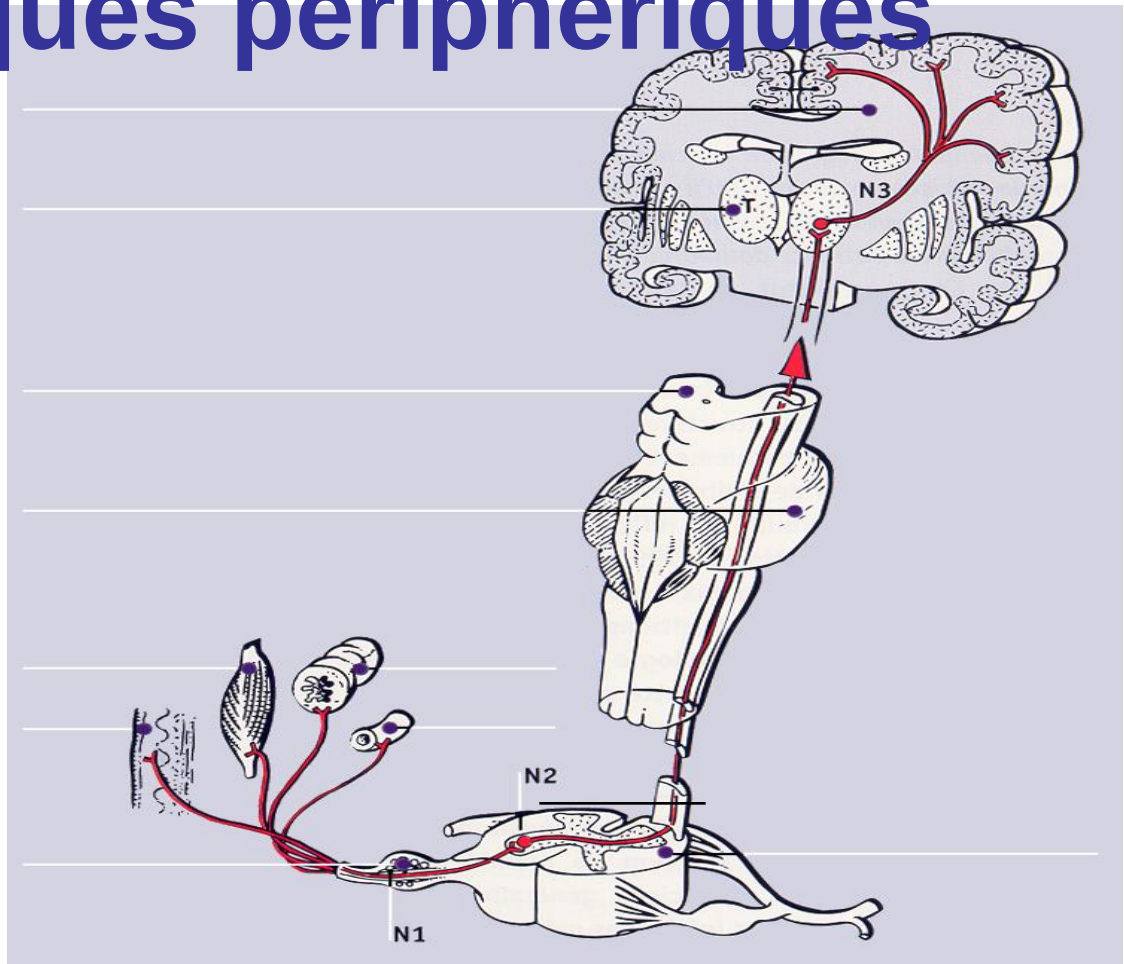
- Analgésiques
  - Systemiques & Topiques
- Anti-dépresseurs
  - Tri-cycliques
  - IRS
  - Mixtes : IRSNa
  - IMAO
  - Agonistes 5HT2/3
- Autres
  - Pregabaline
  - D3

Qualité des études Pharmacologiques: score EULAR

- Haute = 22
- Moyenne = 13
- Basse = 3

Traiter la douleur de la fibromyalgie

- -Analgésiques périphériques
- -Palier 2
- -Palier 3?



ANTALGIQUES 1 ET AINS

- Paracétamol (Vaeroy 1989)

- AINS:
  - Naproxène (Goldenberg 1986)
  - Ibuprofène (Yunus 1989, Russel 1991)
  - Ténoxicam (Carrera 1996)

+ en association avec benzodiazépines

Antalgiques de niveau 2

- Tramadol ?

  Injectable: Biasi 1998

  Tramadol-paracétamol Benett 2003

- Codéine?

< 20% de patients avec antalgiques de niveau 2 (Wolfe 1997)

Tramadol-Paracétamol (Bennett 2003)

Table 2. Pain and Symptoms at Baseline and the Final Visit

Characteristic	Baseline		Final Visit		
	Tramadol/ Acetaminophen (n = 156)	Placebo (n = 157)	Tramadol/ Acetaminophen (n = 156)	Placebo (n = 157)	P Value*
Pain score (mm)†	72 ± 14	72 ± 15	53 ± 32	65 ± 29	<0.001
Pain relief score‡	—	—	1.7 ± 1.4	0.8 ± 1.3	<0.001
Number of tender points	16 ± 2.2	16 ± 2.3	13 ± 4.9	14 ± 4.3	0.04
Average myalgic score§	1.7 ± 0.6	1.7 ± 0.6	1.3 ± 0.8	1.5 ± 0.8	0.06
Sleep questionnaire‖					
Sleep Index 6	62 ± 16	61 ± 17	54 ± 18	54 ± 18	0.78
Sleep Index 9	62 ± 16	61 ± 16	55 ± 17	55 ± 18	0.74

* Comparison between final values based on analysis of covariance adjusting for clinical center and baseline values.

† 0 mm (no pain) to 100 mm (extreme pain) on a visual analog scale.

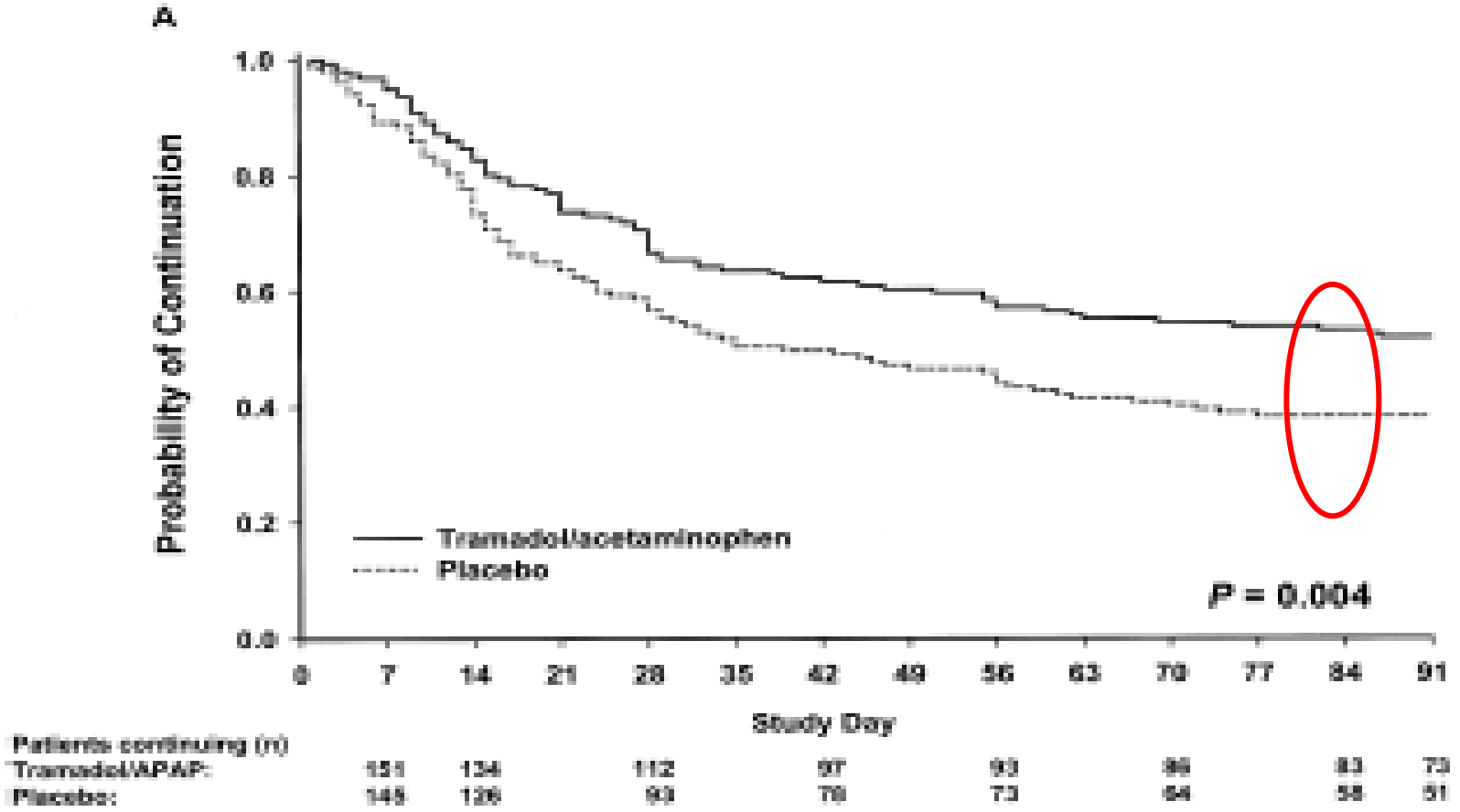
‡ Complete relief = 4, a lot = 3, moderate = 2, slight = 1, none = 0, worse = −1.

§ Calculated from myalgic scores at each tender point, where no pain = 0, patient complains of pain only = 1, patient reacts to pain emotionally = 2, and patient withdraws or flinches = 3.

‖ Lower scores represent better sleep, on a 0 to 100 scale.

Δ=1,2 mm Action antalgique démontrée ?

Tramadol-paracétamol (Bennett 2003)



Opioides pour la fibromyalgie?

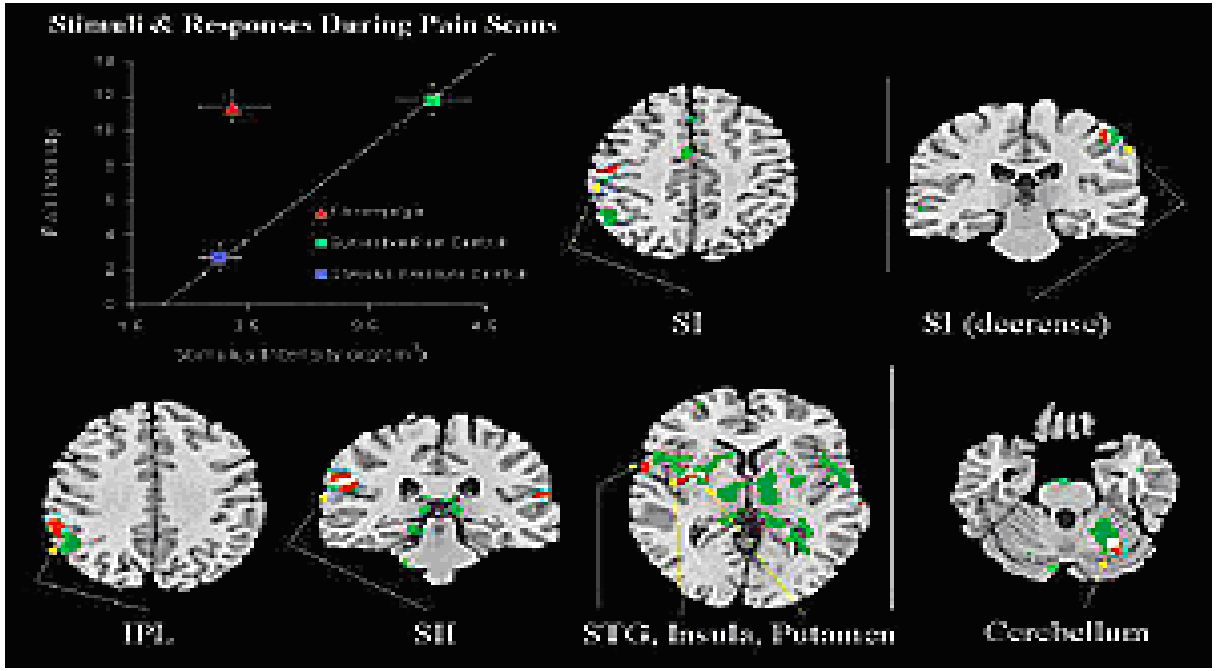
- MORPHINE (Sorensen 1997)
  - Prudence +++ , surtout chez sujets jeunes
  - cf recommandations

Traiter la dysfonction du système nerveux central?

-Antidépresseurs

-Anticonvulsivants

-Autres récepteurs: 5HT3, D3…



Antidépresseurs

- **IMIPRAMINIQUES ET APPARENTES**
  Tricycliques (amitriptyline, clomipramine, désipramine…) et tétracycliques (maprotiline)
- **IRS:** Inhibiteurs Spécifiques de la recapture de la Sérotonine
  fluoxétine, citalopram, paroxétine...
- **IRSNa:** Inhibiteurs de la de la recapture de la Sérotonine et de la Noradrénaline **venlafaxine, milnacipran, duloxetine**
- **NaSSA:** «Noradrenergic Serotonergic Specific Antidepressants»
  mirtazapine
- **Autres: miansérine, néfazodone…**

ANTIDEPRESSEURS TRICYCLIQUES : LE TRAITEMENT?

- Amitriptyline LAROXYL (Carette 1986, 1994, Scudds 1989, Goldenberg 1986, 1996) Effet + rapide mais à 3 mois épuisement de l'effet
- Clomipramine ANAFRANIL (Bibolottti 1986)
- Dothiépine ±PROTHIADEN (Caruso 1997)

ANTIDEPRESSEURS IRS

- Fluoxétine PROZAC (Wolfe 1994, Goldenberg 1996, 2000, Arnold 2002) jusqu'à 80 mg/j
- Citalopram SEROPRAM (Norregaard 1995, Anderberg 2000)
  - Étude 4 mois
  - effet global - , effet sur humeur +
  - effet antalgique à 2 mois, pas à 4 mois

Fluoxétine, Arnold 2002

Fluoxetine for Fibromyalgia/Arnold et al

Table 4. Outcome Measures for Subjects with Fibromyalgia Receiving Fluoxetine or Placebo: Completer Analysis

Measure (score range)	Mean (±SD) Change From Baseline to Endpoint: Fluoxetine (n = 19)	Mean (±SD) Change From Baseline to Endpoint: Placebo (n = 18)	Between-Group Difference (95% Confidence Interval)	*P* Value
Fibromyalgia Impact Questionnaire				
Total score (0–80)	−11.5 ± 14.8	−0.4 ± 15	−11 (−21 to −1)	0.03
Subscores				
Physical Impairment (0–9.99)	−0.9 ± 1.8	−0.9 ± 2.1	0.0 (−1.3 to 1.3)	0.99
Days felt good (0–10.01)	−2.2 ± 4.0	−0.3 ± 3.6	−1.9 (−4.4 to 0.7)	0.14
Work missed* (0–10)	0.0 ± 0.0	0.5 ± 1.2	−0.5 (−1.1 to 0.2)	0.18
Work impairment† (0–10)	−0.7 ± 2.7	−0.7 ± 2.3	0.0 (−2.0 to 2.0)	0.98
Pain (0–10)	−2.3 ± 2.4	−0.1 ± 2.5	−2.2 (−3.8 to −0.5)	0.01
Fatigue (0–10)	−1.6 ± 2.8	0.4 ± 2.8	−2.0 (−3.8 to −0.2)	0.03
Feeling tired upon awakening (0–10)	−1.1 ± 2.9	0.3 ± 2.8	−1.3 (−3.2 to 0.6)	0.18
Stiffness (0–10)	−1.3 ± 3.2	−0.3 ± 2.2	−1.0 (−2.9 to 0.8)	0.26
Anxiety (0–10)	−0.6 ± 2.5	0.1 ± 3.2	−0.7 (−2.7 to 1.2)	0.43
Depression (0–10)	−1.5 ± 2.8	0.5 ± 2.1	−2.0 (−3.7 to −0.4)	0.02
Tender points‡ (0–18)	−2.1 ± 3.8	−0.5 ± 2.9	−1.5 (−4 to 1)	0.22
Myalgic score§	8.6 ± 17.2	2.9 ± 13.3	5.8 (−4.6 to 16.2)	0.27
McGill Pain Questionnaire (0–78)	−11.8 ± 8.3	−4.7 ± 10	−7.2 (−13.3 to −1.1)	0.02

* Not included in total score; fluoxetine (n = 13), placebo (n = 13).
† Not included in total score; fluoxetine (n = 14), placebo (n = 13).
‡ Fluoxetine (n = 16), placebo (n = 15).
§ Fluoxetine (n = 18), placebo (n = 18).

Effet sur douleur, sur dépression, sur fatigu
pas sur atteinte physique, travail

Doses > doses antidépressives

Fluoxetine

FIQ fonction

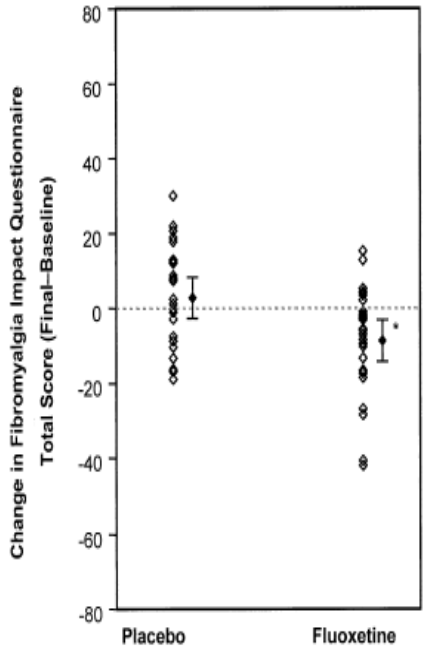


Figure 1. Intent-to-treat analysis of individual change in Fibromyalgia Impact Questionnaire total scores for fluoxetine and placebo treatment groups. The corresponding means with 95% confidence intervals are to the right of the data. The asterisk (*) indicates $P = 0.005$ versus placebo.

FIQ douleur

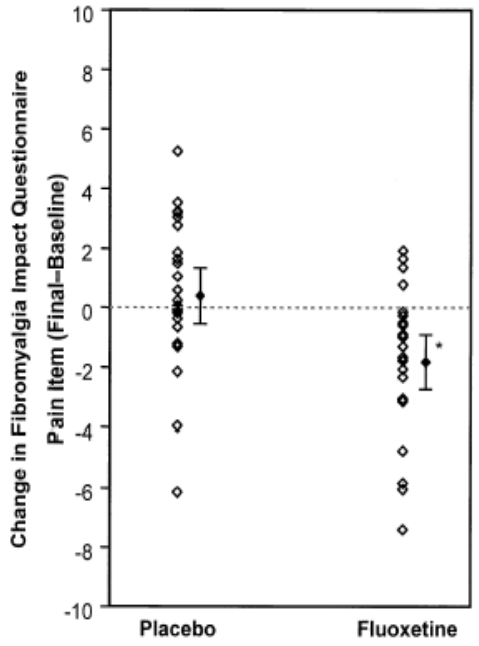


Figure 2. Intent-to-treat analysis of individual change in Fibromyalgia Impact Questionnaire pain scores for fluoxetine and placebo treatment groups. The corresponding means with 95% confidence intervals are to the right of the data. The asterisk (*) indicates $P = 0.002$ versus placebo.

ANTIDEPRESSEURS IRSNa action indépendante de l'effet thymique

- Ritansérine ± ATHYMIL (Olin 1998)
- Venlafaxine EFFEXOR (Dwight 1998, Zijstra 2002, Sayar 2003) études courtes 1 mois
- Duloxétine CYMBALTA Arnold et coll, 2004 (12 semaines)
- Milnacipran IXEL 200 mg Gendreau et coll 2005 (12 semaines),

Duloxétine 60-120 mg/j: douleur

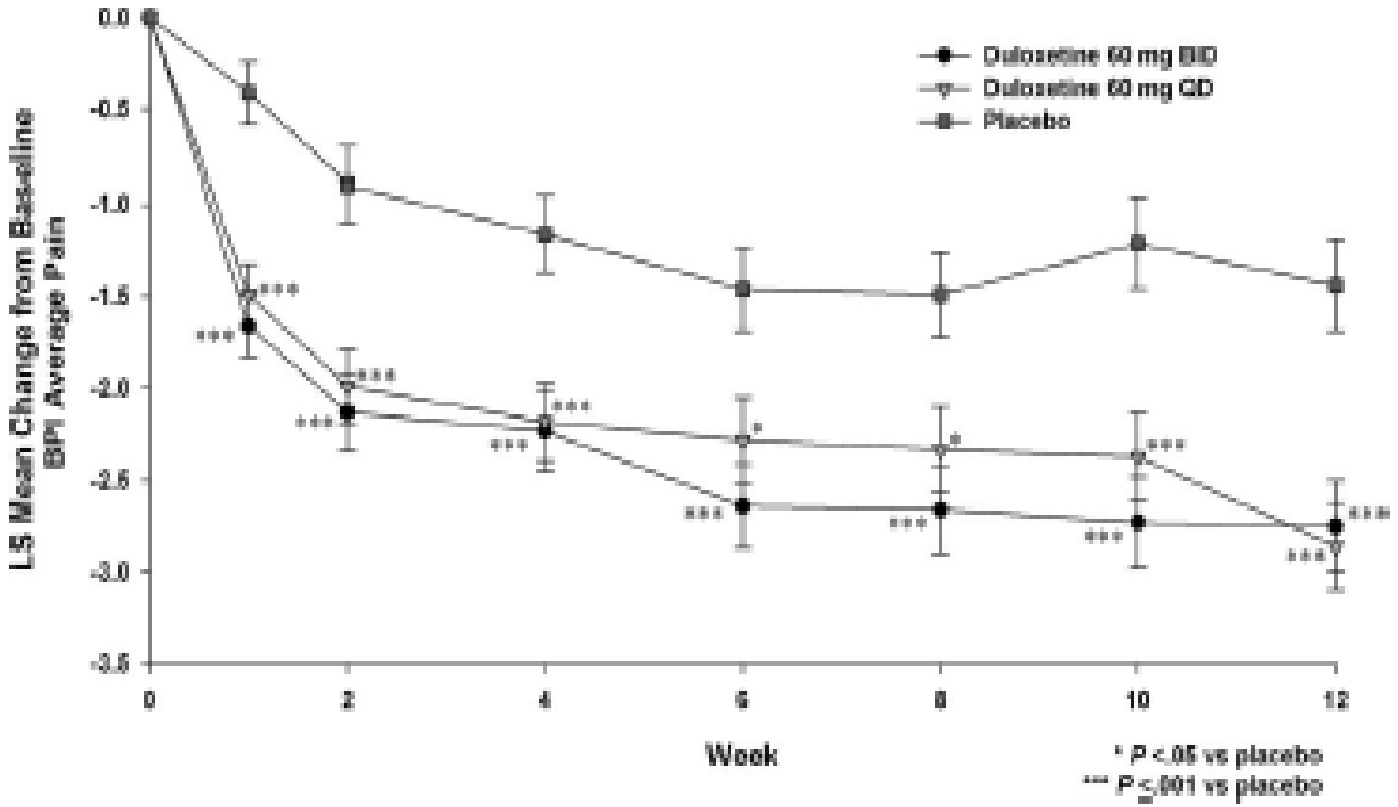


Fig. 2. Least-squares (LS) mean change from baseline in Brief Pain Inventory (BPI) average pain severity score for all randomized patients. Duloxetine 60 mg BID=duloxetine 60 mg twice a day; duloxetine 60 mg QD=duloxetine 60 mg once a day.

Duloxétine 60-120 mg/j: FIQ total

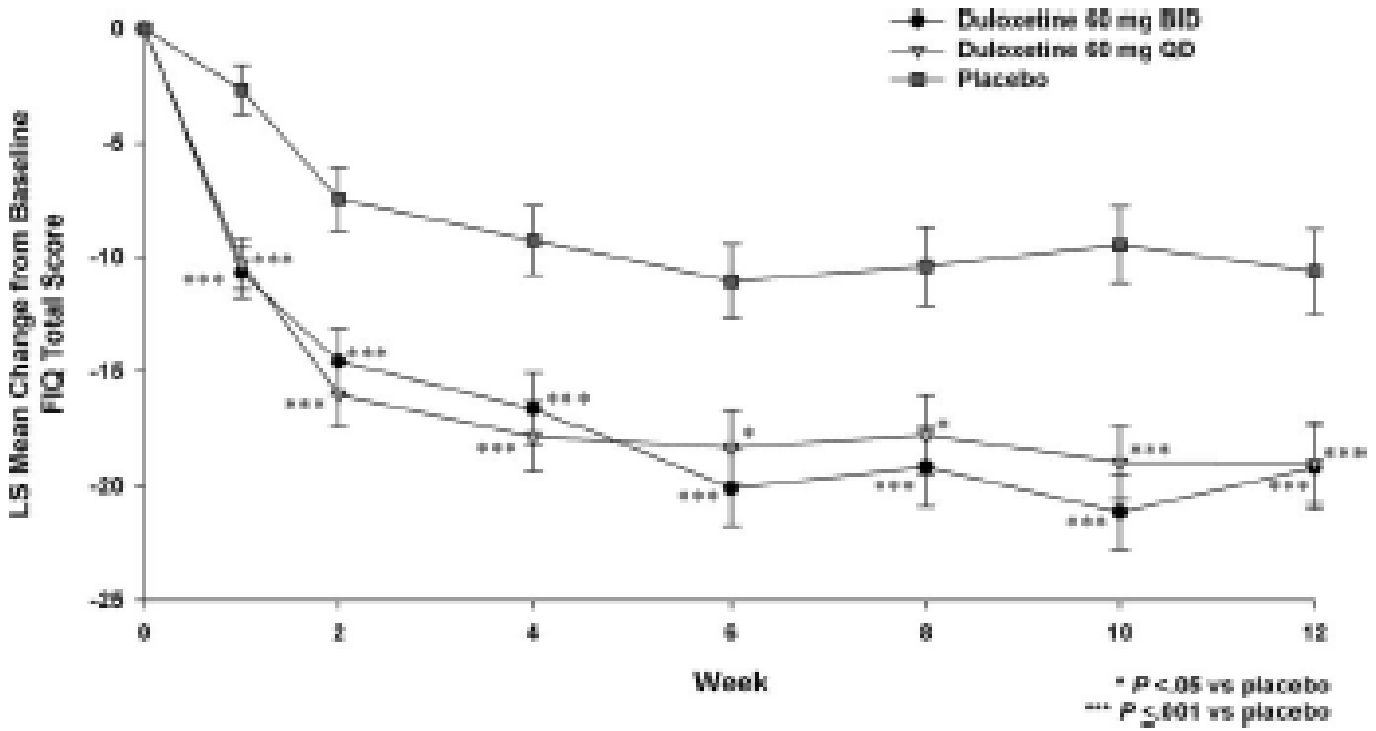


Fig. 3. Least-squares (LS) mean change from baseline in the Fibromyalgia Impact Questionnaire (FIQ) total score for all randomized patients. Duloxetine 60 mg BID = duloxetine 60 mg twice a day; duloxetine 60 mg QD = duloxetine 60 mg once a day.

Duloxétine 60-120: effets secondaires surtout initiaux

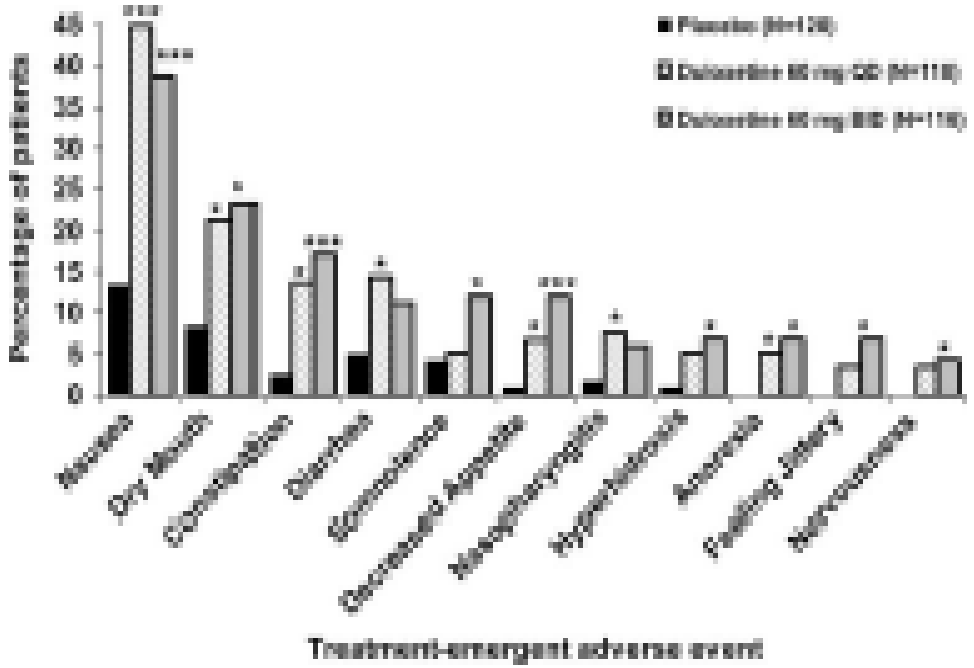


Fig. 4. Treatment-emergent adverse events that were significantly more common in the duloxetine-treated patients compared with the patients on placebo. *P-value <0.05 vs. placebo, **P-value <0.001 vs. placebo. Duloxetine 60 mg BID=duloxetine 60 mg twice a day; duloxetine 60 mg QD=duloxetine 60 mg once a day.

Milnacipran 100-200: effet dose sur douleur

Table 2. Analyses of pain measures (intent to treat analyses using last observation carried forward method). A. Continuous pain measures, or mean change in pain measures from baseline less placebo change. B. Dichotomous pain measures, or the proportion of "responders" for each assessment.

A.	Milnacipran BID, n = 51 [p]	Milnacipran QD, n = 46 [p]	Placebo Score Change from Baseline, n = 28
Daily E-diary pain scores (0–20)	−3.0 ± 3.5 [0.191]	−2.2 ± 3.2 [0.635]	−1.86 ± 3.74
Weekly E-diary pain scores (0–20)	−3.1 ± 3.5 [0.025]	−2.5 ± 3.9 [0.139]	−1.14 ± 3.79
Paper Gracely pain scores (0–20)	−4.7 ± 4.8 [0.010]	−2.9 ± 4.8 [0.317]	−1.7 ± 4.1
Paper VAS pain scores (0–10)	−2.5 ± 2.8 [0.030]	−2.0 ± 3.2 [0.180]	−0.9 ± 2.9
McGill present-pain intensity (0–10)	−2.2 ± 2.7 [0.023]	−1.4 ± 3.2 [0.315]	−0.6 ± 2.7
B.	**BID, n = 51 (%) [p]**	**QD, n = 46 (%) [p]**	**Placebo, n = 28 (%)**
Daily E-diary proportion of responders			
30% pain reduction (≥ −3.3 units)	18 (35) [0.125]	10 (22) [0.772]	5 (18)
50% pain reduction (≥ −4.0 units)	18 (35) [0.066]	10 (22) [0.546]	4 (14)
Weekly E-diary proportion of responders			
30% pain reduction (≥ −3.3 units)	20 (39) [0.023]	13 (28) [0.255]	4 (14)
50% pain reduction (≥ −4.0 units)	19 (37) [0.040]	10 (22) [0.550]	4 (14)
Paper Gracely pain scores			
30% pain reduction (≥ −3.3 units)	23 (45) [0.007]	16 (35) [0.183]	5 (18)
50% pain reduction (≥ −4.0 units)	19 (37) [0.040]	13 (28) [0.250]	4 (14)
Paper VAS pain scores			
30% pain reduction (≥ −3.3 units)	20 (39) [0.136]	16 (35) [0.297]	6 (21)
50% pain reduction (≥ −4.0 units)	15 (29) [0.595]	12 (26) [0.783]	6 (21)

Milnacipran: effet sur douleur chez patients non déprimés

Table 4. Continuous pain measures (nondepressed FM patients only). Intent to treat analyses using last observation carried forward method. Mean change from baseline in pain measures less placebo change.

	Milnacipran BID, n = 43 [p]	Milnacipran QD, n = 43 [p]	Placebo Score Change from Baseline, n = 19
Daily E-diary pain scores (0–20)	−3.0 [0.013]	−2.2 [0.081]	−0.94
Weekly E-diary pain scores (0–20)	−3.1 [0.001]	−2.4 [0.018]	−0.23
Paper Gracely pain scores (0–20)	−4.7 [0.002]	−2.5 [0.110]	−0.7
Paper VAS pain scores (0–10)	−2.5 [0.006]	−1.8 [0.092]	−0.4
McGill present-pain intensity (0–10)	−2.0 [0.014]	−1.2 [0.192]	−0.1

Milnacipran: effet sur la douleur selon statut dépression

Table 3. 50% pain responders[a] taking milnacipran BID by baseline major depressive episode (MDE) status (intent to treat analyses using last observation carried forward method).

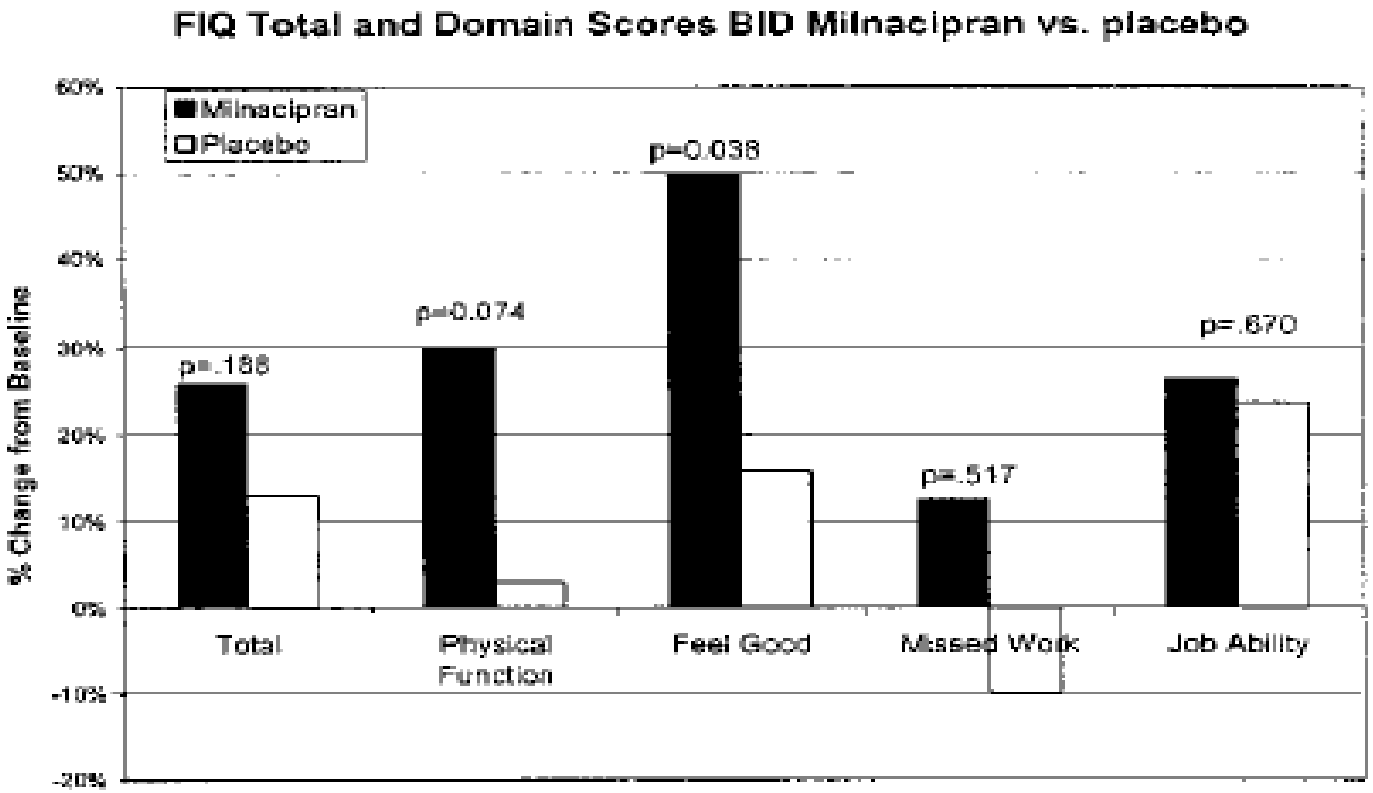
	All Patients, n (%) [p]	MDE Patients, n (%) [p]	Non-MDE Patients, n (%) [p]
Daily E-diary 50% pain reduction			
Milnacipran BID	18 (35) [0.066]	2 (25) [NS]	16 (37) [0.001]
Placebo	4 (14) —	4 (44) —	0 (0) —
Weekly E-diary 50% pain reduction			
Milnacipran BID	19 (37) [0.040]	3 (38) [NS]	16 (37) [0.012]
Placebo	4 (14) —	3 (33) —	1 (5) —

[a] ≥ 4.0 unit reduction on Gracely pain scale.

(résultats sur réduction de 50% de douleur)

Peu de patients déprimés

Milnacipran: effet sur FIQ



FIQ VAS Scores BID Milnacipran vs. Placebo

Milnacipran: changement global

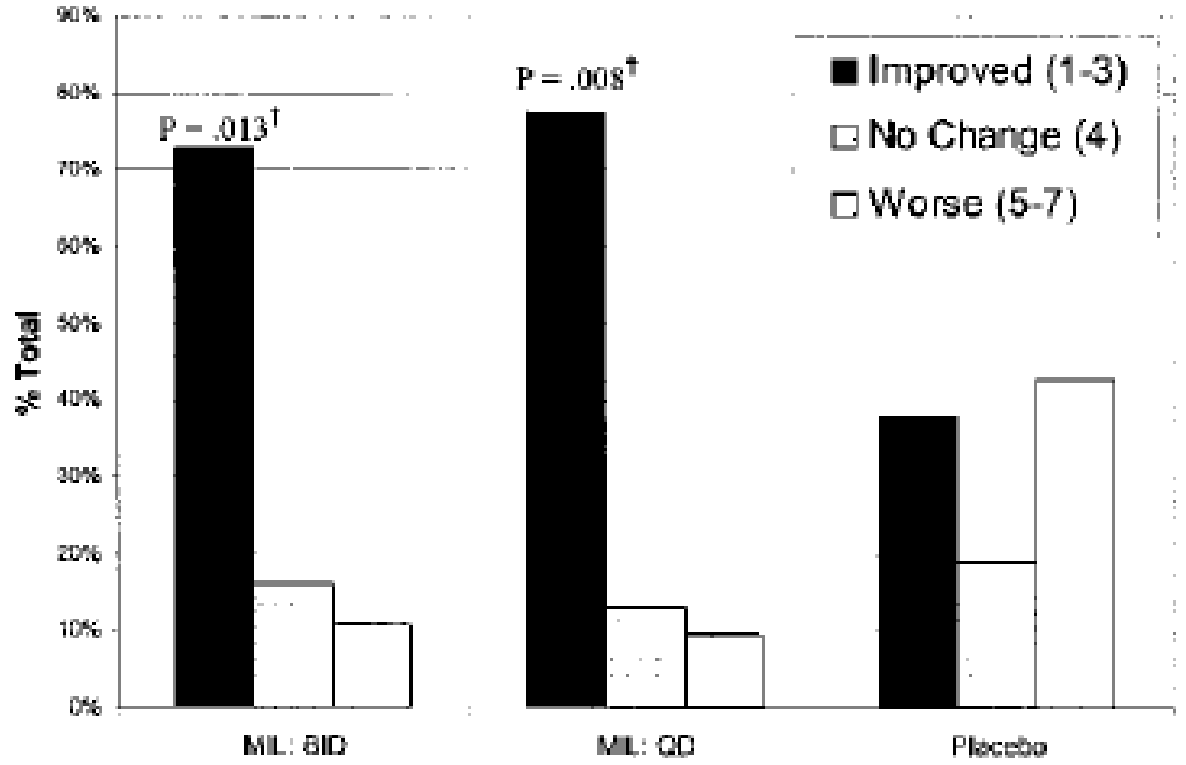


Figure 3. Self-report of change in overall status. Patients were asked to assess their global impression of change in FM severity over the course of the study. The percentage of patients completing the trial who thought they improved, got worse, or experienced no change is illustrated. †Milnacipran (MIL) vs placebo.

ANTIDÉPRESSEURS
ETUDES CONTROLLEES N= 31/42

Effet antalgique + N=17/31

Sommeil ++

Bien supporté,

Effet modeste, rapide, mais non prolongé

AD3C: dès les doses faibles

IRS: doses habituelles voire augmentées (x4)

IRSNa: une voie prometteuse?

ANTIEPILEPTIQUES

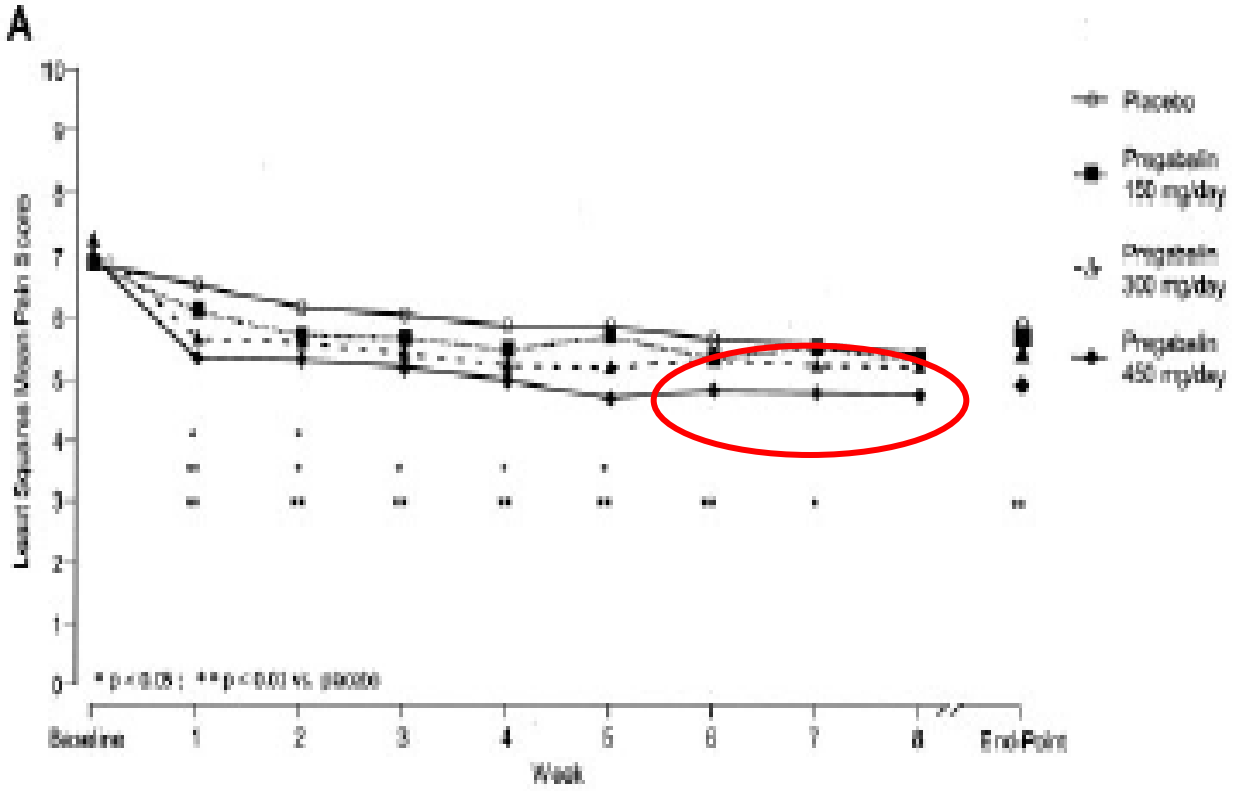
- Prégabaline: Crofford et coll 2005

8 semaines, 300-450 mg

+ Sur douleur, fatigue, sommeil

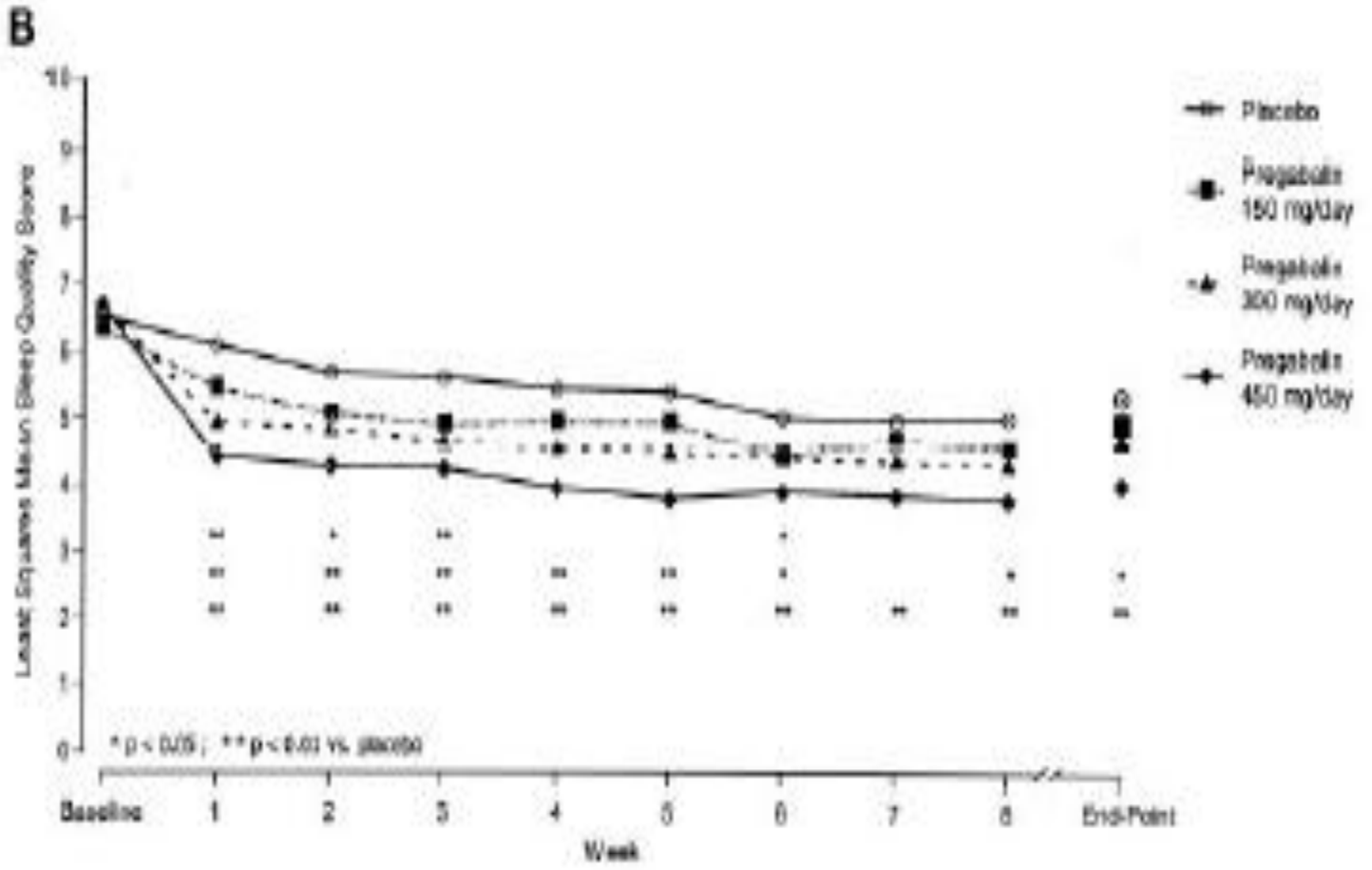
- Autres utilisés, sans preuve: Clonazépam…

Prégabaline: Douleur



Crofford 2005, effet + modeste 450 mg

Prégabaline: Sommeil



Crofford 2005, Effet +

TRAITER L'ANXIETE anxiolytiques?

- Alprazolam TEMESTA (Russel 1991)
- Bromazépam LEXOMIL (Carrera 1996)

Pas efficace seul

MYORELAXANTS

- Cyclobenzaprine : antidépresseur (Carette 1994, Benett 1988, Quimby 1989, Reynolds 1991) effet +
- Carisoprodol (Vaeroy 1989)
- Chlormézanone (Pattrick 1993)

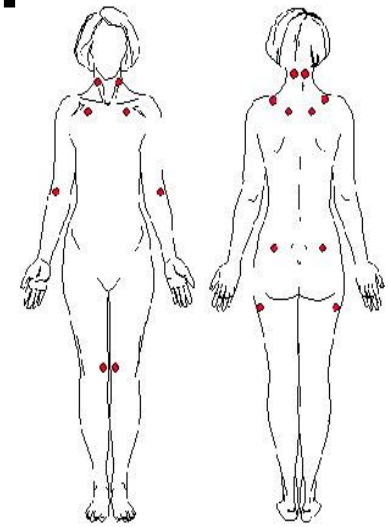
HYPNOTIQUES

- Zolpidem STILNOX (Moldofsky 1996)
- Zopiclone (Drewes 1991, Grönblatt 1993)

Etudes courtes, effet + sur le sommeil seulement

Autres médicaments à action physiopathologique

- GH (Bennett 1998)
- Calcitonine (Bessette 1998)
- Acide malique (Russell 1995)
- SAM e (Jacobsen 1991, Tavoni 1998)
- 5-HTP (Caruso 1990)



GH?

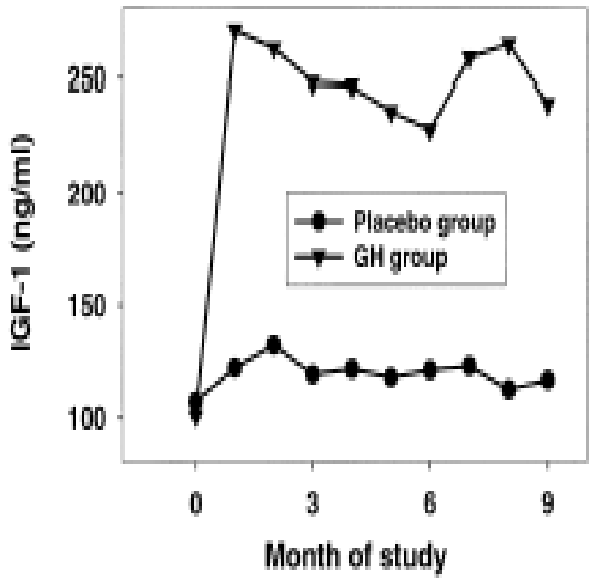


Figure 1. Mean IGF-1 levels in patients tested with growth hormone or placebo.

Between-Group Analysis

There was a significant improvement in the growth hormone treated group compared with the placebo group (Figure 2) at the 9-month evaluation for both the Fibromyalgia Impact Questionnaire Score ($P < 0.04$) and the

FIQ

TPS

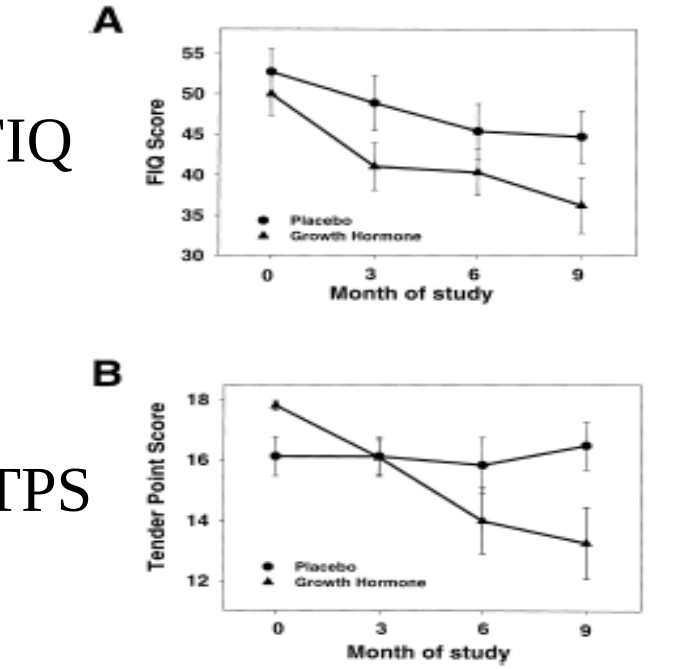


Figure 2. Mean (SD) scores on the Fibromyalgia Impact Questionnaire (graph A) and the number of fibromyalgia tender points (graph B) in patients treated with growth hormone or placebo. Scores at 9 months are significantly different ($P < 0.05$) in the two groups.

Effet sur IGF

Action sur sous-groupe avec IGF basse

Autres récepteurs centraux

- Antagonistes NMDA Ketamine (Graven-Nielsen, 2000)
- Agonistes 5HT3 : tropisétron (Farber 2000), ondansétron
- Agonistes D3:
  - Ropinirole agoniste D3
  - Pramipexole (Holman et coll, 2005) 14 semaines, efficace ++ douleur, FIQ.

Pramipexole

Douleur

FIQ

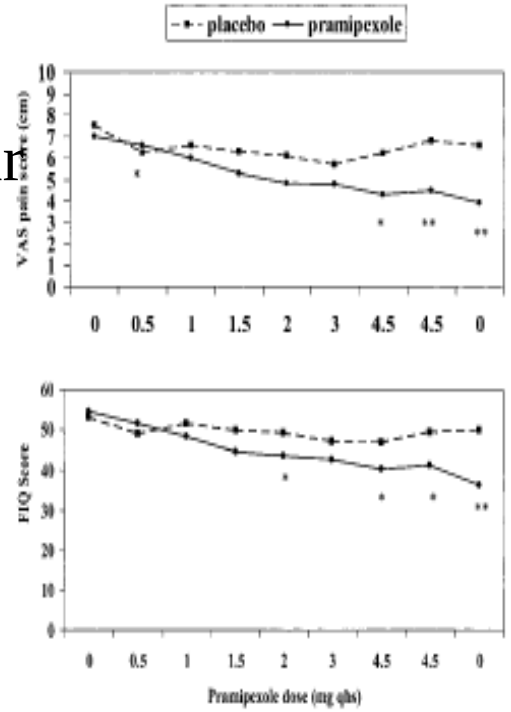


Figure 2. Change in pain scores (10-cm visual analog scale [VAS]) and Fibromyalgia Impact Questionnaire (FIQ) scores in the pramipexole and the placebo groups over 14 weeks. * = $P < 0.05$; ** = $P < 0.01$ for the relative difference between pramipexole and placebo, by 2-tailed t-test.

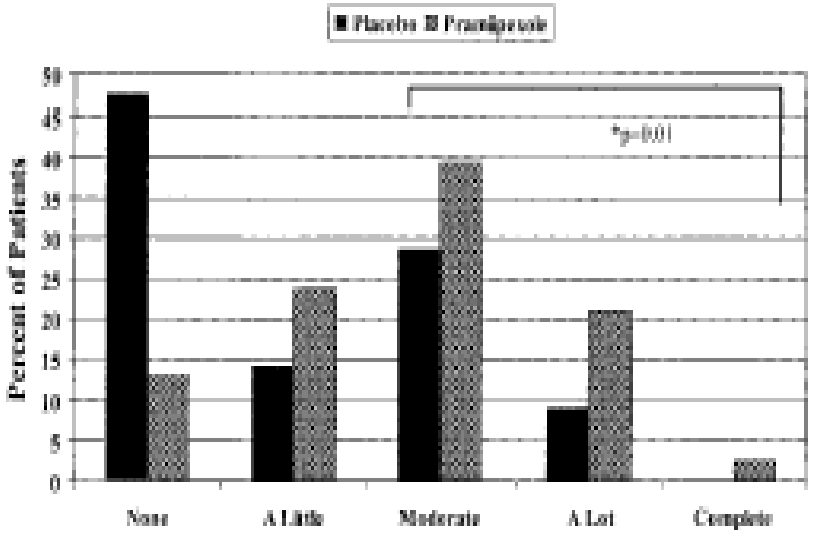


Figure 3. Patients' assessments of improvement in pain from baseline to study end (week 14), by treatment group. Significantly more patients in the pramipexole group experienced moderate or better improvement compared with those in the placebo group, by chi-square test.

Amélioration Douleur Patient

Pramipexole

Table 3. Results of the MDHAQ, FIQ, HAM-d, BAI, and tender point score outcome measures at study end*

	Placebo group		Pramipexole group		Between-group difference at end point (95% CI)	P
	No. of patients	Change, mean ± SEM	No. of patients	Change, mean ± SEM		
MDHAQ subscale scores, range 0–10						
Pain	21	−0.71 ± 0.54	38	−2.48 ± 0.38	−1.77 (−3.07, −0.47)	0.008
Fatigue	21	−0.55 ± 0.46	38	−2.11 ± 0.48	−1.56 (−2.88, −0.24)	0.021
Global status	21	−0.16 ± 0.61	38	−2.52 ± 0.43	−2.35 (−3.82, −0.89)	0.002
Function	21	0.01 ± 0.39	38	−0.83 ± 0.21	−0.84 (−1.64, −0.04)	0.041
Psychiatric	21	−1.47 ± 0.46	38	−1.92 ± 0.43	−0.51 (−1.85, 0.82)	0.44
FIQ total score, range 0–80	21	−3.73 ± 2.79	38	−13.30 ± 2.75	−9.57 (−18.01, −1.05)	0.028
HAM-d total score, range 0–52	21	−1.33 ± 2.14	38	−4.84 ± 1.69	−3.51 (−9.07, 2.05)	0.24
BAI total score, range 0–63	21	−4.38 ± 1.68	38	−7.00 ± 1.67	−2.62 (−7.77, 2.53)	0.31
Tender point score, range 0–54	21	−9.55 ± 1.92	38	−14.58 ± 2.16	−5.03 (−11.52, 1.46)	0.13

* MDHAQ = Multidimensional Health Assessment Questionnaire; FIQ = Fibromyalgia Impact Questionnaire; HAM-d = Hamilton Depression Inventory; BAI = Beck Anxiety Index.

AUTRES (études non contrôlées)

- Vitamines: B1, B6...
- Anabolisants musculaires : acide malique, créatine, carnitine...
- Oligo-éléments: mg, selenium...
- Acides aminés : arginine, tryptophane

Comparaison des *Effect Size*

Approches pharmacologiques			**Non-Pharmacologiques**		
Intervention	Effect size (95% IC)		Intervention	Effect size (95% IC)	
	Douleur	Fonction		Pain	Function
Tricyclique	0.663 (1.812)	0.663 (23.239)	Exercices en milieu aquatique	0.472 (1.873)	0.498 (14.852)
Inhibiteurs mixtes	0.475 (2.18)	Pas calculable	Balneotherapie	1.916 (2.344)	4.147 (21.222)
IMAO	0.685 (1.561)	Pas calculable	Exercice aérobie	0.121 (0.839)	0.218 (2.06)
IRS	0.607 (1.346)	0.782 (3.414)	Renforcement musculaire	2.224 (1.232)	1.039 (8.747)
Antalgiques	2.013 (1.394)	0.189 (10.549)			
Pramipexole	3.848 (1.711)	3.455 (9.216)			

Recommandations 2006 de l'EULAR pour la prise en charge du syndrome fibromyalgique

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