Contents

Part I

Amitriptyline

1 Overview of amitriptyline

1.1 Included trials

A total of 10 randomized comparisons which enrolled 532 patients were identified. In all, 10 randomized comparisons concerned amitriptyline.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for amitriptyline.

The average study size was 59 patients (range 14 to 87). The first study was published in 1986, and the last study was published in 2003.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

1.2 Summary of meta-analysis results

The meta-analysis of the available trials about amitriptyline provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

1.2.1 Amitriptyline

No significant difference was found between **amitriptyline** and **fluvoxamine** in terms of amlioration globale (patient) (RR=1.23, 95% CI 0.66 to 2.30, p=0.5140, 1 trial).

Amitriptyline was superior to **placebo** in terms of FIQ (ES=-0.45, 95% CI -0.83 to -0.07, p=0.0195, 2 trials), douleur (ES=-0.61, 95% CI -1.03 to -0.19, p=0.0043, 6 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0145)(ES=-0.47, 95% CI -0.93 to -0.02, p=0.0408, 3 trials), sommeil (ES=-0.61, 95% CI -0.87 to -0.34, p=0.0000, 5 trials)and severit globale (ES=-0.45, 95% CI -0.79 to -0.10, p=0.0106, 2 trials).
However, no significant difference was found on fatigue (ES=-0.43, 95% CI -0.89 to 0.03, p=0.0698, 4 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0407)(ES=-0.09, 95% CI -0.72 to 0.53, p=0.7662, 1 trial).

Table 1.1: *Main study characteristics - amitriptyline*

Trial	Patients	Treatments	Trial design and method
Amitriptyline			
Amitriptyline versus fluvoxamine			
Nishikai, 2003 [**?**] n = 30 vs. 38	critres ACR 1990	amitriptyline dose moyenne 20 mg/j **versus** fluvoxamine dose moyenne 25mg/j	double blind parallel groups Japan
Amitriptyline versus placebo			
Ginsberg, 1996 [**?**] n = 24 vs. 22	ACR 1990, fibromyalgie "primaire"	amitriptyline LP **versus** placebo	double blind parallel groups 3 centres,
Carette, 1986 [**?**] n = 27 vs. 32	critres de Smythe	amitriptyline 50mg/j **versus** placebo	double blind parallel groups 3 centres,Canada
Carette, 1995 [**?**] n = 22 vs. 22	ACR 1990, score >4 au moins une EVA (/10) de douleur ou d'valuation globale	amitriptyline (25 mg/day) **versus** placebo	double blind cross over
Goldenberg, 1996 [**?**] n = 31 vs. 31	critres ACR et score douleur >=30 sur une EVA et score de Hamilton <=18	amitriptyline 25mg/j **versus** placebo	double blind cross over
Goldenberg (A vs PBO), 1986 [**?**] n = NA vs. NA	fibromyalgia (critres de Yunus modifis)	amitriptyline 25mg le soir **versus** placebo	double blind parallel groups

continued...

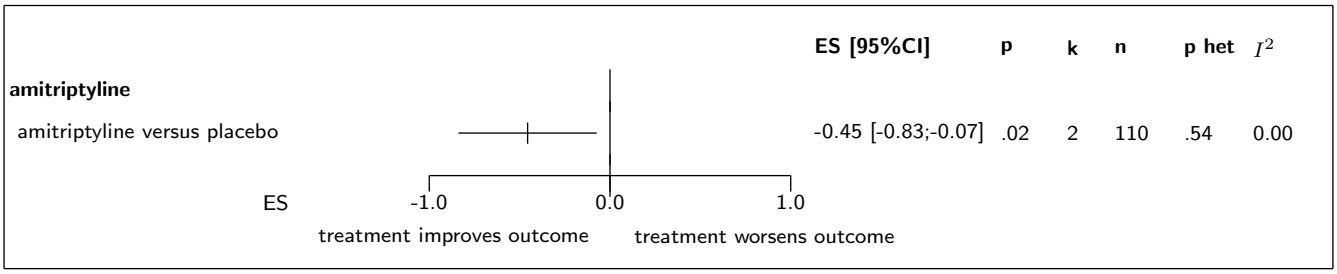
Trial	Patients	Treatments	Trial design and method
Hannonen, 1998 [**?**] n = 42 vs. 45	critres ACR 1990 et un score d'au moins 4 pour 3 des 4 EVA (/10) : sant gnrale, douleur, sommeil, fatigue	amitriptyline 25-37.5 mg/j **versus** placebo	double blind parallel groups Primary endpoint: rpondeur apprci par le mdecin Finland
Heymann, 2001 [**?**] n = 40 vs. 40	critres ACR 1990	amitriptyline 25mg/j **versus** placebo	double blind parallel groups Primary endpoint: aucun critre de jugement principal defini 1 centres,Brsil
Kempenaers, 1994 [**?**] n = 6 vs. 8	yunus criteria	amitryptiline 50 mg daily **versus** placebo	double blind parallel groups
Scudds, 1989 [**?**] n = 36 vs. 36	critres Smythe et Moldofsky, 12 points douloureux sur 14	low dose amitriptyline **versus** placebo	double blind cross over 1 centres,England

Table 1.2: *Summary of all results for amitriptyline*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
amitriptyline versus fluvoxamine						
amlioration globale (patient)	RR=1.23	0.66;2.30	0.5140	1.0000 (0.00)	1	50
amitriptyline versus placebo						
FIQ	ES=-0.45	-0.83;-0.07	0.0195	0.5438 (0.00)	2	110
douleur	ES=-0.61 [1]	-1.03;-0.19	0.0043	0.0145 (0.65) †	6	290
points douloureux (nombre)	ES=-0.47	-0.93;-0.02	0.0408	0.2304 (0.32)	3	130
fatigue	ES=-0.43 [2]	-0.89;0.03	0.0698	0.0407 (0.64) †	4	217
sommeil	ES=-0.61	-0.87;-0.34	0.0000	0.7485 (0.00)	5	231
dpression	ES=-0.09	-0.72;0.53	0.7662	1.0000 (0.00)	1	40
severit globale	ES=-0.45	-0.79;-0.10	0.0106	0.4740 (0.00)	2	134
amlioration globale (clinicien)	RR=1.52	0.95;2.45	0.0821	1.0000 (0.00)	1	59
amlioration globale (patient)	RR=1.48	1.14;1.94	0.0037	0.7531 (0.00)	2	129

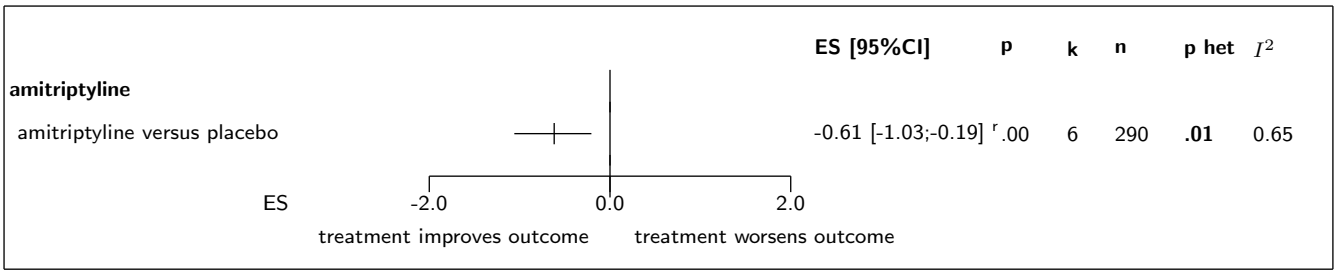
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 1.1: *Forest's plot for FIQ*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; [r]: random effect model used

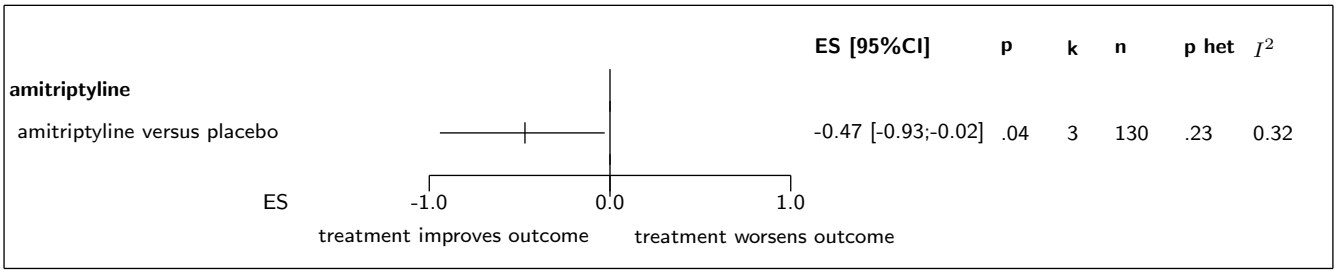
Figure 1.2: *Forest's plot for douleur*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; [r]: random effect model used

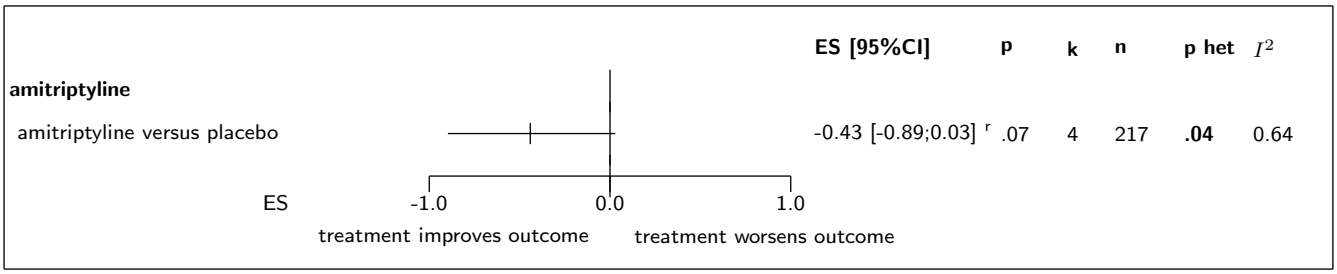
[1] with a random model ($\tau^2 = 0.171$). The results with a fixed effect model was RRFE=-0.55 95% CI -0.79;-0.31
[2] with a random model ($\tau^2 = 0.141$). The results with a fixed effect model was RRFE=-0.35 95% CI -0.62;-0.08

Figure 1.3: *Forest's plot for points douloureux (nombre)*



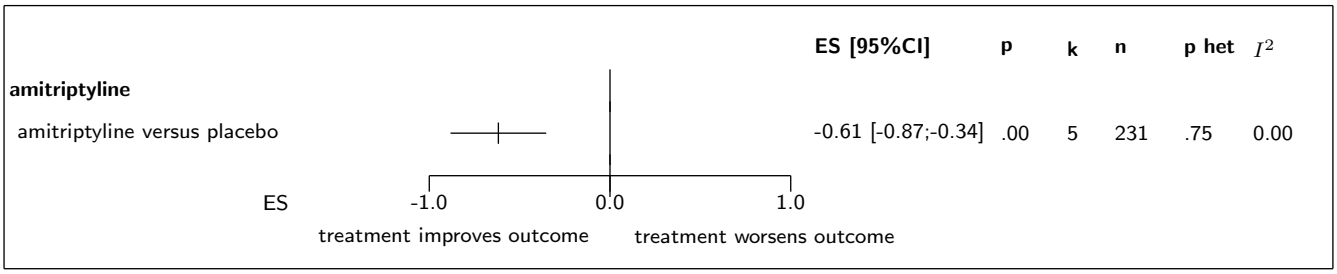
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; [r]: random effect model used

Figure 1.4: *Forest's plot for fatigue*



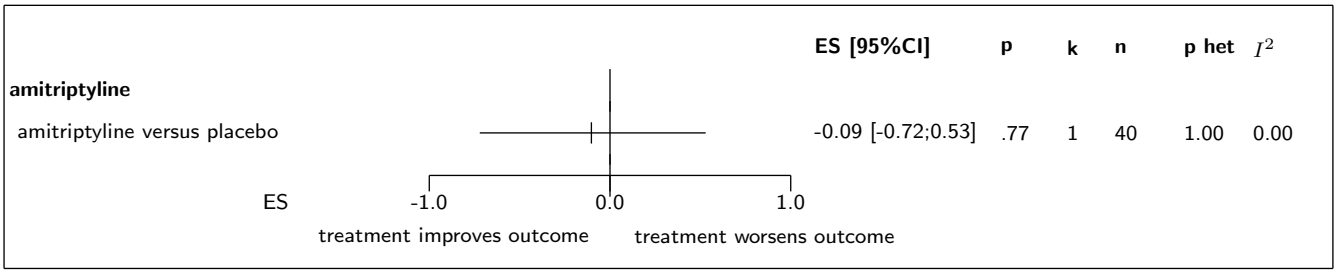
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; [r]: random effect model used

Figure 1.5: *Forest's plot for sommeil*



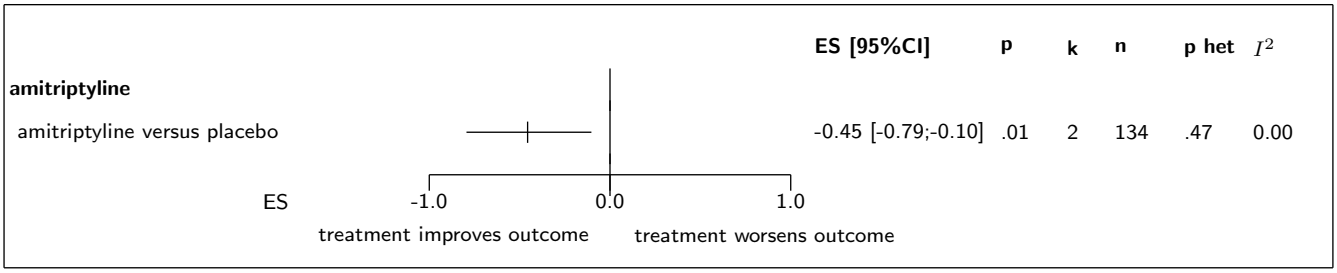
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; [r]: random effect model used

Figure 1.6: *Forest's plot for dpression*



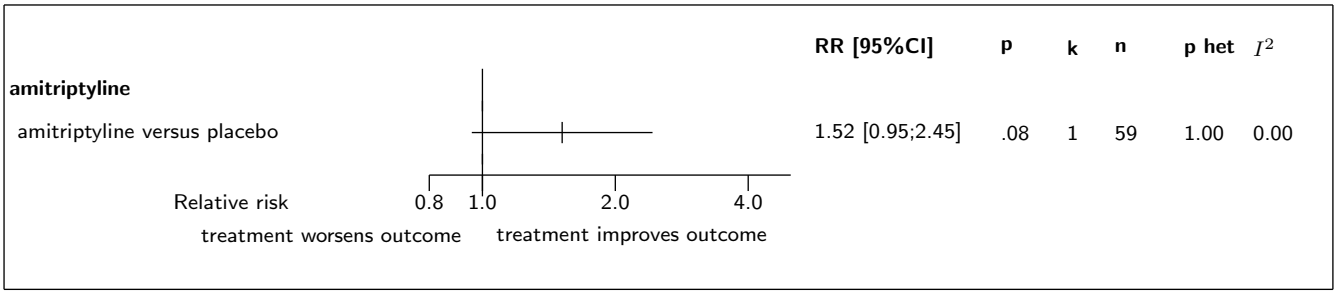
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 1.7: *Forest's plot for severit globale*



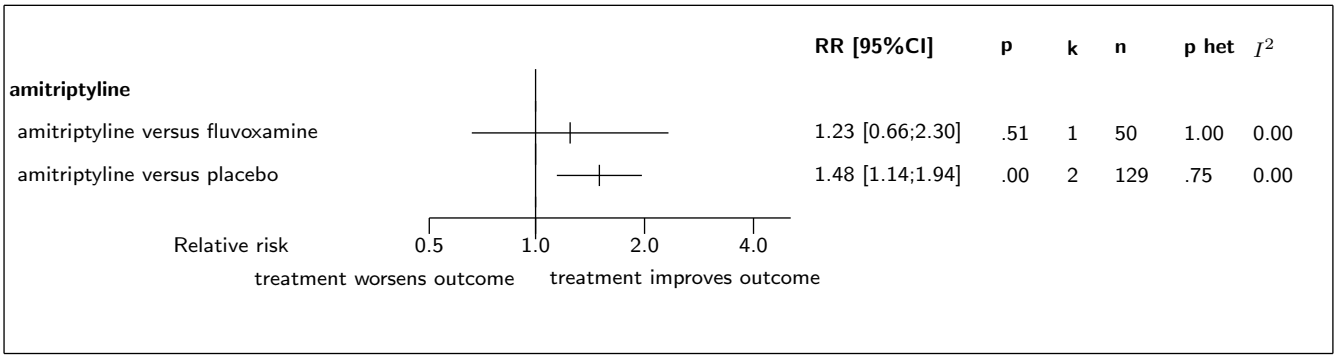
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 1.8: *Forest's plot for amlioration globale (clinicien)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 1.9: *Forest's plot for amlioration globale (patient)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

2 Details

2.1 Available trials

A total of 10 RCTs which randomized 532 patients were identified: it compared amitriptyline with fluvoxamine and 9 trials compared amitriptyline with placebo.
The average study size was 59 patients (range 14 to 87). The first study was published in 1986, and the last study was published in 2003.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Douleur data was reported in 7 trials; 5 trials reported data on sommeil; 5 trials reported data on fatigue; 3 trials reported data on points douloureux (nombre); 3 trials reported data on amlioration globale (patient); 2 trials reported data on severit globale; 2 trials reported data on FIQ; 1 trials reported data on anxit; 1 trials reported data on amlioration globale (clinicien); and 1 trials reported data on dpression.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of amitriptyline.

Table 2.1: *Treatment description - amitriptyline - amitriptyline*

Trial	Studied treatment	Control treatment
Amitriptyline versus fluvoxamine		
Nishikai (2003) [**?**]	Amitriptyline dose moyenne 20 mg/j	Fluvoxamine dose moyenne 25mg/j
Amitriptyline versus placebo		
Ginsberg (1996) [**?**]	amitriptyline LP	placebo
Carette (1986) [**?**]	amitriptyline 50mg/j	placebo
Carette (1995) [**?**]	amitriptyline (25 mg/day)	placebo
Goldenberg (1996) [**?**] [d]	amitriptyline 25mg/j	placebo
Goldenberg (A vs PBO) (1986) [**?**]	amitriptyline 25mg le soir	placebo
Hannonen (1998) [**?**] [f]	amitriptyline 25-37.5 mg/j dose vise 25mg augmente ventuellement 37.5mg si absence de rponse satisfaisante	placebo
Heymann (2001) [**?**] [g]	amitriptyline 25mg/j	placebo
Kempenaers (1994) [**?**] [h]	amitryptiline 50 mg daily	placebo
Scudds (1989) [**?**]	low dose amitriptyline	placebo

d) 4 priodes de traitement : fluoxetine, amitriptyline, assosciation des 2, placebo f) 3 bras: amitriptyline, placebo et moclobemide g) 3e groupe recevant de la nortriptyline h) un 3e groupe recevait du SER282 (un antidiencephale serum)

Table 2.2: *Descriptions of participants - amitriptyline - amitriptyline*

Trial	Patients
Amitriptyline versus fluvoxamine	
Nishikai (2003) [?]	Critres ACR 1990
Amitriptyline versus placebo	
Ginsberg (1996) [?]	ACR 1990, fibromyalgie "primaire"
Carette (1986) [?]	Critres de Smythe
Carette (1995) [?]	ACR 1990, score >4 au moins une EVA (/10) de douleur ou d'valuation globale
Goldenberg (1996) [?]	Critres ACR et score douleur >=30 sur une EVA et score de Hamilton <=18
Goldenberg (A vs PBO) (1986) [?] [e]	Fibromyalgia (critres de Yunus modifis)
Hannonen (1998) [?]	Critres ACR 1990 et un score d'au moins 4 pour 3 des 4 EVA (/10) : sant gnrale, douleur, sommeil, fatigue
Heymann (2001) [?]	Critres ACR 1990
Kempenaers (1994) [?]	Yunus criteria
Scudds (1989) [?]	Critres Smythe et Moldofsky, 12 points douloureux sur 14

e) 3e bras recevant naproxen 500mg 2 fois par jour

Table 2.3: *Main patients characteristics - amitriptyline - amitriptyline*

Trial	Characteristics
Amitriptyline versus fluvoxamine	
Nishikai, 2003 [?]	
Amitriptyline versus placebo	
Ginsberg, 1996 [?]	age (mean), years: 46 ans femmes (%): 82% critres d'inclusion: ACR 1990 nombre de points douloureux: 14.6
Carette, 1986 [?]	age (mean), years: 40.9y femmes (%): 27% critres d'inclusion: Smythe douleur: 6.03 /10
Carette, 1995 [?]	age (mean), years: 43.8 ans femmes (%): 95.5% nombre de points douloureux: 16 douleur: 7.12 (EVA/10) fatigue: 7.84 (EVA/10)
Goldenberg, 1996 [?]	age (mean), years: 43.2 y femmes (%): 90.3% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 57.3 douleur: 68.4 (EVA) fatigue: 73 (EVA) depression: 12.4 (Beck)
Goldenberg (A vs PBO), 1986 [?]	age (mean), years: 43.8y femmes (%): 95%
Hannonen, 1998 [?]	age (mean), years: 49.29y critres d'inclusion: ACR douleur: 5.86 fatigue: 5.81
Heymann, 2001 [?]	age (mean), years: 51.4y critres d'inclusion: ACR 1990 nombre de points douloureux: 16.2 (/18) fibromyalgia Impact Questionnaire: 65.45
Kempenaers, 1994 [?]	age (mean), years: 38 ans critres d'inclusion: Yunus nombre de points douloureux: 16 (/18) douleur: 64 (/100) depression: 11 (/76) anxit: 18 (/52)
Scudds, 1989 [?]	age (mean), years: 39.9 y femmes (%): 88.8% critres d'inclusion: Smythe et Moldofsky

Table 2.4: *Design and methodological quality of trials - amitriptyline - amitriptyline*

Trial	Design	Duration	Centre	Primary endpoint
Amitriptyline versus fluvoxamine				
Nishikai, 2003 [?] n=68	Parallel groups double blind	4 semaines inclusion period: 1991-2001	Japan	

continued...

Trial	Design	Duration	Centre	Primary endpoint
Amitriptyline versus placebo				
Ginsberg, 1996 [?] n=46	Parallel groups double blind	8 weeks inclusion period: dec 1991 - jan 1993	3 centres	
Carette, 1986 [?] n=59	Parallel groups double blind	9 weeks	Canada 3 centres	
Carette, 1995 [?] n=44	Cross over double blind	2 mois		
Goldenberg, 1996 [?] (d) n=62	Cross over double blind	6 semaines		
Goldenberg (A vs PBO), 1986 [?] n=NaN	Parallel groups double blind			
Hannonen, 1998 [?] n=87	Parallel groups double blind	12 semaines	Finland	rpondeur apprci par le mdecin
Heymann, 2001 [?] n=80	Parallel groups double blind	8 semaines inclusion period: mars 1992 - aout 1996	Brsil 1 centres	aucun critre de jugement principal defini
Kempenaers, 1994 [?] n=14	Parallel groups double blind	8 semaines		
Scudds, 1989 [?] n=72	Cross over double blind	10 semaines	England 1 centres	

d) 4 priodes spares par un wash out de 2 semaines

2.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Amitriptyline versus fluvoxamine

The single study eligible for this comparison provided data on **amlioration globale (patient)**. No statistically significant difference between the groups was found in amlioration globale (patient), with a RR of 1.23 (95% CI 0.66 to 2.30, p=0.5140).

Amitriptyline versus placebo

A total of 2 of the 9 studies eligible for this comparison provided data on **FIQ**. The analysis detected a statistically significant difference in favor of amitriptyline in FIQ, with a ES of -0.45 (95% CI -0.83 to -0.07, p=0.0195). No heterogeneity was detected (p = 0.5438, I^2 = 0.00%).
A total of 6 of the 9 studies eligible for this comparison provided data on **douleur**. The analysis detected a statistically significant difference in favor of amitriptyline in douleur, with a ES of -0.61 (95% CI -1.03 to -0.19, p=0.0043). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0145, I^2 = 0.65%).

A total of 3 of the 9 studies eligible for this comparison provided data on **points douloureux (nombre)**. The analysis detected a statistically significant difference in favor of amitriptyline in points douloureux (nombre), with a ES of -0.47 (95% CI -0.93 to -0.02, p=0.0408). No heterogeneity was detected (p = 0.2304, I^2 = 0.32%).
A total of 4 of the 9 studies eligible for this comparison provided data on **fatigue**. When pooled together, there was no statistically significant difference between the groups in fatigue, with a ES of -0.43 (95% CI -0.89 to 0.03, p=0.0698). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0407, I^2 = 0.64%).
A total of 5 of the 9 studies eligible for this comparison provided data on **sommeil**. The analysis detected a statistically significant difference in favor of amitriptyline in sommeil, with a ES of -0.61 (95% CI -0.87 to -0.34, p=0.0000). No heterogeneity was detected (p = 0.7485, I^2 = 0.00%).
Only one of the 9 studies eligible for this comparison provided data on **dpression**. No statistically significant difference between the groups was found in dpression, with a ES of -0.09 (95% CI -0.72 to 0.53, p=0.7662).
A total of 2 of the 9 studies eligible for this comparison provided data on **severit globale**. The analysis detected a statistically significant difference in favor of amitriptyline in severit globale, with a ES of -0.45 (95% CI -0.79 to -0.10, p=0.0106). No heterogeneity was detected (p = 0.4740, I^2 = 0.00%).
Only one of the 9 studies eligible for this comparison provided data on **amlioration globale (clinicien)**. No statistically significant difference between the groups was found in amlioration globale (clinicien), with a RR of 1.52 (95% CI 0.95 to 2.45, p=0.0821).
A total of 2 of the 9 studies eligible for this comparison provided data on **amlioration globale (patient)**. The analysis detected a statistically significant difference in favor of amitriptyline in amlioration globale (patient), with a RR of 1.48 (95% CI 1.14 to 1.94, p=0.0037). No heterogeneity was detected (p = 0.7531, I^2 = 0.00%).

Table 2.5: *Results details - amitriptyline - amitriptyline*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
amitriptyline versus fluvoxamine						
amlioration globale (patient)	RR=1.23	[0.66;2.30]	0.5140	1.0000 (I^2=0.00)	1	50
amitriptyline versus placebo						
FIQ	ES=-0.45	[-0.83;-0.07]	0.0195	0.5438 (I^2=0.00)	2	110
douleur	ES=-0.61	[-1.03;-0.19]	0.0043	0.0145 (I^2=0.65)	6	290
points douloureux (nombre)	ES=-0.47	[-0.93;-0.02]	0.0408	0.2304 (I^2=0.32)	3	130
fatigue	ES=-0.43	[-0.89;0.03]	0.0698	0.0407 (I^2=0.64)	4	217
sommeil	ES=-0.61	[-0.87;-0.34]	0.0000	0.7485 (I^2=0.00)	5	231
dpression	ES=-0.09	[-0.72;0.53]	0.7662	1.0000 (I^2=0.00)	1	40
severit globale	ES=-0.45	[-0.79;-0.10]	0.0106	0.4740 (I^2=0.00)	2	134
amlioration globale (clinicien)	RR=1.52	[0.95;2.45]	0.0821	1.0000 (I^2=0.00)	1	59
amlioration globale (patient)	RR=1.48	[1.14;1.94]	0.0037	0.7531 (I^2=0.00)	2	129

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 2.1: *Forest's plot for FIQ*

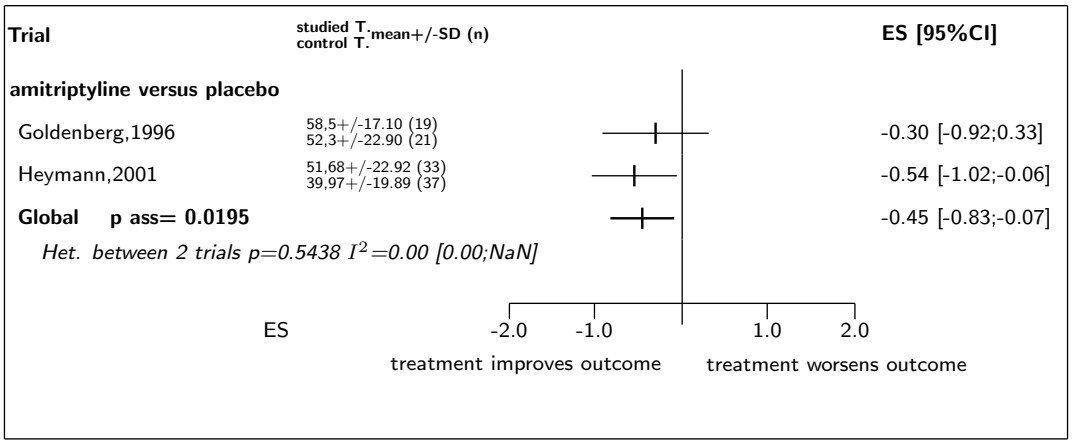


Figure 2.2: *Forest's plot for Douleur*

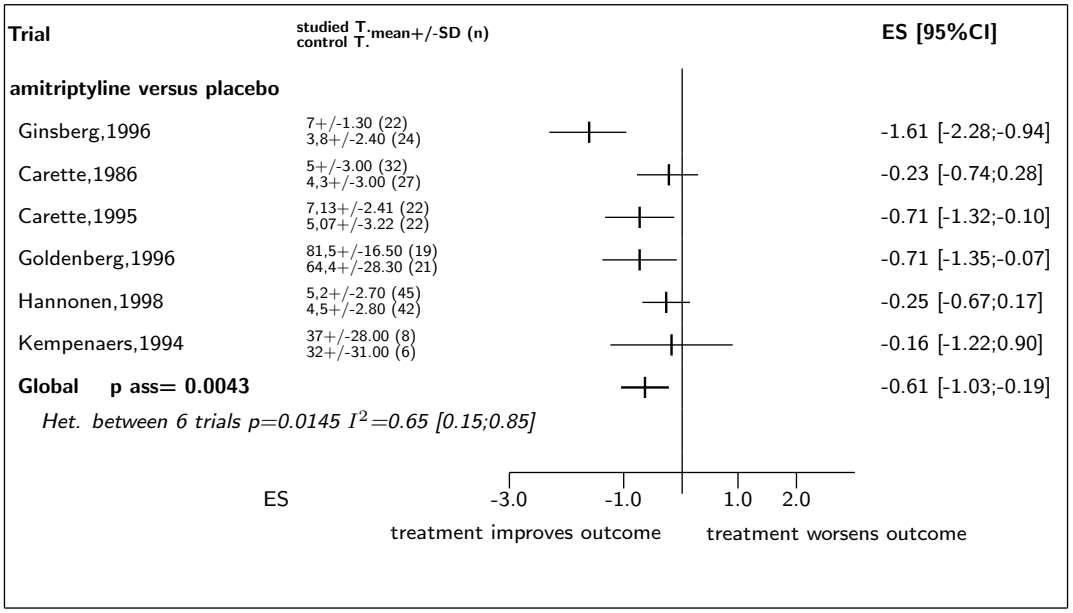


Figure 2.3: *Forest's plot for Points douloureux (nombre)*

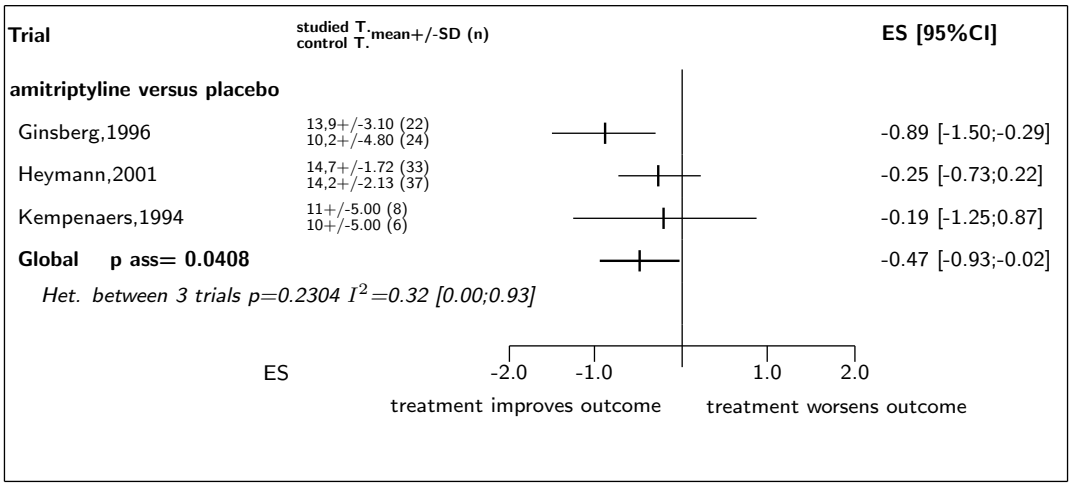


Figure 2.4: *Forest's plot for Fatigue*

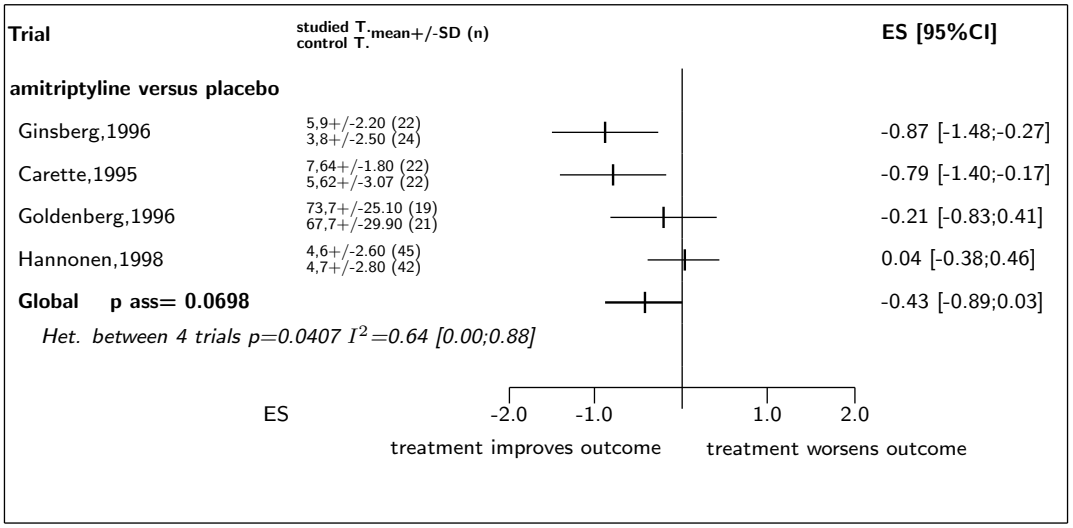


Figure 2.5: *Forest's plot for Sommeil*

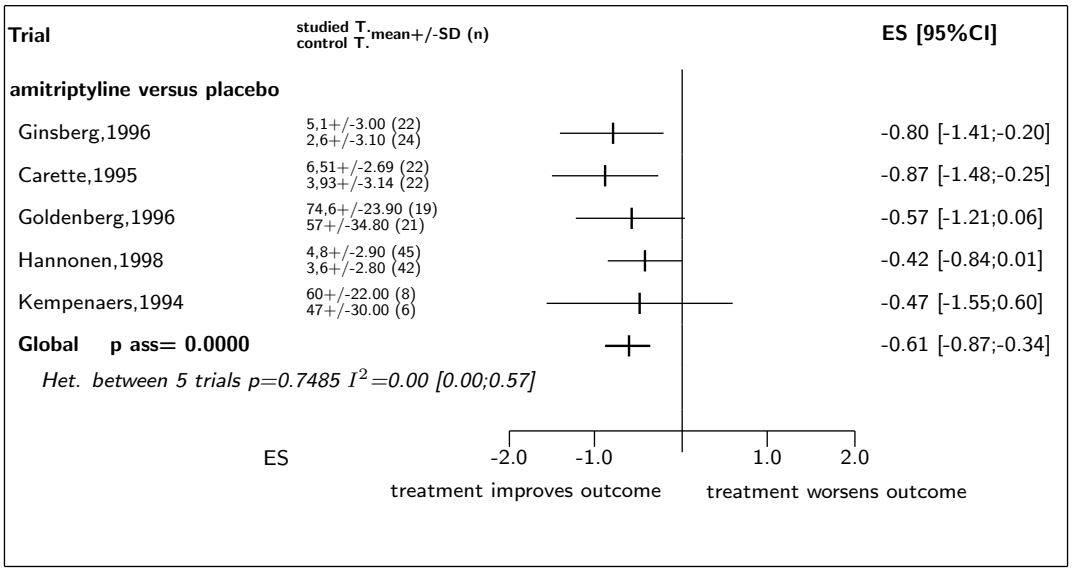


Figure 2.6: *Forest's plot for Dpression*

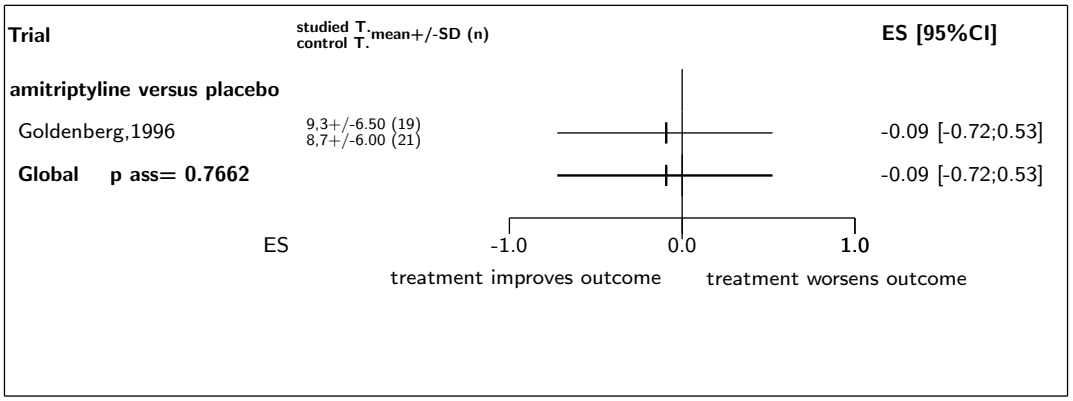


Figure 2.7: *Forest's plot for Severit globale*

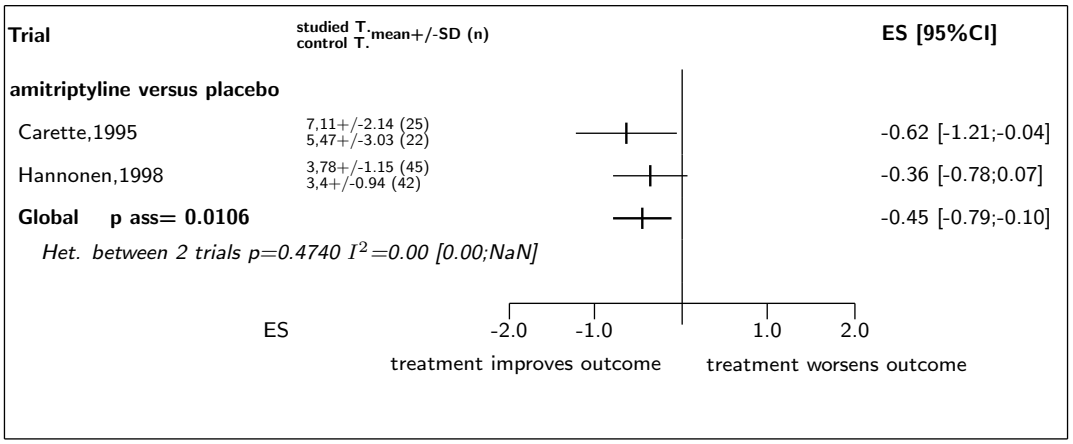


Figure 2.8: *Forest's plot for amlioration globale (clinicien)*

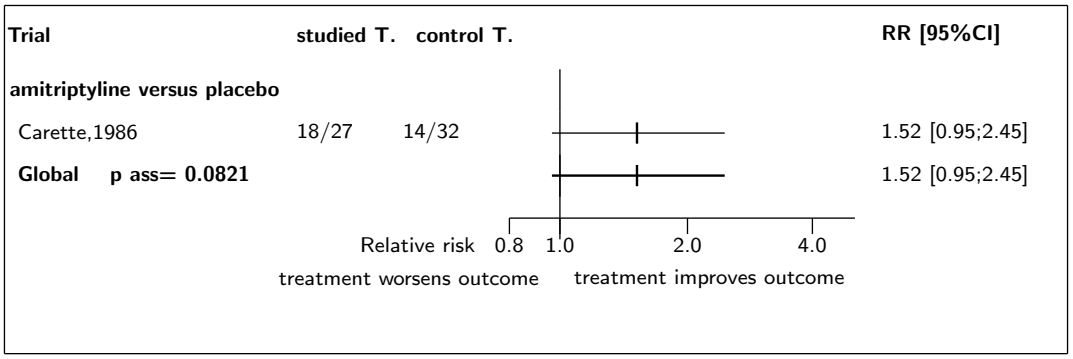
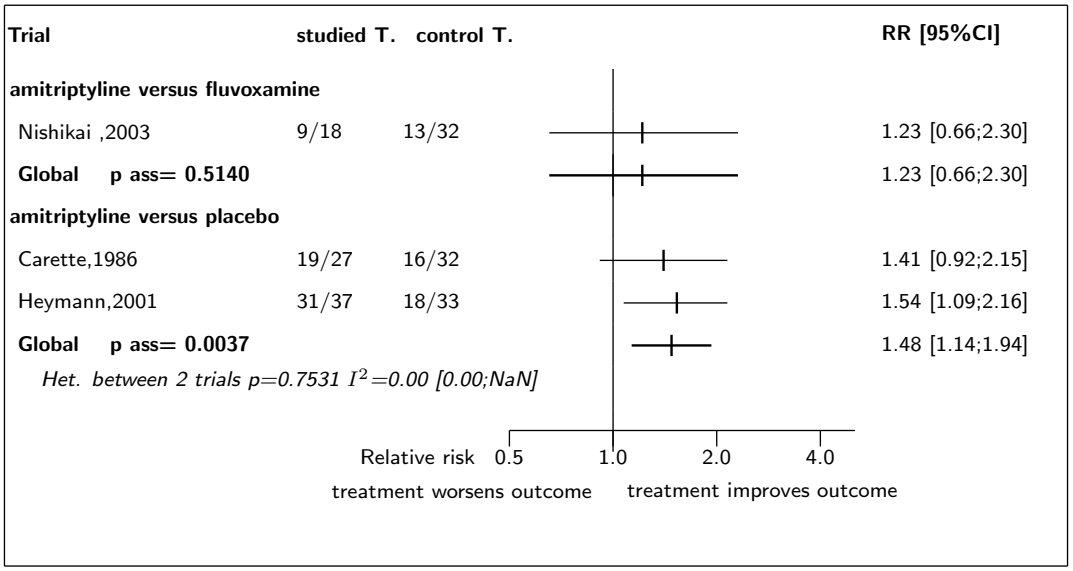


Figure 2.9: *Forest's plot for amlioration globale (patient)*



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3 Global meta-analysis: all amitriptyline

3.1 Global meta-analysis: all amitriptyline versus fluvoxamine

Table 3.1: *All amitriptylineversus fluvoxamine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
amlioration globale (patient)	RR=1.23	0.66;2.30	0.5140	1.0000 (0.00)	1	50

legend B

3.2 Global meta-analysis: all amitriptyline versus placebo

Table 3.2: *All amitriptylineversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
FIQ	ES=-0.45	-0.83;-0.07	0.0195	0.5438 (0.00)	2	110
douleur	ES=-0.61 [1]	-1.03;-0.19	0.0043	0.0145 (0.65) †	6	290
points douloureux (nombre)	ES=-0.47	-0.93;-0.02	0.0408	0.2304 (0.32)	3	130
fatigue	ES=-0.43 [2]	-0.89;0.03	0.0698	0.0407 (0.64) †	4	217
sommeil	ES=-0.61	-0.87;-0.34	0.0000	0.7485 (0.00)	5	231
dpression	ES=-0.09	-0.72;0.53	0.7662	1.0000 (0.00)	1	40
severit globale	ES=-0.45	-0.79;-0.10	0.0106	0.4740 (0.00)	2	134
amlioration globale (clinicien)	RR=1.52	0.95;2.45	0.0821	1.0000 (0.00)	1	59
amlioration globale (patient)	RR=1.48	1.14;1.94	0.0037	0.7531 (0.00)	2	129

legend B

4 Ongoing studies of amitriptyline

No ongoing trial was identified.

5 Excluded studies for amitriptyline

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 5.1: *Excluded studies of amitriptyline*

Study	Exclusion reason
Nicolodi (1996) [**?**]	pas d'valuation de l'effet thrapeutique, essai purement explicatif
Ozerbil (2006) [**?**]	essai de physiopathologie. pas de critre clinique
Ozgocmen (2006) [**?**]	essai en ouvert non l'abris d'un biais de selection et/ou de mesure
Ozgocmen (2006) [**?**]	essai en ouvert

[1] with a random model ($\tau^2 = 0.171$). The results with a fixed effect model was RRFE=-0.55 95% CI -0.79;-0.31
[2] with a random model ($\tau^2 = 0.141$). The results with a fixed effect model was RRFE=-0.35 95% CI -0.62;-0.08

Part II

Analgesics

6 Overview of analgesics

No completed trial meeting the eligibility criteria was available.

7 Ongoing studies of Analgesics

No ongoing trial was identified.

8 Excluded studies for Analgesics

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 8.1: *Excluded studies of Analgesics*

Study	**Exclusion reason**
Frost (1986) [**?**]	
Graven Nielsen (2000) [**?**]	

Part III

Duloxetine

9 Overview of duloxetine

9.1 Included trials

A total of 8 randomized comparisons which enrolled 2126 patients were identified. In all, 3 randomized comparisons concerned duloxetine 120mg , one duloxetine 20mg and 4 duloxetine 60mg.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for duloxetine 120mg, in section **??** (page **??**) for duloxetine 20mg and in section **??** (page **??**) for duloxetine 60mg.

The average study size was 265 patients (range 207 to 330). The first study was published in 2004, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We found 2 unpublished trials.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

9.2 Summary of meta-analysis results

The meta-analysis of the available trials about duloxetine provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

9.2.1 Duloxetine 120mg

Duloxetine 120mg was superior to **placebo** in terms of douleur (ES=-0.38, 95% CI -0.55 to -0.21, p=0.0000, 3 trials), CGI-severity (ES=-0.35, 95% CI -0.50 to -0.21, p=0.0000, 3 trials), points douloureux (nombre) (ES=-0.36, 95% CI -0.55 to -0.16, p=0.0000, 2 trials), dpression (ES=-0.21, 95% CI -0.41 to -0.02, p=0.0332, 2 trials), severit globale (ES=-0.36, 95% CI -0.51 to -0.21, p=0.0000, 3 trials)and patient Global Impression of Improvement (PGI-I) (ES=-0.22, 95% CI -0.40 to -0.05, p=0.0128, 3 trials).
However, no significant difference was found on FIQ (ES=-0.28, 95% CI -0.57 to 0.01, p=0.0605, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0219)(ES=-0.13, 95% CI -0.31 to 0.05, p=0.1524, 2 trials), anxit (ES=-0.18, 95% CI -0.48 to 0.11, p=0.2185, 1 trial)and sheehan disability scale (ES=-0.25, 95% CI -0.67 to 0.17, p=0.2399, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0247)

9.2.2 Duloxetine 20mg

Duloxetine 20mg was superior to **placebo** in terms of patient Global Impression of Improvement (PGI-I) (ES=-0.35, 95% CI -0.63 to -0.07, p=0.0133, 1 trial).
However, no significant difference was found on FIQ (ES=-0.27, 95% CI -0.55 to 0.01, p=0.0545, 1 trial), douleur (ES=-0.22, 95% CI -0.50 to 0.06, p=0.1170, 1 trial), CGI-severity (ES=-0.26, 95% CI -0.54 to 0.01, p=0.0638, 1 trial), fatigue (ES=0.04, 95% CI -0.24 to 0.31, p=0.7832, 1 trial), sheehan disability scale (ES=-0.10, 95% CI -0.37 to 0.18, p=0.4868, 1 trial)and severit globale (ES=-0.26, 95% CI -0.54 to 0.01, p=0.0638, 1 trial).

9.2.3 Duloxetine 60mg

Data were insufficient to compare **duloxetine 60mg** to **duloxetine 120mg**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Duloxetine 60mg was superior to **placebo** in terms of FIQ (ES=-0.34, 95% CI -0.49 to -0.20, p=0.0000, 3 trials), douleur (ES=-0.32, 95% CI -0.50 to -0.14, p=0.0000, 3 trials), CGI-severity (ES=-0.31, 95% CI -0.45 to -0.18, p=0.0000, 3 trials), dpression (ES=-0.27, 95% CI -0.44 to -0.10, p=0.0022, 2 trials), severit globale (ES=-0.36, 95% CI -0.53 to -0.18, p=0.0000, 2 trials)and patient Global Impression of Improvement (PGI-I) (ES=-0.16, 95% CI -0.30 to -0.03, p=0.0172, 3 trials).
However, no significant difference was found on points douloureux (nombre) (ES=-0.01, 95% CI -0.28 to 0.25, p=0.9338, 1 trial), fatigue (ES=-0.08, 95% CI -0.31 to 0.15, p=0.4876, 1 trial)and sheehan disability scale (ES=0.03, 95% CI -0.15 to 0.20, p=0.7738, 2 trials).

Table 9.1: *Main study characteristics - duloxetine*

Trial	Patients	Treatments	Trial design and method
Duloxetine 120mg			
Duloxetine 120mg versus placebo			
Arnold, 2004 [**?**] n = 104 vs. 103	critres ACR, 18 ans et plus, score douleur du FIG >=4 (/10)	duloxetine 60 mg deux fois par jour **versus** placebo	double blind parallel groups Primary endpoint: FIG-douleur 18 centres,US
Russell 120mg/j (study 6222), 2008 [**?**] n = 147 vs. 144	critres ACR; score de douleur de la Brief pain Inventory modified short form >=4;	duloxetine 120 mg/j **versus** placebo	double blind parallel groups Primary endpoint: brief Pain Inventory (BPI) et Patient Global Impressions of Improvement (PGI-I) 38 centres,USA, Puerto Rico
Arnold (twice daily), 2005 [**?**] n = 116 vs. 120	femmes souffrant d'une fibromylgie primaire avec ou sans depression majeurecritre ACR, score douleur Brief pain inventory >=4	duloxetine 60mg 2 fois par jour **versus** placebo	double blind Primary endpoint: self-reported Brief Pain Inventory 21 centres,US
Duloxetine 20mg			
Duloxetine 20mg versus placebo			
Russell 20mg/j (study 6222), 2008 [**?**] n = 79 vs. 144	critre ACR; score de douleur de la Brief pain Inventory modified short form >=4;	duloxetine 20 mg/j **versus** placebo	double blind parallel groups Primary endpoint: brief Pain Inventory (BPI) et Patient Global Impressions of Improvement (PGI-I) 38 centres,USA, Puerto Rico
Duloxetine 60mg			
Duloxetine 60mg versus duloxetine 120mg			
Chappell study 9075, 0 [**?**] n = 104 vs. 203	critres ACR, >18 ans, score de douleur BPI >=4	duloxetine 60mg une fois par jour **versus** duloxetine 120 mg une fois par jour	double blind parallel groups 33 centres,7 countries

continued...

Trial	Patients	Treatments	Trial design and method
Duloxetine 60mg versus placebo			
Russell 60mg/j, 2008 [**?**] n = 150 vs. 144	critres ACR; score de douleur de la Brief pain Inventory modified short form >=4;	duloxetine 60 mg/j **versus** placebo	double blind parallel groups Primary endpoint: brief Pain Inventory (BPI) et Patient Global Impressions of Improvement (PGI-I) 38 centres,USA, Puerto Rico
study 9072 (F1J MC HMEF), 0 n = 162 vs. 168	critre ACR, avec ou sans depression majeure	duloxetine 60 ou 120 mg/j **versus** placebo	double blind parallel groups Primary endpoint: BPI, PGI-improvement 36 centres,5 countries
Arnold (once daily), 2005 [**?**] n = 118 vs. 120	femmes souffrant d'une fibromylgie primaire avec ou sans depression majeure, critre ACR et score douleur Brief pain inventory >=4	duloxetine 60mg une fois par jour **versus** placebo	double blind parallel groups Primary endpoint: self-reported Brief Pain Inventory 21 centres,US

Table 9.2: *Summary of all results for duloxetine 120mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
duloxetine 120mg versus placebo						
FIQ	ES=-0.28 [1]	-0.57;0.01	0.0605	0.0219 (0.74) †	3	721
douleur	ES=-0.38	-0.55;-0.21	0.0000	0.2496 (0.28)	3	727
CGI-severity	ES=-0.35	-0.50;-0.21	0.0000	0.7651 (0.00)	3	720
points douloureux (nombre)	ES=-0.36	-0.55;-0.16	0.0000	0.3415 (0.00)	2	409
fatigue	ES=-0.13	-0.31;0.05	0.1524	0.8761 (0.00)	2	495
dpression	ES=-0.21	-0.41;-0.02	0.0332	0.5044 (0.00)	2	396
anxit	ES=-0.18	-0.48;0.11	0.2185	1.0000 (0.00)	1	179
sheehan disability scale	ES=-0.25 [2]	-0.67;0.17	0.2399	0.0247 (0.80) †	2	475
severit globale	ES=-0.36	-0.51;-0.21	0.0000	0.8080 (0.00)	3	705
patient Global Impression of Improvement (PGI-I)	ES=-0.22	-0.40;-0.05	0.0128	0.2468 (0.29)	3	720

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 9.3: *Summary of all results for duloxetine 20mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
duloxetine 20mg versus placebo						
FIQ	ES=-0.27	-0.55;0.01	0.0545	1.0000 (0.00)	1	223
douleur	ES=-0.22	-0.50;0.06	0.1170	1.0000 (0.00)	1	223
CGI-severity	ES=-0.26	-0.54;0.01	0.0638	1.0000 (0.00)	1	223
fatigue	ES=0.04	-0.24;0.31	0.7832	1.0000 (0.00)	1	223
sheehan disability scale	ES=-0.10	-0.37;0.18	0.4868	1.0000 (0.00)	1	223
severit globale	ES=-0.26	-0.54;0.01	0.0638	1.0000 (0.00)	1	223
patient Global Impression of Improvement (PGI-I)	ES=-0.35	-0.63;-0.07	0.0133	1.0000 (0.00)	1	223

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 9.4: *Summary of all results for duloxetine 60mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
duloxetine 60mg versus duloxetine 120mg						
No data were presented in the trial identified						
duloxetine 60mg versus placebo						
FIQ	ES=-0.34	-0.49;-0.20	0.0000	0.3245 (0.11)	3	840
douleur	ES=-0.32	-0.50;-0.14	0.0000	0.1736 (0.43)	3	853
CGI-severity	ES=-0.31	-0.45;-0.18	0.0000	0.7356 (0.00)	3	835
points douloureux (nombre)	ES=-0.01	-0.28;0.25	0.9338	1.0000 (0.00)	1	220
fatigue	ES=-0.08	-0.31;0.15	0.4876	1.0000 (0.00)	1	294
dpression	ES=-0.27	-0.44;-0.10	0.0022	0.5362 (0.00)	2	535
sheehan disability scale	ES=0.03	-0.15;0.20	0.7738	0.2721 (0.17)	2	597
severit globale	ES=-0.36	-0.53;-0.18	0.0000	0.8235 (0.00)	2	517

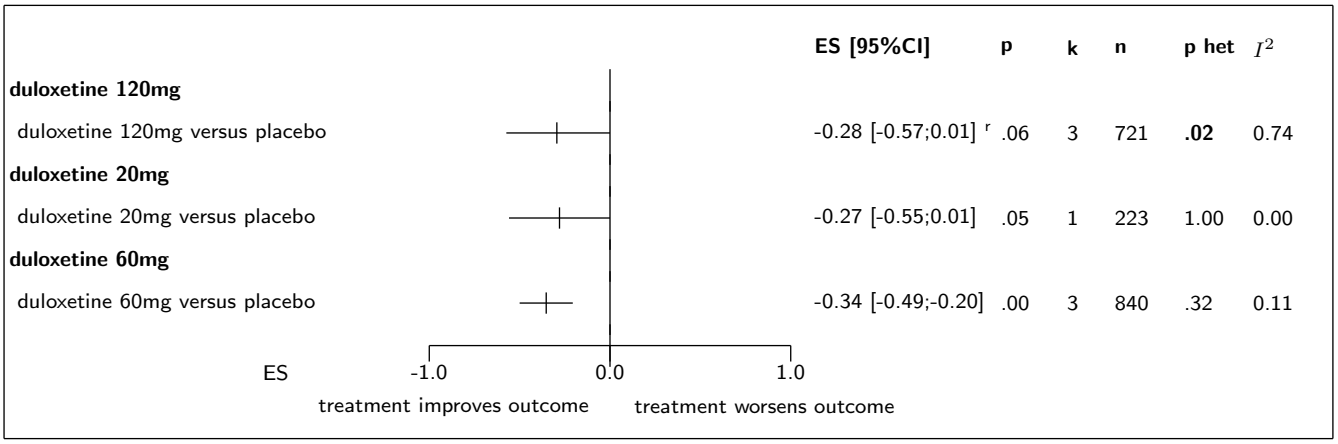
continued...

[1] with a random model ($\tau^2 = 0.048$). The results with a fixed effect model was RRFE=-0.26 95% CI -0.40;-0.11
[2] with a random model ($\tau^2 = 0.073$). The results with a fixed effect model was RRFE=-0.21 95% CI -0.39;-0.03

Endpoint	Effect	95% CI	p ass	p het	k	n
patient Global Impression of Improvement (PGI-I)	ES=-0.16	-0.30;-0.03	0.0172	0.5175 (0.00)	3	841

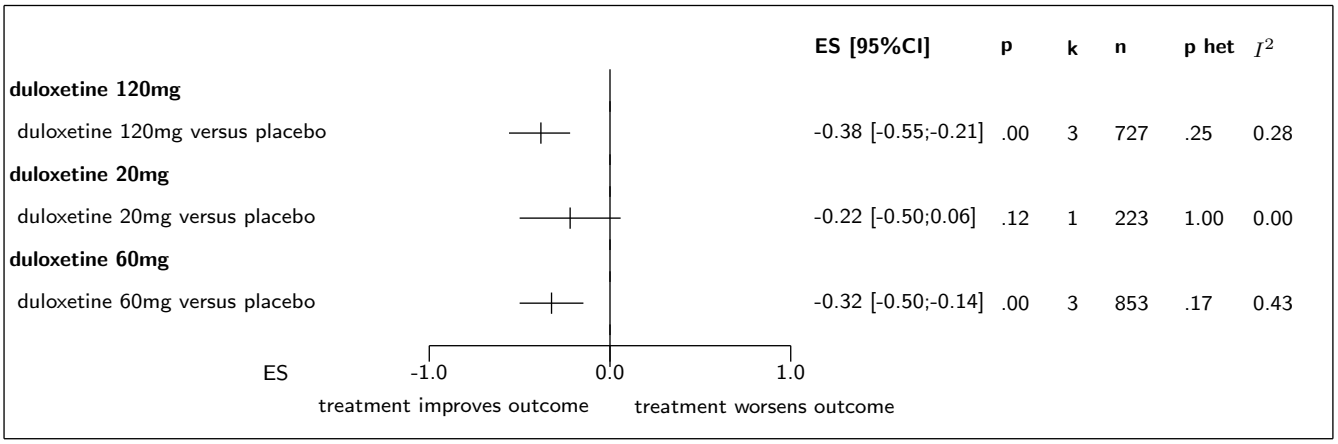
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 9.1: *Forest's plot for FIQ*



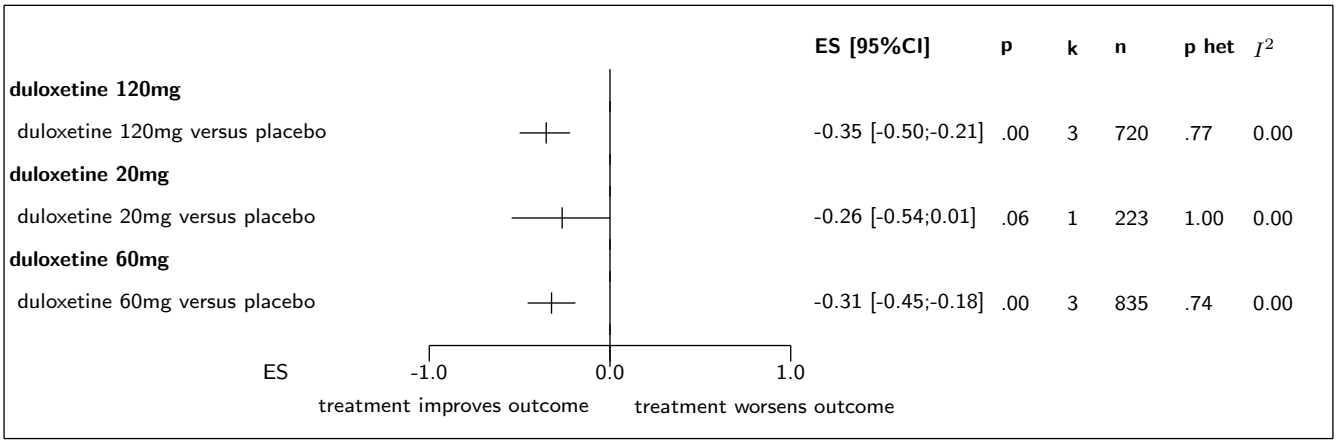
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; r: random effect model used

Figure 9.2: *Forest's plot for douleur*



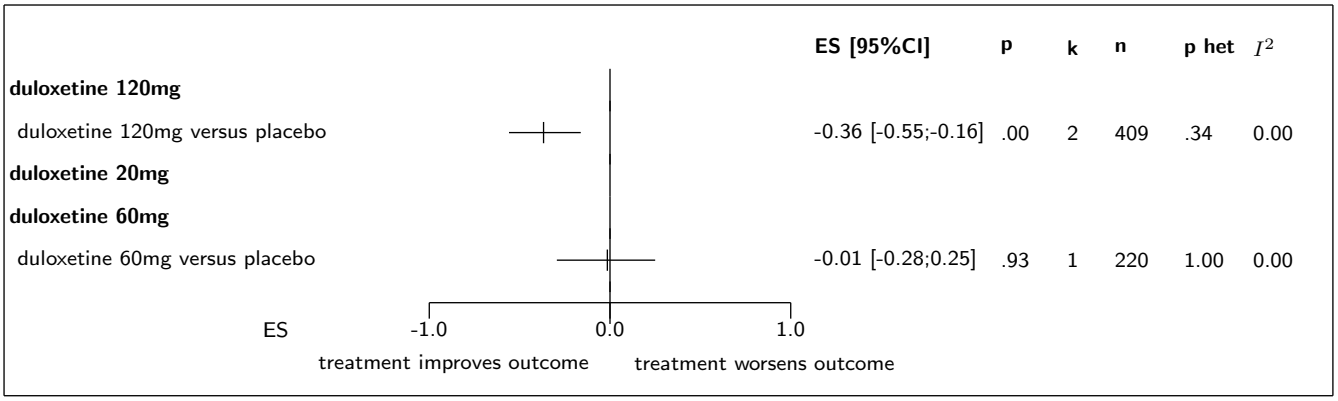
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; r: random effect model used

Figure 9.3: *Forest's plot for CGI-severity*



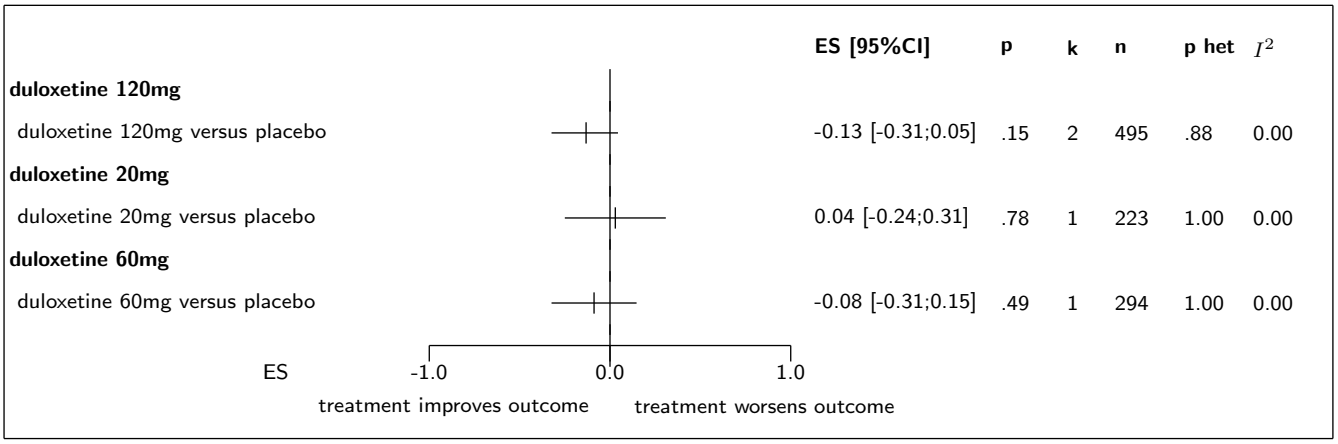
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.4: *Forest's plot for points douloureux (nombre)*



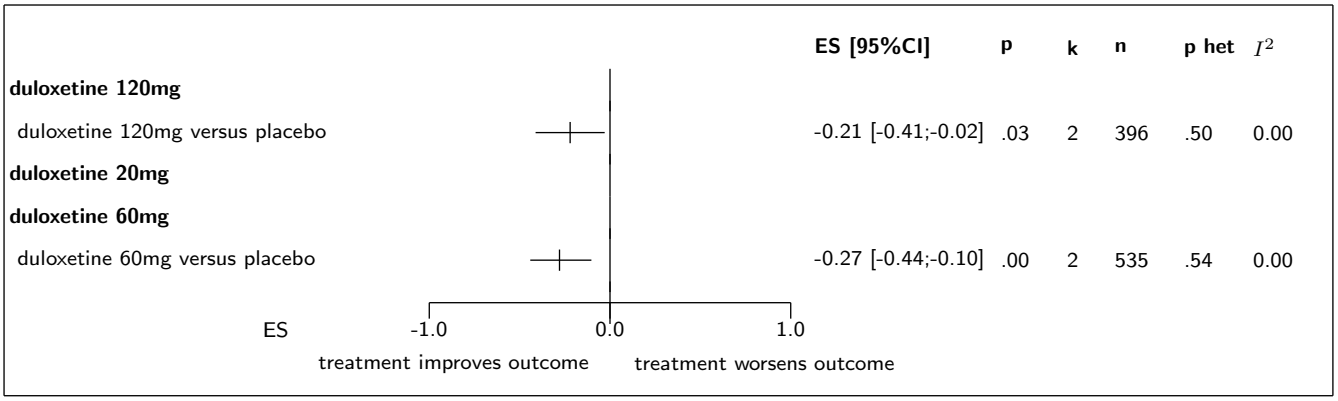
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.5: *Forest's plot for fatigue*



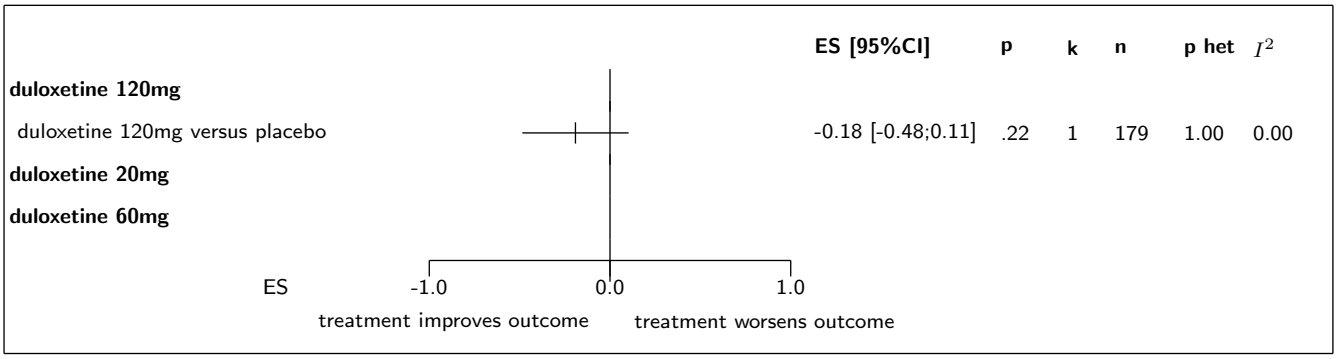
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.6: *Forest's plot for dpression*



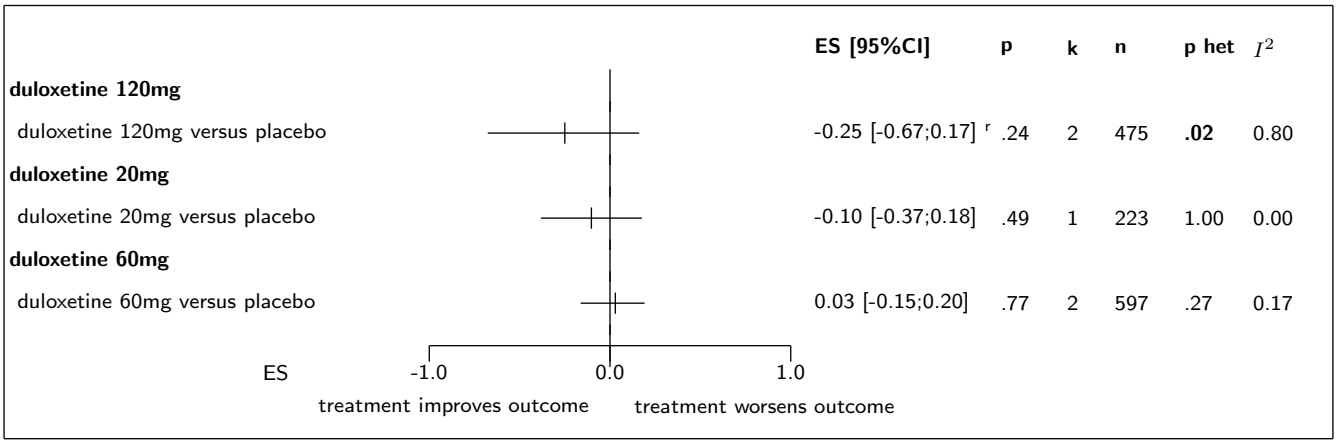
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.7: *Forest's plot for anxit*



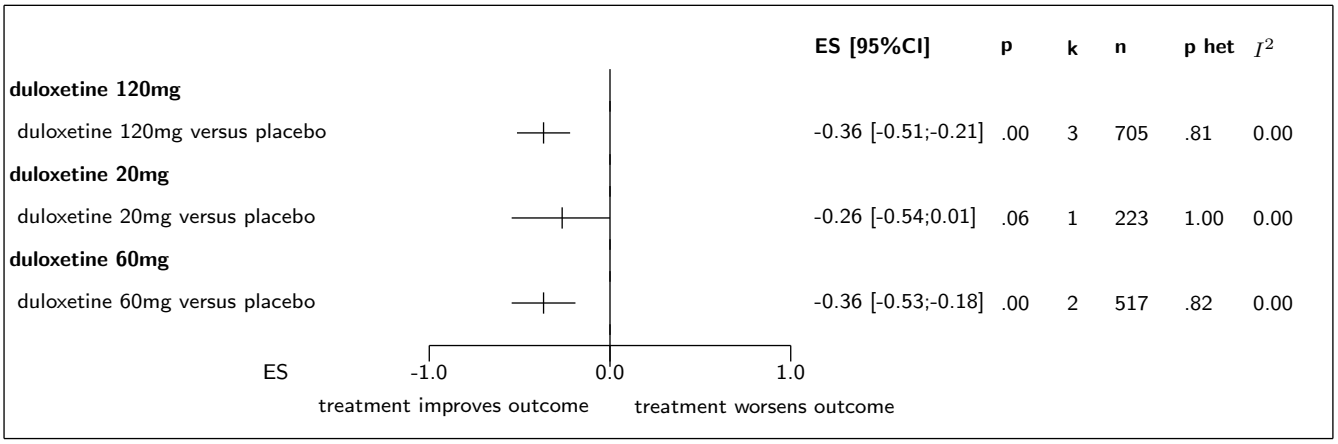
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.8: *Forest's plot for sheehan disability scale*



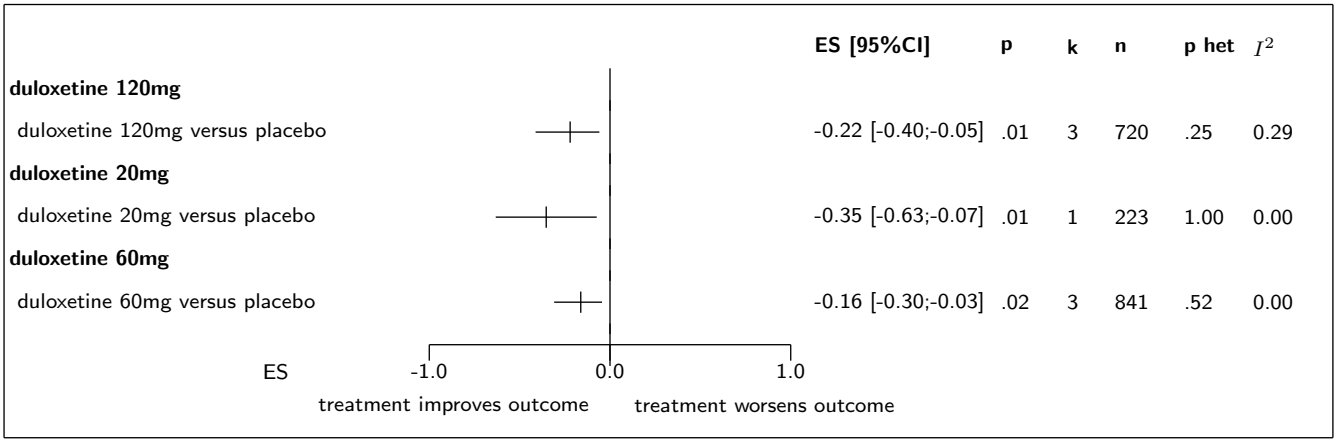
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.9: *Forest's plot for severit globale*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 9.10: *Forest's plot for patient Global Impression of Improvement (PGI-I)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

10 Detailed results for duloxetine 120mg

10.1 Available trials

A total of 3 RCTs which randomized 734 patients were identified: all compared duloxetine 120mg with placebo.
The average study size was 244 patients (range 207 to 291). The first study was published in 2004, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Severit globale data was reported in 3 trials; 3 trials reported data on FIQ; 3 trials reported data on patient Global Impression of Improvement (PGI-I); 3 trials reported data on douleur; 3 trials reported data on CGI-severity; 2 trials reported data on points douloureux (nombre); 2 trials reported data on sheehan disability scale; 2 trials reported data on dpression; 2 trials reported data on fatigue; 1 trials reported data on anxit; and 1 trials reported data on depression - chelle de Beck.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of duloxetine 120mg.

Table 10.1: *Treatment description - duloxetine - duloxetine 120mg*

Trial	Studied treatment	Control treatment
Duloxetine 120mg versus placebo		
Arnold (2004) [**?**]	duloxetine 60 mg deux fois par jour	placebo
Russell 120mg/j (study 6222) (2008) [**?**] [b]	duloxetine 120 mg/j	placebo
Arnold (twice daily) (2005) [**?**] [c]	duloxetine 60mg 2 fois par jour	placebo

b) 4 bras : duloxetine 20 mg/j, 60 mg/j, 120 mg/j, placebo c) 3e groupe recevant duloxetine 60mg une fois par jour

Table 10.2: *Descriptions of participants - duloxetine - duloxetine 120mg*

Trial	Patients
Duloxetine 120mg versus placebo	
Arnold (2004) [**?**]	Critres ACR, 18 ans et plus, score douleur du FIG >=4 (/10)
Russell 120mg/j (study 6222) (2008) [**?**]	Critres ACR; score de douleur de la Brief pain Inventory modified short form >=4;
Arnold (twice daily) (2005) [**?**]	Femmes souffrant d'une fibromylgie primaire avec ou sans depression majeurecritre ACR, score douleur Brief pain inventory >=4

Table 10.3: *Main patients characteristics - duloxetine - duloxetine 120mg*

Trial	Characteristics
Duloxetine 120mg versus placebo	
Arnold, 2004 [**?**]	age (mean), years: 49.1 femmes (%): 88.9 critres d'inclusion: ACR nombre de points douloureux: 16.6 (/18) fibromyalgia Impact Questionnaire: 49.5 (0-80) douleur: 6.95 FIG douleur (0-10) fatigue: 7.4 FIG fatigue (0-10) depression: 12.95 Beck II (0-63) anxit: 10.5 Beck anxiety (0-63)
Russell 120mg/j (study 6222), 2008 [**?**]	age (mean), years: 50.5 ans femmes (%): 96% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 53.3 douleur: 6.7 BPI average pain 0-10 depression: 10.6 (HAMD-17)
Arnold (twice daily), 2005 [**?**]	age (mean), years: 49.6 ans femmes (%): 100% critres d'inclusion: ACR nombre de points douloureux: 17 (/18) fibromyalgia Impact Questionnaire: 52.3 (/80) douleur: 6.45 (/10, BPI pain severety) depression: 11.3 (/52, Hamilton)

Table 10.4: *Design and methodological quality of trials - duloxetine - duloxetine 120mg*

Trial	Design	Duration	Centre	Primary endpoint
Duloxetine 120mg versus placebo				
Arnold, 2004 [**?**] n=207	Parallel groups double blind	12 semaines inclusion period: Jul 2001 - Mar 2002	US 18 centres	FIG-douleur
Russell 120mg/j (study 6222), 2008 [**?**] n=291	Parallel groups double blind	3 mois inclusion period: Juin 2005 - Jun 2007	USA, Puerto Rico 38 centres	Brief Pain Inventory (BPI) et Patient Global Impressions of Improvement (PGI-I)
Arnold (twice daily), 2005 [**?**] n=236	double blind	inclusion period: nov 2002 - oct 2003	US 21 centres	self-reported Brief Pain Inventory

10.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Duloxetine 120mg versus placebo

All the 3 studies had extractable data about the number of participants with **FIQ**. When pooled

together, there was no statistically significant difference between the groups in FIQ, with a ES of -0.28 (95% CI -0.57 to 0.01, p=0.0605). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0219, I^2 = 0.74%).
All the 3 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of duloxetine 120mg in douleur, with a ES of -0.38 (95% CI -0.55 to -0.21, p=0.0000). No heterogeneity was detected (p = 0.2496, I^2 = 0.28%).
All the 3 studies had extractable data about the number of participants with **CGI-severity**. The analysis detected a statistically significant difference in favor of duloxetine 120mg in CGI-severity, with a ES of -0.35 (95% CI -0.50 to -0.21, p=0.0000). No heterogeneity was detected (p = 0.7651, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **points douloureux (nombre)**. The analysis detected a statistically significant difference in favor of duloxetine 120mg in points douloureux (nombre), with a ES of -0.36 (95% CI -0.55 to -0.16, p=0.0000). No heterogeneity was detected (p = 0.3415, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **fatigue**. When pooled together, there was no statistically significant difference between the groups in fatigue, with a ES of -0.13 (95% CI -0.31 to 0.05, p=0.1524). No heterogeneity was detected (p = 0.8761, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **dpression**. The analysis detected a statistically significant difference in favor of duloxetine 120mg in dpression, with a ES of -0.21 (95% CI -0.41 to -0.02, p=0.0332). No heterogeneity was detected (p = 0.5044, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **anxit**. No statistically significant difference between the groups was found in anxit, with a ES of -0.18 (95% CI -0.48 to 0.11, p=0.2185).
A total of 2 of the 3 studies eligible for this comparison provided data on **sheehan disability scale**. When pooled together, there was no statistically significant difference between the groups in sheehan disability scale, with a ES of -0.25 (95% CI -0.67 to 0.17, p=0.2399). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0247, I^2 = 0.80%).
All the 3 studies had extractable data about the number of participants with **severit globale**. The analysis detected a statistically significant difference in favor of duloxetine 120mg in severit globale, with a ES of -0.36 (95% CI -0.51 to -0.21, p=0.0000). No heterogeneity was detected (p = 0.8080, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **patient Global Impression of Improvement (PGI-I)**. The analysis detected a statistically significant difference in favor of duloxetine 120mg in patient Global Impression of Improvement (PGI-I), with a ES of -0.22 (95% CI -0.40 to -0.05, p=0.0128). No heterogeneity was detected (p = 0.2468, I^2 = 0.29%).

Table 10.5: *Results details - duloxetine - duloxetine 120mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
duloxetine 120mg versus placebo						
FIQ	ES=-0.28	[-0.57;0.01]	0.0605	0.0219 (I^2=0.74)	3	721
douleur	ES=-0.38	[-0.55;-0.21]	0.0000	0.2496 (I^2=0.28)	3	727
CGI-severity	ES=-0.35	[-0.50;-0.21]	0.0000	0.7651 (I^2=0.00)	3	720
points douloureux (nombre)	ES=-0.36	[-0.55;-0.16]	0.0000	0.3415 (I^2=0.00)	2	409
fatigue	ES=-0.13	[-0.31;0.05]	0.1524	0.8761 (I^2=0.00)	2	495

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dpression	ES=-0.21	[-0.41;-0.02]	0.0332	0.5044 (I^2=0.00)	2	396
anxit	ES=-0.18	[-0.48;0.11]	0.2185	1.0000 (I^2=0.00)	1	179
sheehan disability scale	ES=-0.25	[-0.67;0.17]	0.2399	0.0247 (I^2=0.80)	2	475
severit globale	ES=-0.36	[-0.51;-0.21]	0.0000	0.8080 (I^2=0.00)	3	705
patient Global Impression of Improvement (PGI-I)	ES=-0.22	[-0.40;-0.05]	0.0128	0.2468 (I^2=0.29)	3	720

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 10.1: *Forest's plot for FIQ*

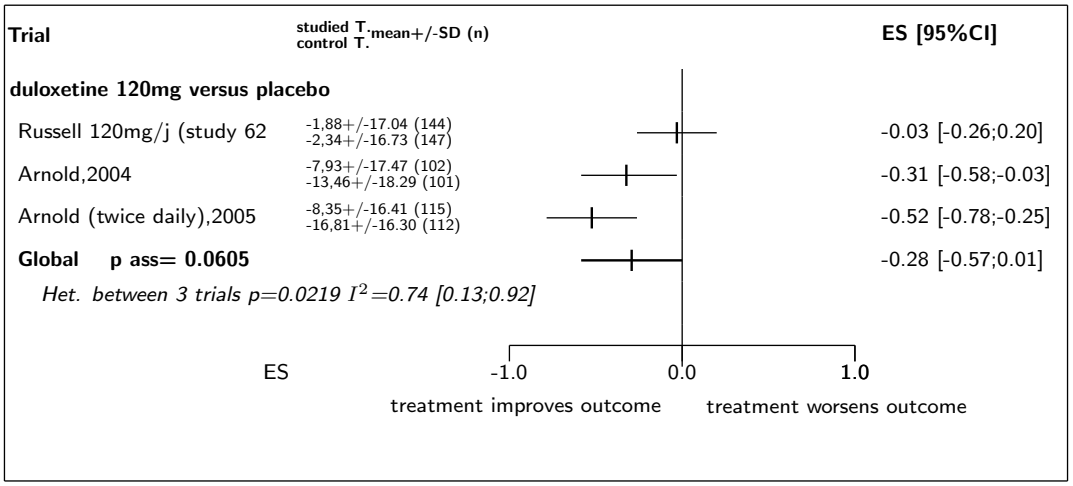


Figure 10.2: *Forest's plot for Douleur*

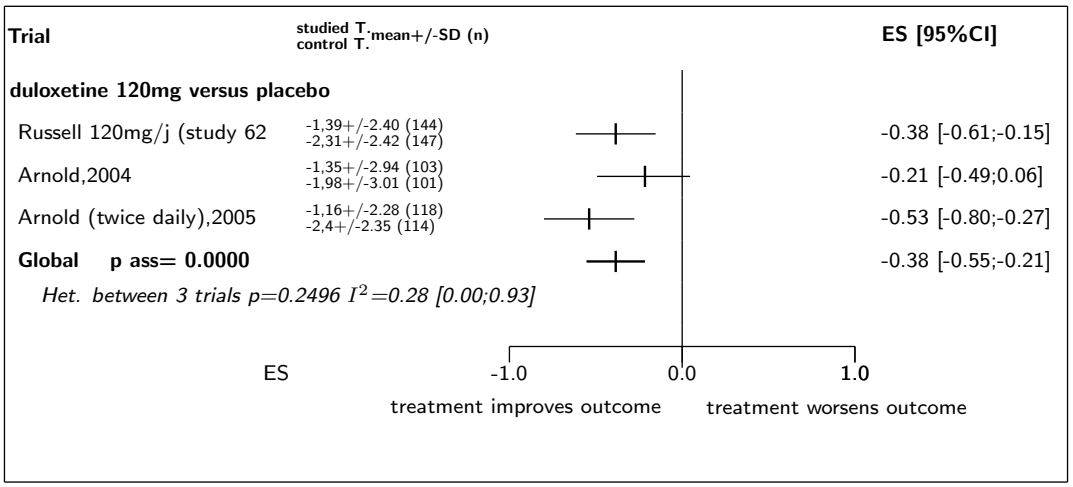


Figure 10.3: *Forest's plot for CGI-severity*

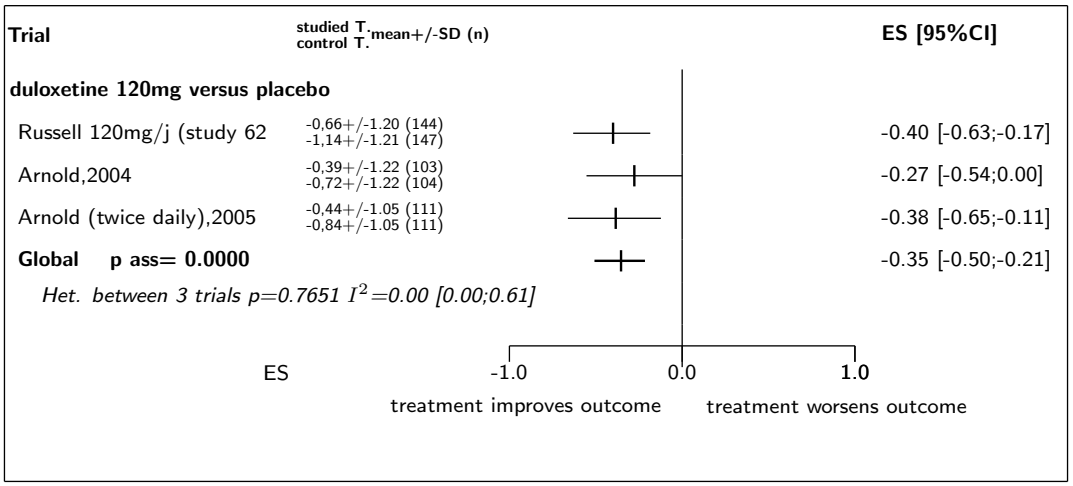


Figure 10.4: *Forest's plot for Points douloureux (nombre)*

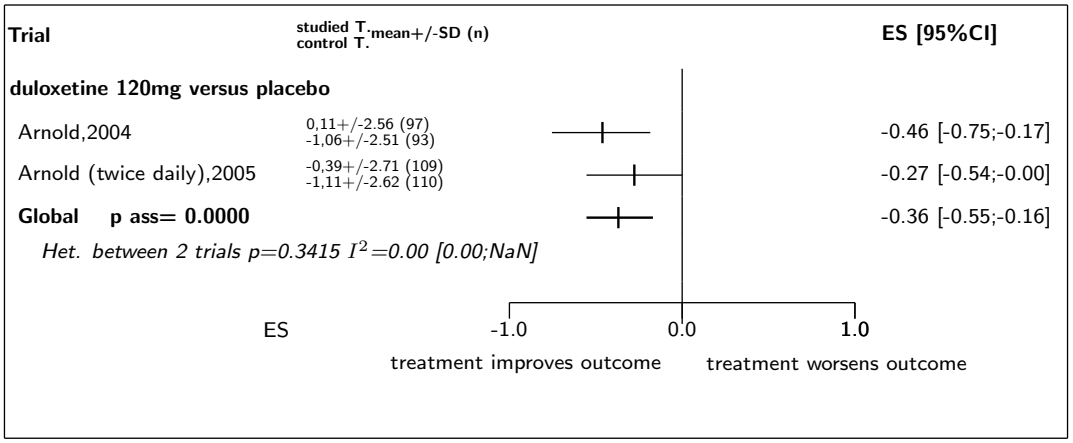


Figure 10.5: *Forest's plot for Fatigue*

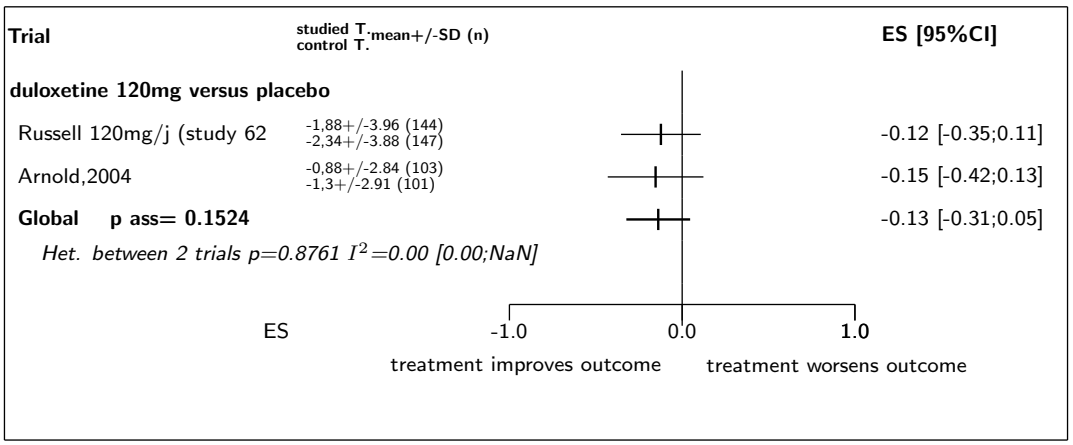


Figure 10.6: *Forest's plot for Dpression*

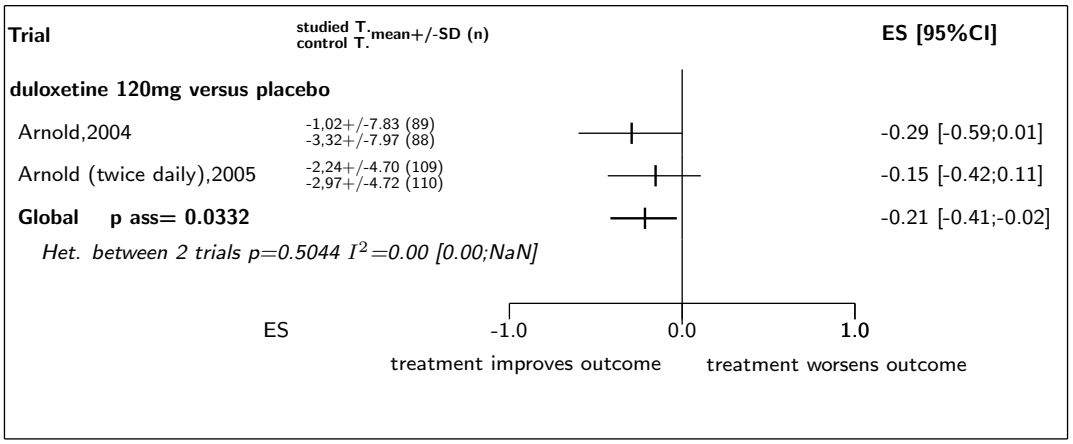


Figure 10.7: *Forest's plot for Anxit*

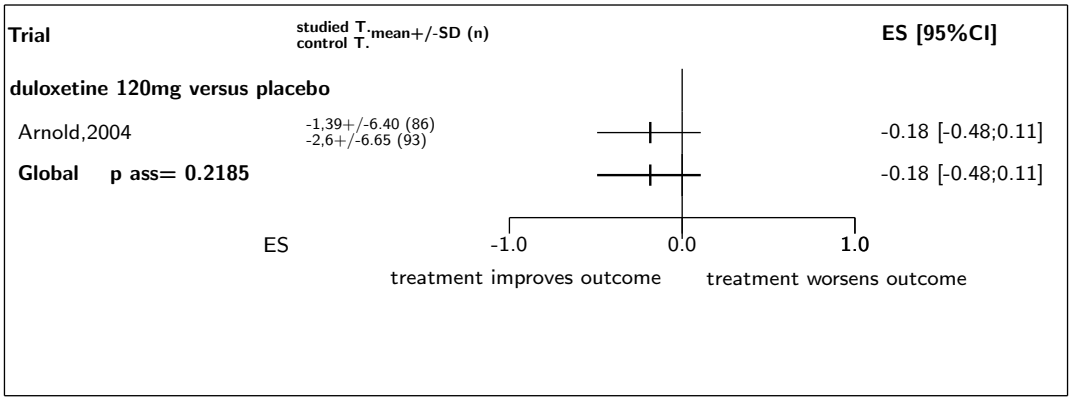


Figure 10.8: *Forest's plot for Sheehan disability scale*

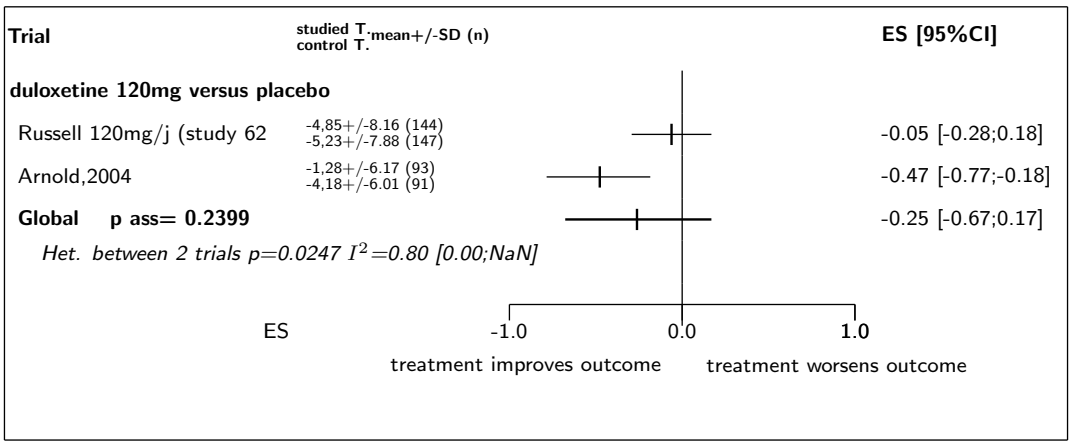


Figure 10.9: *Forest's plot for Severit globale*

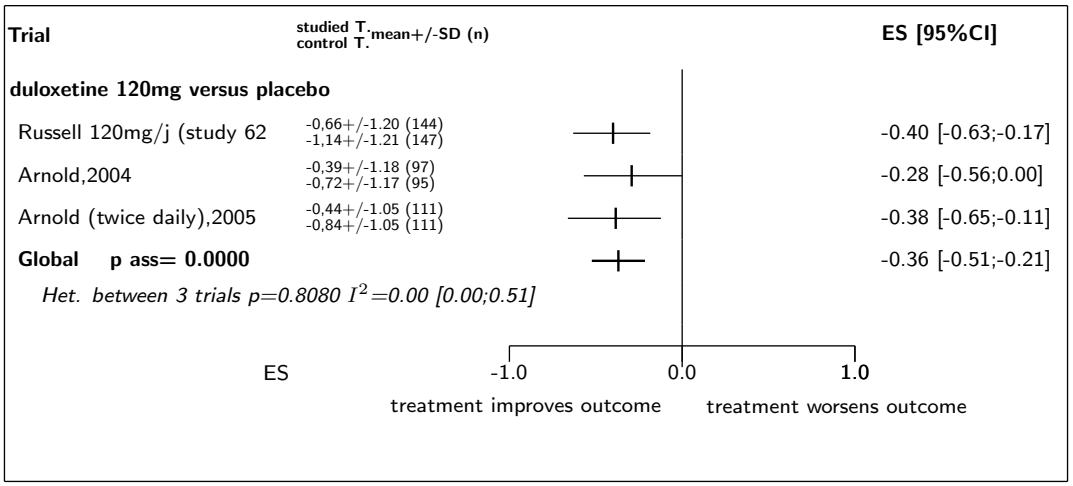
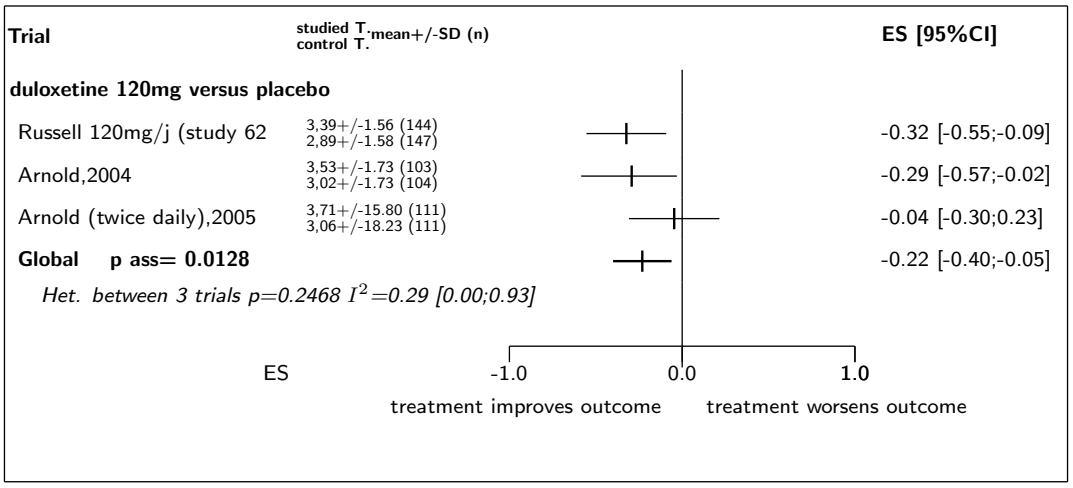


Figure 10.10: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*



References

[1] Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50:2974-84. [PMID=15457467]

[2] Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, Walker DJ, Chappell AS, Arnold LM. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136:432-44. [PMID=18395345]

[3] Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005;119:5-15. [PMID=16298061]

11 Detailed results for duloxetine 20mg

11.1 Available trials

Only one trial which randomized 223 patients was identified: it compared duloxetine 20mg with placebo.
This trial included 223 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
Severit globale data was reported in 1 trials; 1 trials reported data on FIQ; 1 trials reported data on sheehan disability scale; 1 trials reported data on patient Global Impression of Improvement (PGI-I); 1 trials reported data on fatigue; 1 trials reported data on douleur; and 1 trials reported data on CGI-severity.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of duloxetine 20mg.

Table 11.1: *Treatment description - duloxetine - duloxetine 20mg*

Trial	Studied treatment	Control treatment
Duloxetine 20mg versus placebo		
Russell 20mg/j (study 6222) (2008) [**?**] [a]	duloxetine 20 mg/j	placebo

a) 4 bras : duloxetine 20 mg/j, 60 mg/j, 120 mg/j, placebo

Table 11.2: *Descriptions of participants - duloxetine - duloxetine 20mg*

Trial	Patients
Duloxetine 20mg versus placebo	
Russell 20mg/j (study 6222) (2008) [**?**]	Critre ACR; score de douleur de la Brief pain Inventory modified short form >=4;

Table 11.3: *Main patients characteristics - duloxetine - duloxetine 20mg*

Trial	Characteristics
Duloxetine 20mg versus placebo	
Russell 20mg/j (study 6222), 2008 [**?**]	age (mean), years: 50.5 ans femmes (%): 96% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 53.3 douleur: 6.7 BPI average pain 0-10 depression: 10.6 (HAMD-17)

Table 11.4: *Design and methodological quality of trials - duloxetine - duloxetine 20mg*

Trial	Design	Duration	Centre	Primary endpoint
Duloxetine 20mg versus placebo				
Russell 20mg/j (study 6222), 2008 [**?**] n=223	Parallel groups double blind confirmatory trial at low risk of bias	3 mois inclusion period: Juin 2005 - Jun 2007	USA, Puerto Rico 38 centres	Brief Pain Inventory (BPI) et Patient Global Impressions of Improvement (PGI-I)

11.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Duloxetine 20mg versus placebo

The single study eligible for this comparison provided data on **FIQ**. No statistically significant difference between the groups was found in FIQ, with a ES of -0.27 (95% CI -0.55 to 0.01, p=0.0545).
The single study eligible for this comparison provided data on **douleur**. No statistically significant difference between the groups was found in douleur, with a ES of -0.22 (95% CI -0.50 to 0.06, p=0.1170).
The single study eligible for this comparison provided data on **CGI-severity**. No statistically significant difference between the groups was found in CGI-severity, with a ES of -0.26 (95% CI -0.54 to 0.01, p=0.0638).
The single study eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of 0.04 (95% CI -0.24 to 0.31, p=0.7832).
The single study eligible for this comparison provided data on **sheehan disability scale**. No statistically significant difference between the groups was found in sheehan disability scale, with a ES of -0.10 (95% CI -0.37 to 0.18, p=0.4868).
The single study eligible for this comparison provided data on **severit globale**. No statistically significant difference between the groups was found in severit globale, with a ES of -0.26 (95% CI -0.54 to 0.01, p=0.0638).
The single study eligible for this comparison provided data on **patient Global Impression of Improvement (PGI-I)**. The analysis detected a statistically significant difference in favor of duloxetine 20mg in patient Global Impression of Improvement (PGI-I), with a ES of -0.35 (95% CI -0.63 to -0.07, p=0.0133).

Table 11.5: *Results details - duloxetine - duloxetine 20mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
duloxetine 20mg versus placebo						
FIQ	ES=-0.27	[-0.55;0.01]	0.0545	1.0000 (I^2=0.00)	1	223
douleur	ES=-0.22	[-0.50;0.06]	0.1170	1.0000 (I^2=0.00)	1	223
CGI-severity	ES=-0.26	[-0.54;0.01]	0.0638	1.0000 (I^2=0.00)	1	223
fatigue	ES=0.04	[-0.24;0.31]	0.7832	1.0000 (I^2=0.00)	1	223
sheehan disability scale	ES=-0.10	[-0.37;0.18]	0.4868	1.0000 (I^2=0.00)	1	223

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
severit globale	ES=-0.26	[-0.54;0.01]	0.0638	1.0000 (I^2=0.00)	1	223
patient Global Impression of Improvement (PGI-I)	ES=-0.35	[-0.63;-0.07]	0.0133	1.0000 (I^2=0.00)	1	223

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 11.1: *Forest's plot for FIQ*

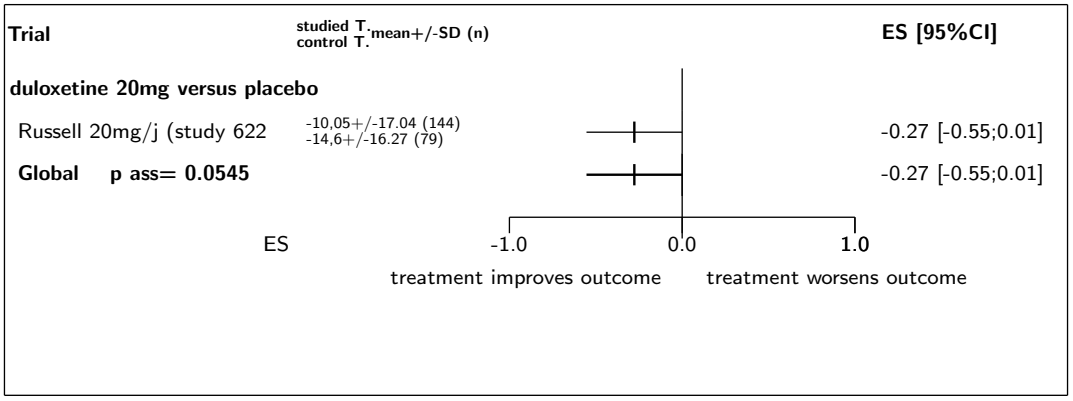


Figure 11.2: *Forest's plot for Douleur*

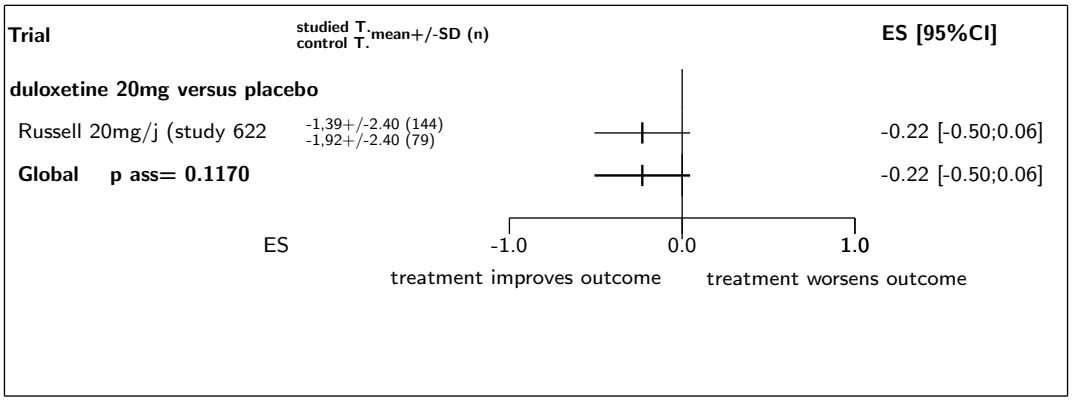


Figure 11.3: *Forest's plot for CGI-severity*

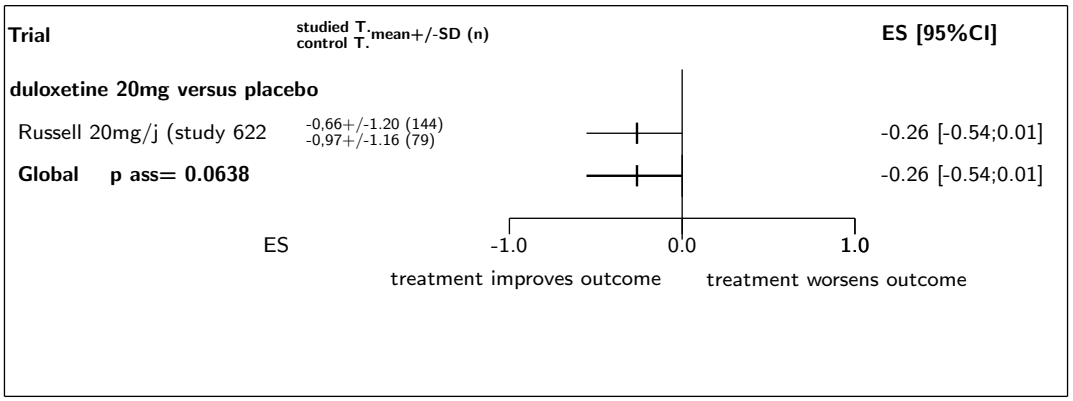


Figure 11.4: *Forest's plot for Fatigue*

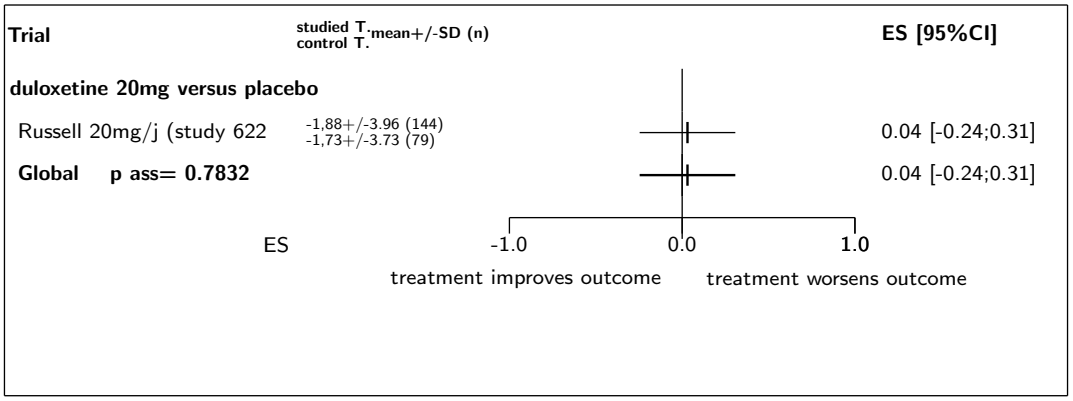


Figure 11.5: *Forest's plot for Sheehan disability scale*

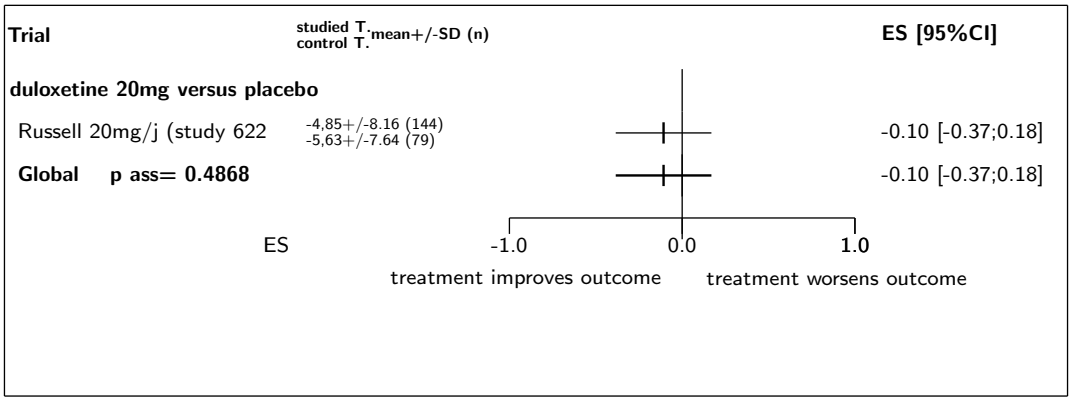


Figure 11.6: *Forest's plot for Severit globale*

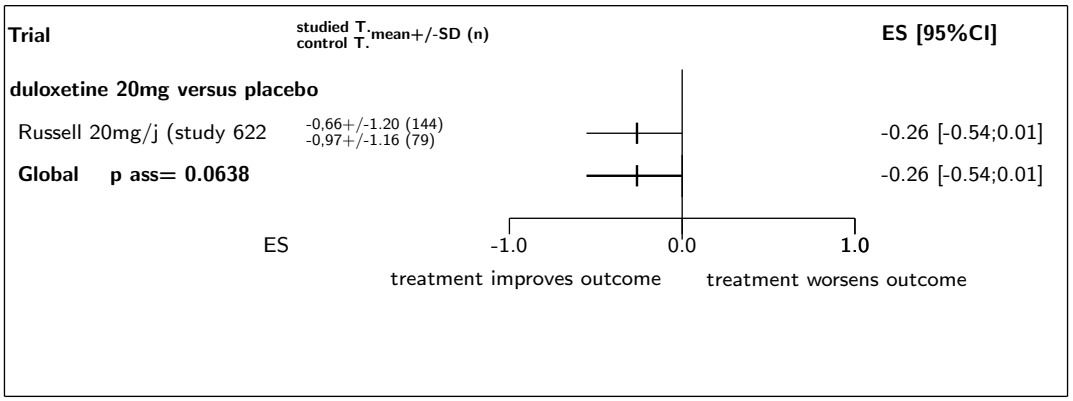
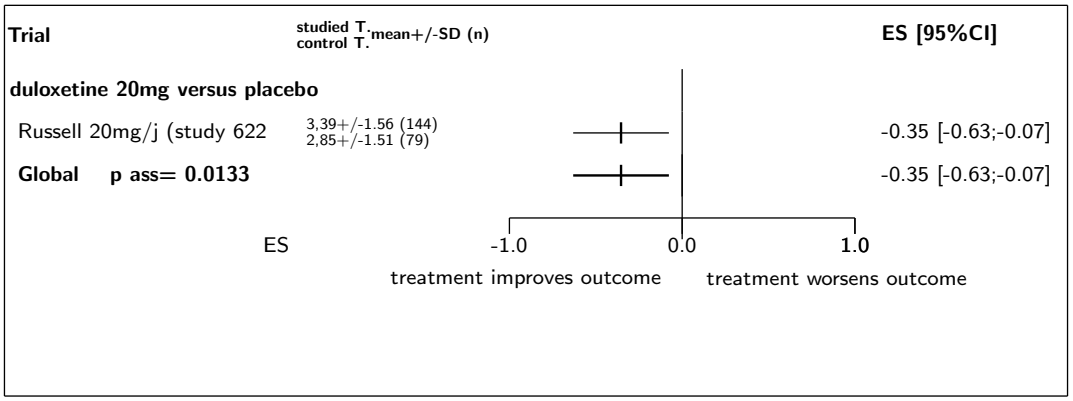


Figure 11.7: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*



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[1] Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, Walker DJ, Chappell AS, Arnold LM. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136:432-44. [PMID=18395345]

12 Detailed results for duloxetine 60mg

12.1 Available trials

A total of 4 RCTs which randomized 1169 patients were identified: it compared duloxetine 60mg with duloxetine 120mg and 3 trials compared duloxetine 60mg with placebo.
The average study size was 292 patients (range 238 to 330). The first study was published in 2005, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We found 2 unpublished trials.
Douleur data was reported in 3 trials; 3 trials reported data on patient Global Impression of Improvement (PGI-I); 3 trials reported data on FIQ; 3 trials reported data on CGI-severity; 2 trials reported data on sheehan disability scale; 2 trials reported data on severit globale; 2 trials reported data on dpression; 1 trials reported data on points douloureux (nombre); 1 trials reported data on depression - chelle de Beck; and 1 trials reported data on fatigue.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of duloxetine 60mg.

Table 12.1: *Treatment description - duloxetine - duloxetine 60mg*

Trial	Studied treatment	Control treatment
Duloxetine 60mg versus duloxetine 120mg		
Chappell study 9075 (0) [**?**]	duloxetine 60mg une fois par jour	duloxetine 120 mg une fois par jour
Duloxetine 60mg versus placebo		
Russell 60mg/j (2008) [**?**] [a]	duloxetine 60 mg/j	placebo
study 9072 (F1J MC HMEF) (0)	duloxetine 60 ou 120 mg/j	placebo
Arnold (once daily) (2005) [**?**] [c]	duloxetine 60mg une fois par jour	placebo

a) 4 bras : duloxetine 20 mg/j, 60 mg/j, 120 mg/j, placebo
c) 3e groupe recevant duloxetine 60mg 2 fois par jour

Table 12.2: *Descriptions of participants - duloxetine - duloxetine 60mg*

Trial	Patients
Duloxetine 60mg versus duloxetine 120mg	
Chappell study 9075 (0) [**?**]	Critres ACR, >18 ans, score de douleur BPI >=4
Duloxetine 60mg versus placebo	
Russell 60mg/j (2008) [**?**]	Critres ACR; score de douleur de la Brief pain Inventory modified short form >=4;

continued...

Trial	Patients
study 9072 (F1J MC HMEF) (0)	Critre ACR, avec ou sans depression majeure
Arnold (once daily) (2005) [?]	Femmes souffrant d'une fibromylgie primaire avec ou sans depression majeure, critre ACR et score douleur Brief pain inventory >=4

Table 12.3: *Main patients characteristics - duloxetine - duloxetine 60mg*

Trial	Characteristics
Duloxetine 60mg versus duloxetine 120mg	
Chappell study 9075, 0 [?]	age (mean), years: 49 ans femmes (%): 95.7% douleur: 6.7 (BPI average pain score)
Duloxetine 60mg versus placebo	
Russell 60mg/j, 2008 [?]	age (mean), years: 50.5 ans femmes (%): 96% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 53.3 douleur: 6.7 BPI average pain 0-10 depression: 10.6 (HAMD-17)
study 9072 (F1J MC HMEF), 0	age (mean), years: 50.4 ans femmes (%): 93.3% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 7.34 douleur: 6.52 BPI depression: 14.6 BDI-II
Arnold (once daily), 2005 [?]	age (mean), years: 49.6 ans femmes (%): 100% critres d'inclusion: ACR nombre de points douloureux: 17 (/18) fibromyalgia Impact Questionnaire: 52.3 (/80) douleur: 6.45 (/10, BPI pain severety) depression: 11.3 (/52, Hamilton)

Table 12.4: *Design and methodological quality of trials - duloxetine - duloxetine 60mg*

Trial	Design	Duration	Centre	Primary endpoint
Duloxetine 60mg versus duloxetine 120mg				
Chappell study 9075, 0 [?] [a] n=307	Parallel groups double blind confirmatory trial at low risk of bias	52 semaines inclusion period: Jul 2005 -	7 countries 33 centres	
Duloxetine 60mg versus placebo				
Russell 60mg/j, 2008 [?] n=294	Parallel groups double blind	3 mois inclusion period: Juin 2005 - Jun 2007	USA, Puerto Rico 38 centres	Brief Pain Inventory (BPI) et Patient Global Impressions of Improvement (PGI-I)

continued...

Trial	Design	Duration	Centre	Primary end-point
study 9072 (F1J MC HMEF), 0 n=330	Parallel groups double blind	27 semaines inclusion period: sept 2005 -	5 countries 36 centres	BPI, PGI-improvement
Arnold (once daily), 2005 [?] n=238	Parallel groups double blind	inclusion period: nov 2002 - oct 2003	US 21 centres	self-reported Brief Pain Inventory

a) tude de safety

12.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Duloxetine 60mg versus duloxetine 120mg

No data were presented in the 1 trial identified

Duloxetine 60mg versus placebo

All the 3 studies had extractable data about the number of participants with **FIQ**. The analysis detected a statistically significant difference in favor of duloxetine 60mg in FIQ, with a ES of -0.34 (95% CI -0.49 to -0.20, p=0.0000). No heterogeneity was detected (p = 0.3245, I^2 = 0.11%).
All the 3 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of duloxetine 60mg in douleur, with a ES of -0.32 (95% CI -0.50 to -0.14, p=0.0000). No heterogeneity was detected (p = 0.1736, I^2 = 0.43%).
All the 3 studies had extractable data about the number of participants with **CGI-severity**. The analysis detected a statistically significant difference in favor of duloxetine 60mg in CGI-severity, with a ES of -0.31 (95% CI -0.45 to -0.18, p=0.0000). No heterogeneity was detected (p = 0.7356, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **points douloureux (nombre)**. No statistically significant difference between the groups was found in points douloureux (nombre), with a ES of -0.01 (95% CI -0.28 to 0.25, p=0.9338).
Only one of the 3 studies eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of -0.08 (95% CI -0.31 to 0.15, p=0.4876).
A total of 2 of the 3 studies eligible for this comparison provided data on **dpression**. The analysis detected a statistically significant difference in favor of duloxetine 60mg in dpression, with a ES of -0.27 (95% CI -0.44 to -0.10, p=0.0022). No heterogeneity was detected (p = 0.5362, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **sheehan disability scale**. When pooled together, there was no statistically significant difference between the groups in sheehan disability scale, with a ES of 0.03 (95% CI -0.15 to 0.20, p=0.7738). No heterogeneity was detected (p = 0.2721, I^2 = 0.17%).
A total of 2 of the 3 studies eligible for this comparison provided data on **severit globale**. The analysis detected a statistically significant difference in favor of duloxetine 60mg in severit globale, with a ES of -0.36 (95% CI -0.53 to -0.18, p=0.0000). No heterogeneity was detected (p = 0.8235, I^2 = 0.00%).

All the 3 studies had extractable data about the number of participants with **patient Global Impression of Improvement (PGI-I)**. The analysis detected a statistically significant difference in favor of duloxetine 60mg in patient Global Impression of Improvement (PGI-I), with a ES of -0.16 (95% CI -0.30 to -0.03, p=0.0172). No heterogeneity was detected (p = 0.5175, I^2 = 0.00%).

Table 12.5: *Results details - duloxetine - duloxetine 60mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
duloxetine 60mg versus duloxetine 120mg						
No data were presented in the trial identified						
duloxetine 60mg versus placebo						
FIQ	ES=-0.34	[-0.49;-0.20]	0.0000	0.3245 (I^2=0.11)	3	840
douleur	ES=-0.32	[-0.50;-0.14]	0.0000	0.1736 (I^2=0.43)	3	853
CGI-severity	ES=-0.31	[-0.45;-0.18]	0.0000	0.7356 (I^2=0.00)	3	835
points douloureux (nombre)	ES=-0.01	[-0.28;0.25]	0.9338	1.0000 (I^2=0.00)	1	220
fatigue	ES=-0.08	[-0.31;0.15]	0.4876	1.0000 (I^2=0.00)	1	294
dpression	ES=-0.27	[-0.44;-0.10]	0.0022	0.5362 (I^2=0.00)	2	535
sheehan disability scale	ES=0.03	[-0.15;0.20]	0.7738	0.2721 (I^2=0.17)	2	597
severit globale	ES=-0.36	[-0.53;-0.18]	0.0000	0.8235 (I^2=0.00)	2	517
patient Global Impression of Improvement (PGI-I)	ES=-0.16	[-0.30;-0.03]	0.0172	0.5175 (I^2=0.00)	3	841

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 12.1: *Forest's plot for FIQ*

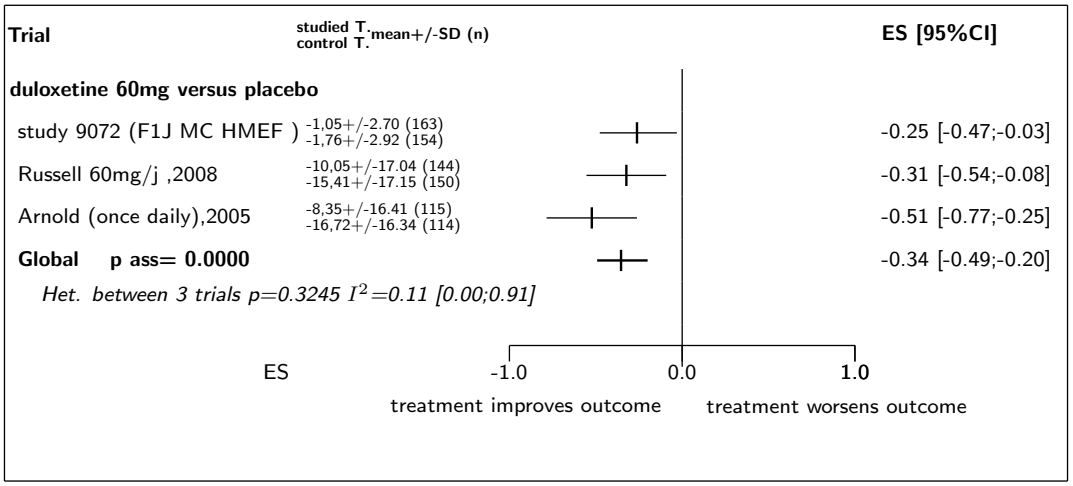


Figure 12.2: *Forest's plot for Douleur*

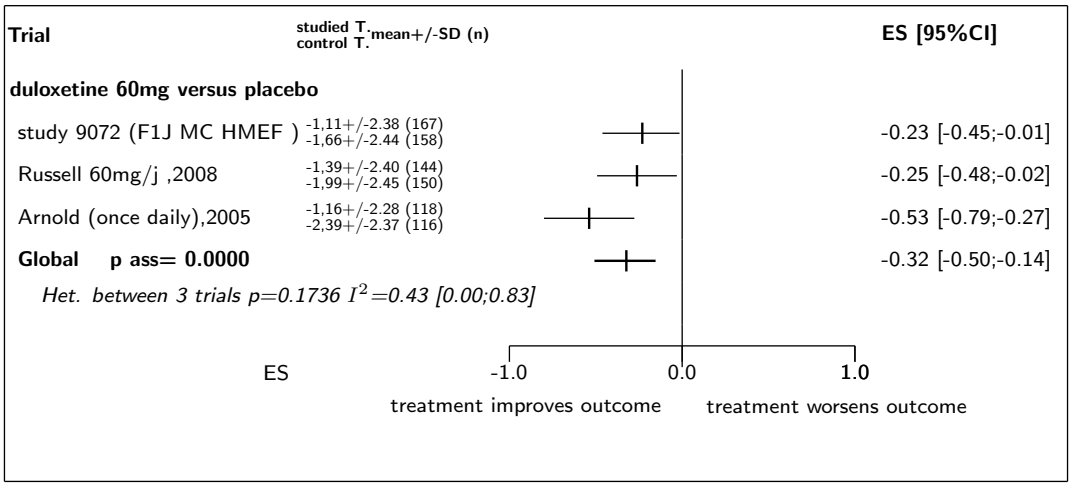


Figure 12.3: *Forest's plot for CGI-severity*

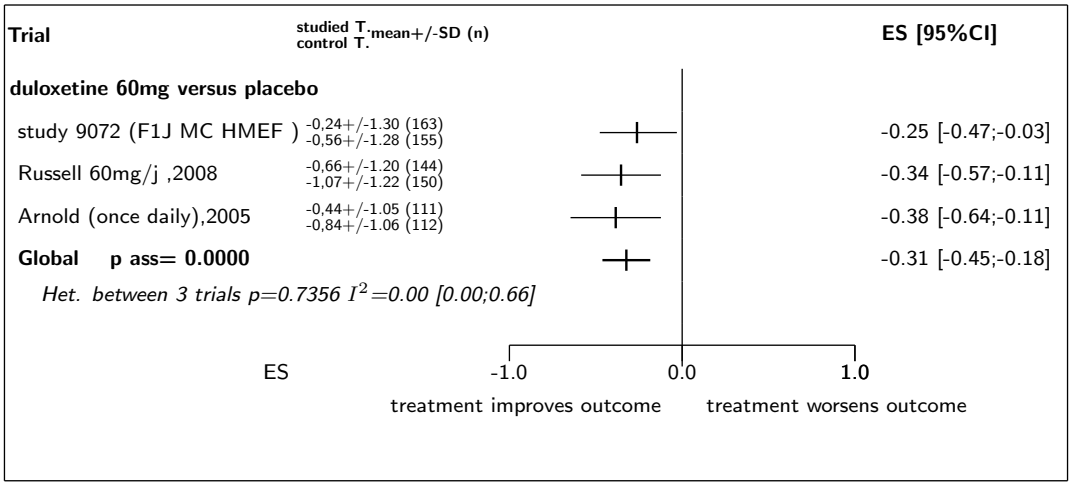


Figure 12.4: *Forest's plot for Points douloureux (nombre)*

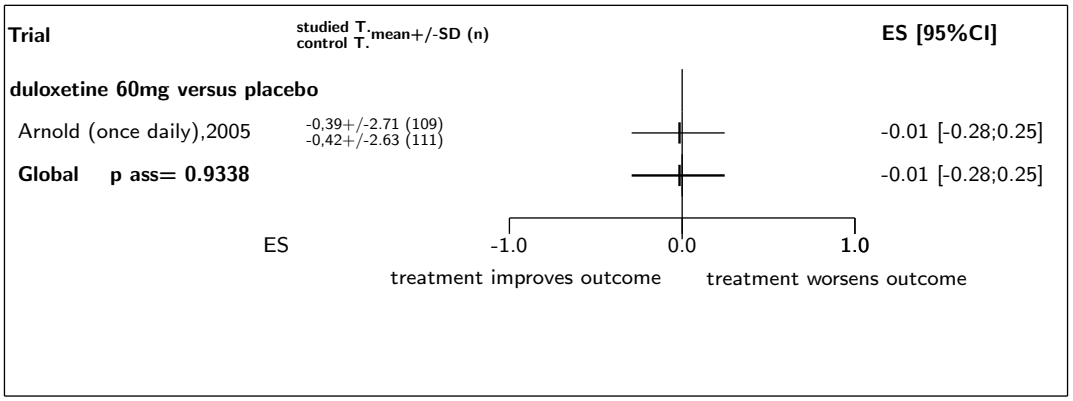


Figure 12.5: *Forest's plot for Fatigue*

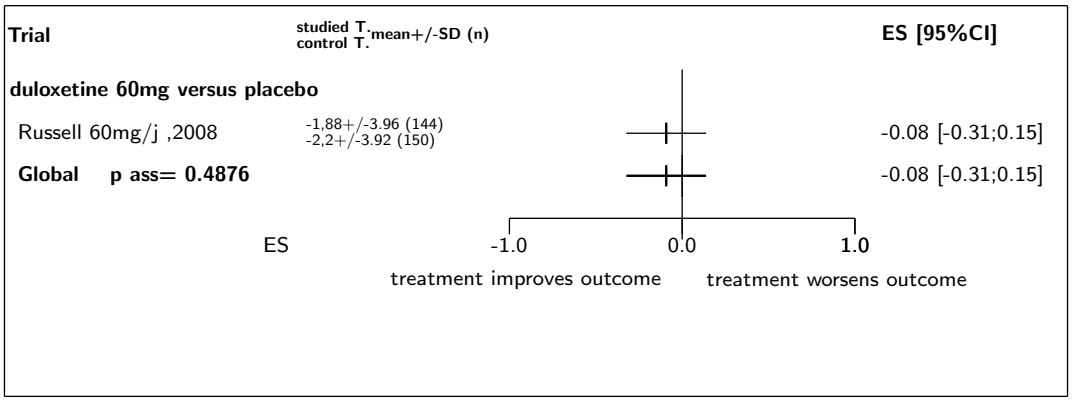


Figure 12.6: *Forest's plot for Dpression*

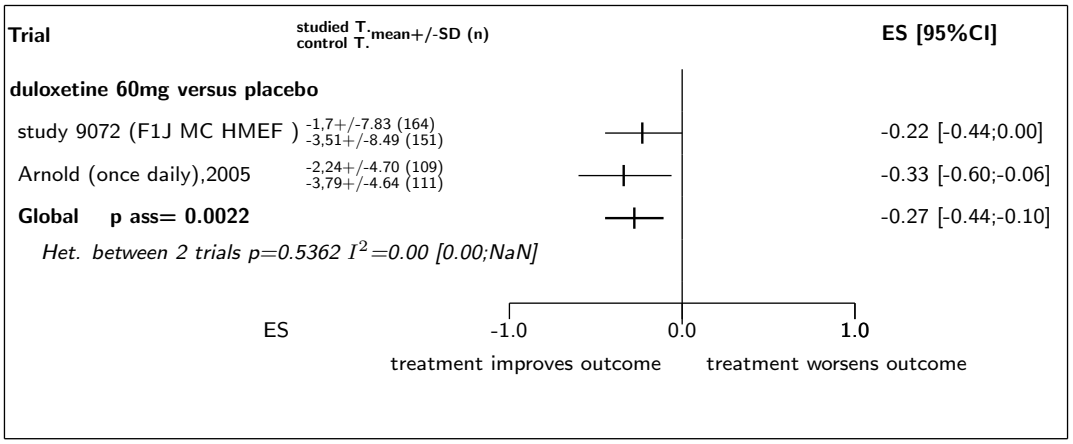


Figure 12.7: *Forest's plot for Sheehan disability scale*

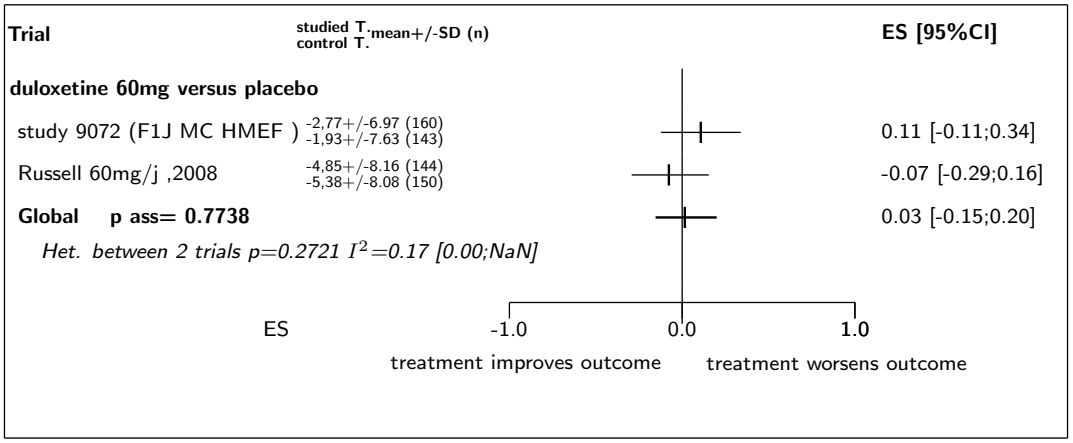


Figure 12.8: *Forest's plot for Severit globale*

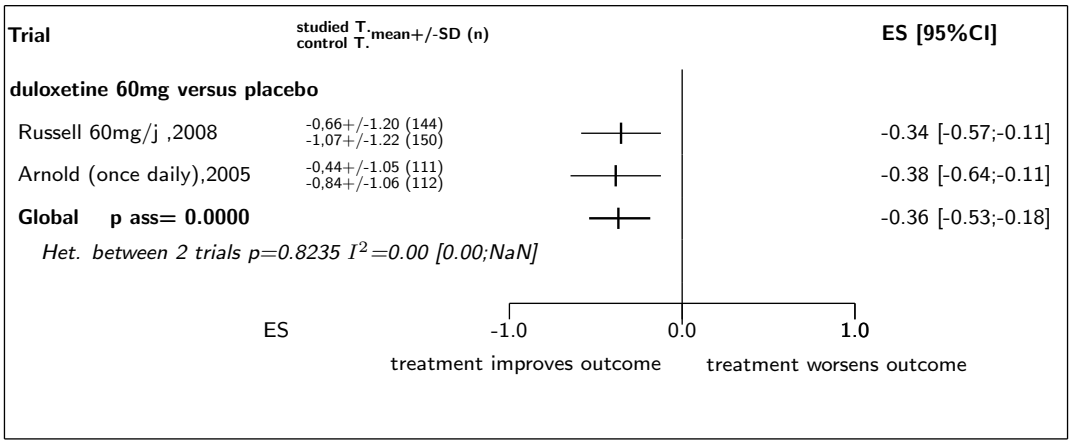
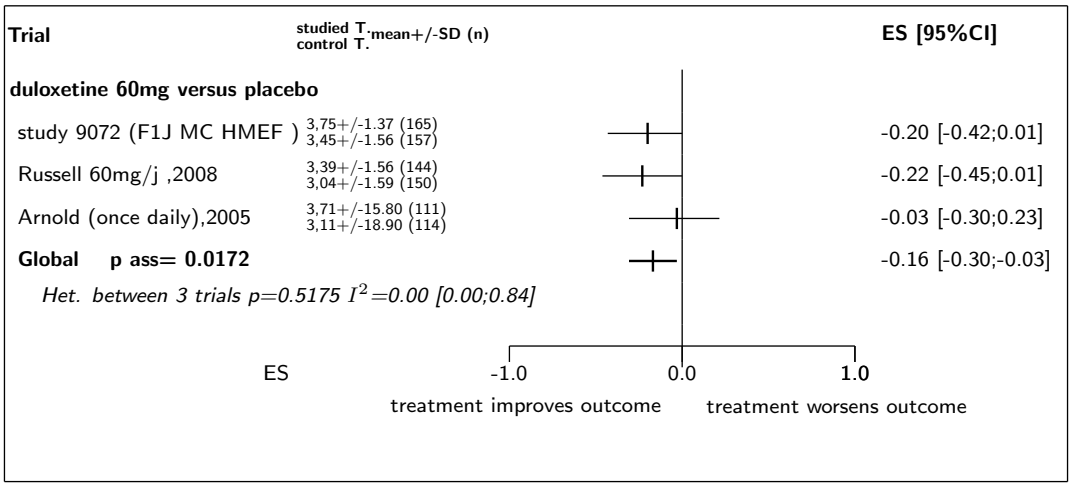


Figure 12.9: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*



References

[1] Chappell AS et al. A 1-year safety and efficacy study of duloxetine in patients with fibromyalgia. Ann Rheum Dis 2008; 67(suppl 2): 253.

[2] Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, Walker DJ, Chappell AS, Arnold LM. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136:432-44. [PMID=18395345]

[3] Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or

without major depressive disorder. Pain 2005;119:5-15. [PMID=16298061]

13 Global meta-analysis: all duloxetine

13.1 Global meta-analysis: all duloxetine versus duloxetine 120mg

Table 13.1: *All duloxetineversus duloxetine 120mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

legend B

13.2 Global meta-analysis: all duloxetine versus placebo

Table 13.2: *All duloxetineversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
FIQ	ES=-0.31	-0.43;-0.18	0.0000	0.1003 (0.44)	7	1784
douleur	ES=-0.33	-0.44;-0.23	0.0000	0.2859 (0.19)	7	1803
CGI-severity	ES=-0.32	-0.42;-0.23	0.0000	0.9565 (0.00)	7	1778
points douloureux (nombre)	ES=-0.24	-0.49;0.01	0.0607	0.0761 (0.61)	3	629
fatigue	ES=-0.08	-0.20;0.04	0.2066	0.7928 (0.00)	4	1012
dpression	ES=-0.24	-0.37;-0.12	0.0000	0.8066 (0.00)	4	931
anxit	ES=-0.18	-0.48;0.11	0.2185	1.0000 (0.00)	1	179
sheehan disability scale	ES=-0.10 [1]	-0.27;0.08	0.2661	0.0417 (0.60) †	5	1295
severit globale	ES=-0.34	-0.45;-0.24	0.0000	0.9712 (0.00)	6	1445
patient Global Impression of Improvement (PGI-I)	ES=-0.21	-0.30;-0.12	0.0000	0.4752 (0.00)	7	1784

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14 Ongoing studies of duloxetine

A total of 2 ongoing studies were still ongoing at the date of this report. A list of these ongoing studies with a brief description is given table **??**.

[1] with a random model ($\tau^2 = 0.024$). The results with a fixed effect model was RRFE=-0.08 95% CI -0.19;0.03

Table 14.1: *Ongoing studies for duloxetine*

Study	**Description**
F1J-MC-HMEF (study 9072) NCT00233025	duloxetine 60/120mg **vs.** placebo
F1J-US-HMGB (study 12220)	duloxetine dose flexible 60/120mg une fois par jour **vs.** placebo critre ACR, score BPI >=4

15 Excluded studies for duloxetine

No trial was excluded.

Part IV

Fluoxetine

16 Overview of fluoxetine

16.1 Included trials

A total of 4 randomized comparisons which enrolled 226 patients were identified. In all, 4 randomized comparisons concerned fluoxetine.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for fluoxetine.

The average study size was 56 patients (range 42 to 62). The first study was published in 1994, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

16.2 Summary of meta-analysis results

The meta-analysis of the available trials about fluoxetine provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

16.2.1 Fluoxetine

No significant difference was found between **fluoxetine** and **amitriptyline** in terms of FIQ (ES=-0.22, 95% CI -0.82 to 0.38, p=0.4804, 1 trial), douleur (ES=-0.25, 95% CI -0.85 to 0.35, p=0.4128, 1 trial), fatigue (ES=0.03, 95% CI -0.57 to 0.63, p=0.9149, 1 trial)and sommeil (ES=0.29, 95% CI -0.31 to 0.89, p=0.3507, 1 trial).

Fluoxetine was superior to **placebo** in terms of FIQ (ES=-0.71, 95% CI -1.11 to -0.31, p=0.0000, 2 trials), douleur (ES=-0.72, 95% CI -1.29 to -0.15, p=0.0126, 3 trials)and severit globale (ES=-0.56, 95% CI -1.07 to -0.06, p=0.0276, 2 trials).
However, no significant difference was found on points douloureux (nombre) (ES=-0.46, 95% CI -1.12 to 0.20, p=0.1744, 1 trial), fatigue (ES=-0.34, 95% CI -0.69 to 0.02, p=0.0635, 3 trials), sommeil (ES=-0.21, 95% CI -0.71 to 0.28, p=0.3989, 2 trials), dpression (ES=-0.67, 95% CI -1.52 to 0.17, p=0.1195, 1 trial), anxit (ES=-0.47, 95% CI -1.31 to 0.36, p=0.2668, 1 trial)and HAQ functional disability (ES=-0.17, 95% CI -1.00 to 0.66, p=0.6896, 1 trial).

Table 16.1: *Main study characteristics - fluoxetine*

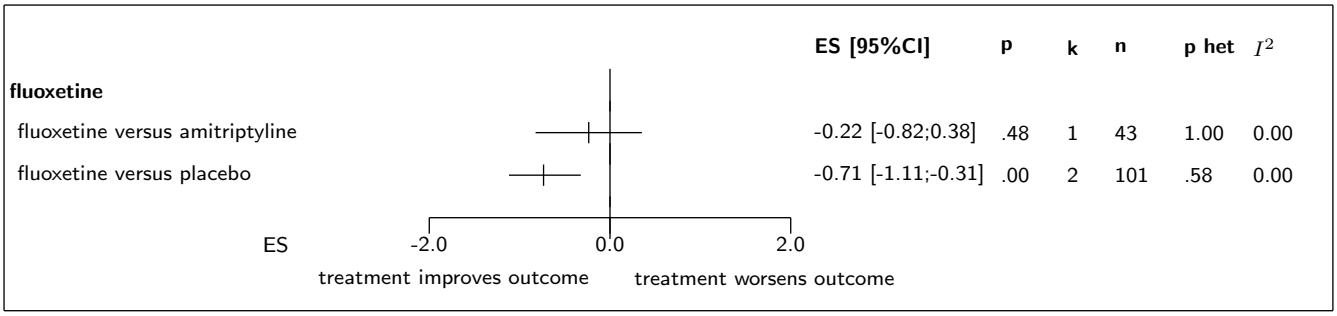
Trial	Patients	Treatments	Trial design and method
Fluoxetine			
Fluoxetine versus amitriptyline			
Goldenberg (fluo vs amit), 1996 [**?**, **?**]	n = 31 vs. 31	fluoxetine 20mg/j **versus** amitriptyline 25mg/j	double blind parallel groups
Fluoxetine versus placebo			
Arnold, 2002 [**?**]	n = 30 vs. 30	fluoxetine 10-80 mg/j **versus** placebo	double blind parallel groups Primary endpoint: FIQ total score and pain score
Goldenberg (vs PBO), 1996 [**?**]	n = 31 vs. 31	fluoxetine 20mg/j **versus** placebo	double blind cross over
Wolfe, 1994 [**?**]	n = 21 vs. 21	fluoxetine 20 mg/d **versus** placebo	double blind parallel groups

Table 16.2: *Summary of all results for fluoxetine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fluoxetine versus amitriptyline						
FIQ	ES=-0.22	-0.82;0.38	0.4804	1.0000 (0.00)	1	43
douleur	ES=-0.25	-0.85;0.35	0.4128	1.0000 (0.00)	1	43
fatigue	ES=0.03	-0.57;0.63	0.9149	1.0000 (0.00)	1	43
sommeil	ES=0.29	-0.31;0.89	0.3507	1.0000 (0.00)	1	43
fluoxetine versus placebo						
FIQ	ES=-0.71	-1.11;-0.31	0.0000	0.5769 (0.00)	2	101
douleur	ES=-0.72	-1.29;-0.15	0.0126	0.1109 (0.55)	3	125
points douloureux (nombre)	ES=-0.46	-1.12;0.20	0.1744	1.0000 (0.00)	1	36
fatigue	ES=-0.34	-0.69;0.02	0.0635	0.4937 (0.00)	3	125
sommeil	ES=-0.21	-0.71;0.28	0.3989	0.5281 (0.00)	2	65
dpression	ES=-0.67	-1.52;0.17	0.1195	1.0000 (0.00)	1	24
anxit	ES=-0.47	-1.31;0.36	0.2668	1.0000 (0.00)	1	24
HAQ functional disability	ES=-0.17	-1.00;0.66	0.6896	1.0000 (0.00)	1	24
severit globale	ES=-0.56	-1.07;-0.06	0.0276	0.7454 (0.00)	2	65

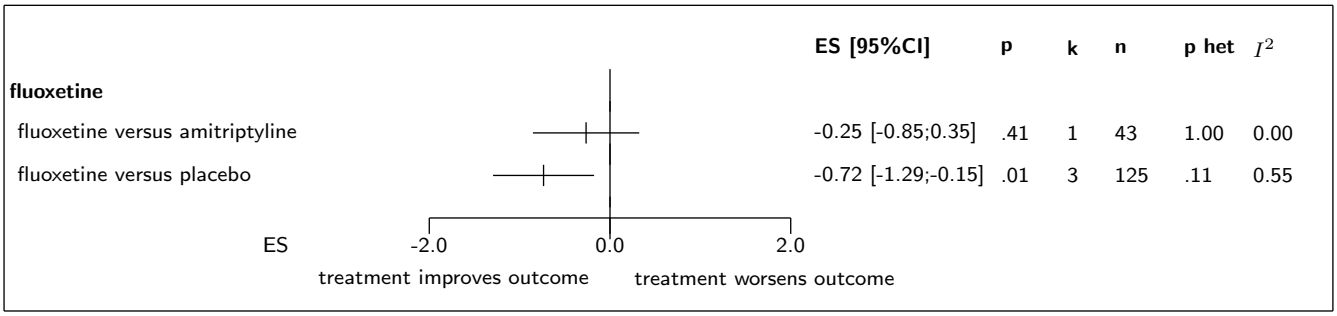
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 16.1: *Forest's plot for FIQ*



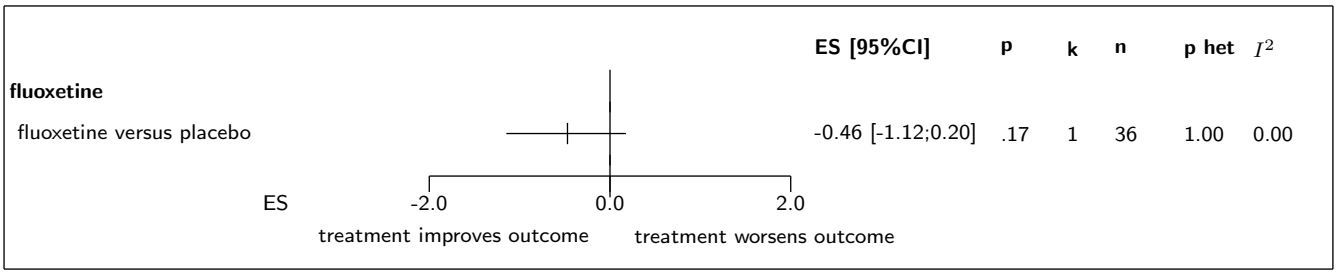
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.2: *Forest's plot for douleur*



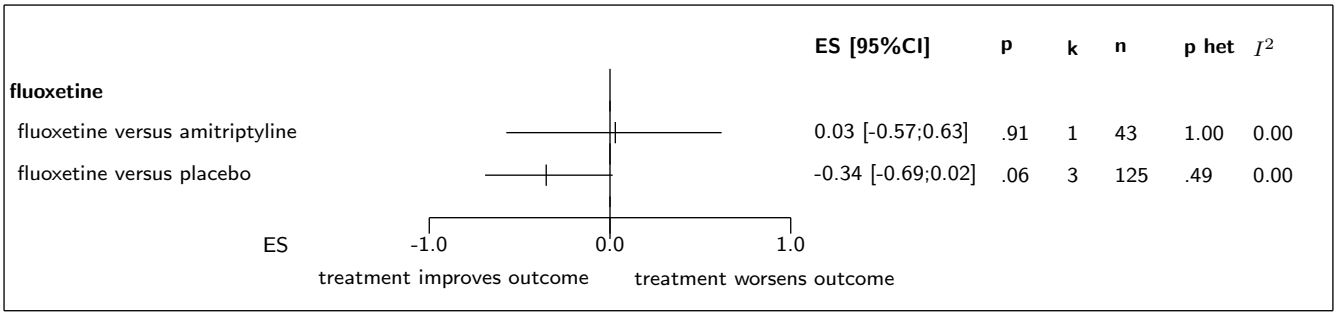
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.3: *Forest's plot for points douloureux (nombre)*



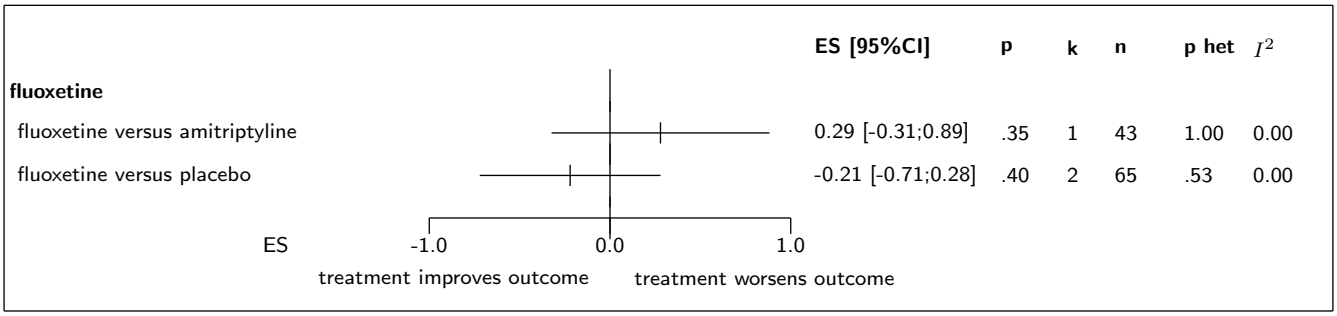
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.4: *Forest's plot for fatigue*



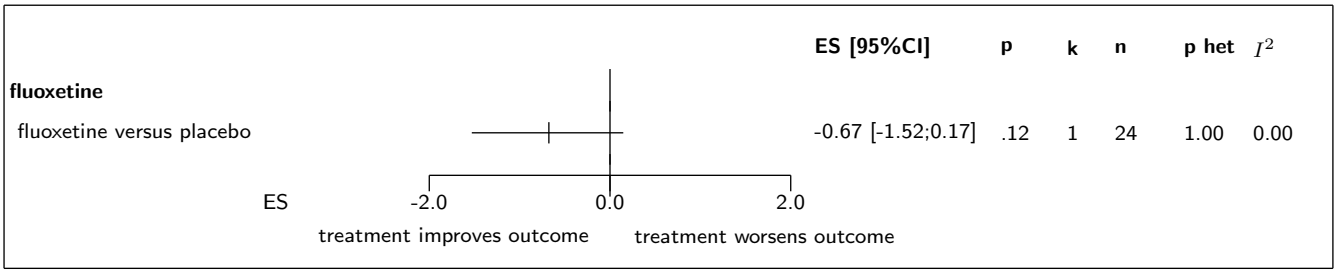
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.5: *Forest's plot for sommeil*



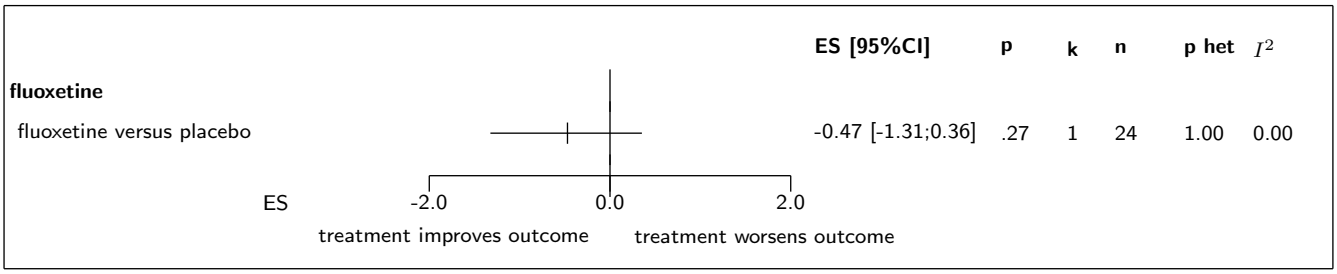
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.6: *Forest's plot for dpression*



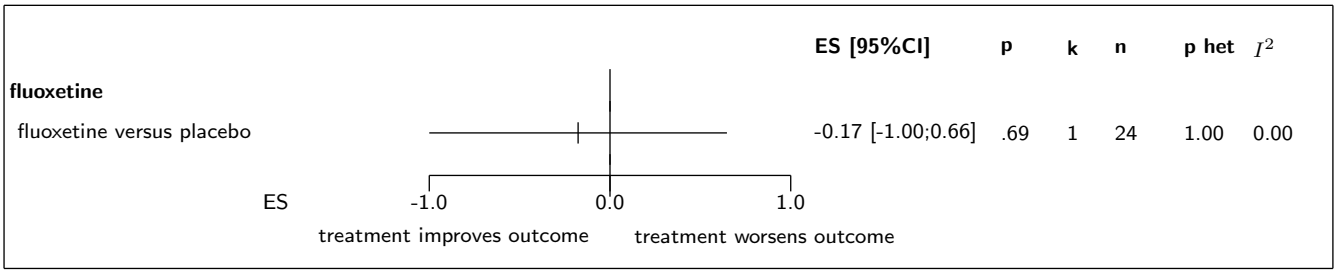
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.7: *Forest's plot for anxit*



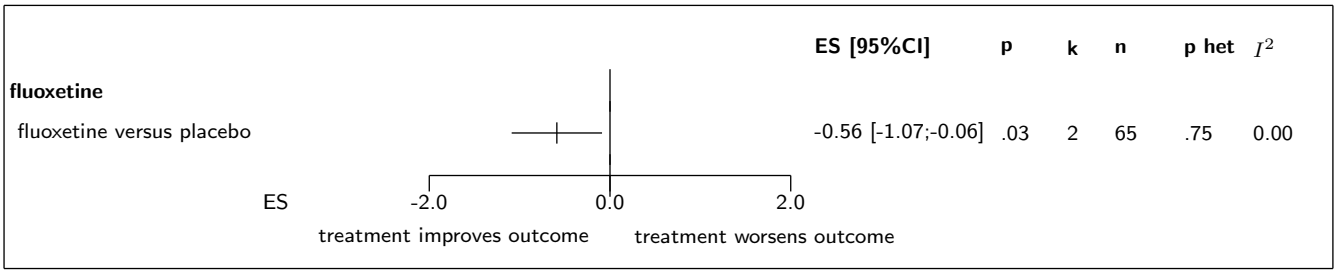
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.8: *Forest's plot for HAQ functional disability*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 16.9: *Forest's plot for severit globale*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

17 Details

17.1 Available trials

A total of 4 RCTs which randomized 226 patients were identified: it compared fluoxetine with amitriptyline and 3 trials compared fluoxetine with placebo.
The average study size was 56 patients (range 42 to 62). The first study was published in 1994, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Fatigue data was reported in 4 trials; 4 trials reported data on douleur; 3 trials reported data on depression - chelle de Beck; 3 trials reported data on sommeil; 3 trials reported data on FIQ; 2 trials reported data on severit globale; 1 trials reported data on anxit; 1 trials reported data on points douloureux (nombre); 1 trials reported data on HAQ functional disability; and 1 trials reported data on dpression.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of fluoxetine.

Table 17.1: *Treatment description - fluoxetine - fluoxetine*

Trial	Studied treatment	Control treatment
Fluoxetine versus amitriptyline		
Goldenberg (fluo vs amit) (1996) [**?**, **?**] [a]	fluoxetine 20mg/j	amitriptyline 25mg/j
Fluoxetine versus placebo		
Arnold (2002) [**?**]	fluoxetine 10-80 mg/j	placebo
Goldenberg (vs PBO) (1996) [**?**] [b]	fluoxetine 20mg/j	placebo
Wolfe (1994) [**?**]	fluoxetine 20 mg/d	placebo

a) cross over de 4 priodes : placebo, amitriptyline seule, fluoxetine seule, association amitriptyline + fluoxetine b) cross over de 4 priodes : placebo, amitriptyline seule, fluoxetine seule, association amitriptyline + fluoxetine

Table 17.2: *Descriptions of participants - fluoxetine - fluoxetine*

Trial	Patients
Fluoxetine versus amitriptyline	
Goldenberg (fluo vs amit) (1996) [**?**, **?**]	
Fluoxetine versus placebo	

continued...

Trial	Patients	
Arnold (2002) [?]	**Inclusion criteria:** at least 18 years of age;American College of Rheumatology 1990 criteriafor fibromyalgia	**Exclusion criteria:** evidence of traumaticinjury, inflammatory rheumatic disease, or infectiousor endocrine-related arthropathy; clinically unstablemedical illness; a history of seizure, head trauma, orstroke; a lifetime history of hypomania, mania, psychosis,or dementia; alcohol or substance dependence during thepast 6 months; a substantial risk of suicide; any currentAxis I diagnosis; a score of 10 or greater on the 17-itemHamilton Depression Rating Scale; received monoamineoxidase inhibitors, tricyclics, lithium, SSRIs, or other antidepressantswithin 2 weeks before randomization; receivedinvestigational medications within 3 months beforerandomization; or previously received fluoxetine forfibromyalgia.
Goldenberg (vs PBO) (1996) [?]		
Wolfe (1994) [?]	**Inclusion criteria:** female, 21-70 years, 7 to 14 tender points, widespread pain according ACR criteria, pain score >1 on a 0 to 3 VAS	**Exclusion criteria:**

Table 17.3: *Main patients characteristics - fluoxetine - fluoxetine*

Trial	Characteristics
Fluoxetine versus amitriptyline	
Goldenberg (fluo vs amit), 1996 [?, ?]	age (mean), years: 43.2 ans femmes (%): 90% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 57.3 douleur: 68.4 (VAS) fatigue: 73 (VAS)
Fluoxetine versus placebo	
Arnold, 2002 [?]	age (mean), years: 46 ans femmes (%): 100% critres d'inclusion: ACR nombre de points douloureux: 17 (/18) fibromyalgia Impact Questionnaire: 43 douleur: 6.05 FIQ subscore fatigue: 7.5 FIQ subscore depression: 2.6 FIQ subscore anxit: 3/10 FIQ subscore
Goldenberg (vs PBO), 1996 [?]	age (mean), years: 43.2 ans femmes (%): 90% critres d'inclusion: ACR fibromyalgia Impact Questionnaire: 57.3 douleur: 68.4 (VAS) fatigue: 73 (VAS)
Wolfe, 1994 [?]	age (mean), years: 50.5y femmes (%): 100% critres d'inclusion: ACR equivalent nombre de points douloureux: 17.9 fibromyalgia Impact Questionnaire: NA douleur: 1.75 (VAS 0-3) fatigue: 9.85 (VAS 0-15) depression: 2.85 (AIMS) anxit: 4.4 (AIMS)

Table 17.4: *Design and methodological quality of trials - fluoxetine - fluoxetine*

Trial	Design	Duration	Centre	Primary endpoint
Fluoxetine versus amitriptyline				
Goldenberg (fluo vs amit), 1996 [?, ?] [(a)] n=62	Parallel groups double blind	6 semaines		
Fluoxetine versus placebo				
Arnold, 2002 [?] n=60	Parallel groups double blind	12 semaines inclusion period: Mar 1998 - Jun 2000		FIQ total score and pain score
Goldenberg (vs PBO), 1996 [?] [(b)] n=62	Cross over double blind	6 semaines		
Wolfe, 1994 [?] n=42	Parallel groups double blind	6 weeks		

continued...

Trial	Design	Duration	Centre	Primary endpoint

a) cross over 4 priodes de 6 semaines b) cross over 4 priodes de 6 semaines

17.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Fluoxetine versus amitriptyline

The single study eligible for this comparison provided data on **FIQ**. No statistically significant difference between the groups was found in FIQ, with a ES of -0.22 (95% CI -0.82 to 0.38, p=0.4804).
The single study eligible for this comparison provided data on **douleur**. No statistically significant difference between the groups was found in douleur, with a ES of -0.25 (95% CI -0.85 to 0.35, p=0.4128).
The single study eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of 0.03 (95% CI -0.57 to 0.63, p=0.9149).
The single study eligible for this comparison provided data on **sommeil**. No statistically significant difference between the groups was found in sommeil, with a ES of 0.29 (95% CI -0.31 to 0.89, p=0.3507).

Fluoxetine versus placebo

A total of 2 of the 3 studies eligible for this comparison provided data on **FIQ**. The analysis detected a statistically significant difference in favor of fluoxetine in FIQ, with a ES of -0.71 (95% CI -1.11 to -0.31, p=0.0000). No heterogeneity was detected (p = 0.5769, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of fluoxetine in douleur, with a ES of -0.72 (95% CI -1.29 to -0.15, p=0.0126). No heterogeneity was detected (p = 0.1109, I^2 = 0.55%).
Only one of the 3 studies eligible for this comparison provided data on **points douloureux (nombre)**. No statistically significant difference between the groups was found in points douloureux (nombre), with a ES of -0.46 (95% CI -1.12 to 0.20, p=0.1744).
All the 3 studies had extractable data about the number of participants with **fatigue**. When pooled together, there was no statistically significant difference between the groups in fatigue, with a ES of -0.34 (95% CI -0.69 to 0.02, p=0.0635). No heterogeneity was detected (p = 0.4937, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **sommeil**. When pooled together, there was no statistically significant difference between the groups in sommeil, with a ES of -0.21 (95% CI -0.71 to 0.28, p=0.3989). No heterogeneity was detected (p = 0.5281, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **dpression**. No statistically significant difference between the groups was found in dpression, with a ES of -0.67 (95% CI -1.52 to 0.17, p=0.1195).
Only one of the 3 studies eligible for this comparison provided data on **anxit**. No statistically significant difference between the groups was found in anxit, with a ES of -0.47 (95% CI -1.31 to 0.36, p=0.2668).
Only one of the 3 studies eligible for this comparison provided data on **HAQ functional disability**. No statistically significant difference between the groups was found in HAQ functional disability, with a ES of -0.17 (95% CI -1.00 to 0.66, p=0.6896).

A total of 2 of the 3 studies eligible for this comparison provided data on **severit globale**. The analysis detected a statistically significant difference in favor of fluoxetine in severit globale, with a ES of -0.56 (95% CI -1.07 to -0.06, p=0.0276). No heterogeneity was detected (p = 0.7454, I^2 = 0.00%).

Table 17.5: *Results details - fluoxetine - fluoxetine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fluoxetine versus amitriptyline						
FIQ	ES=-0.22	[-0.82;0.38]	0.4804	1.0000 (I^2=0.00)	1	43
douleur	ES=-0.25	[-0.85;0.35]	0.4128	1.0000 (I^2=0.00)	1	43
fatigue	ES=0.03	[-0.57;0.63]	0.9149	1.0000 (I^2=0.00)	1	43
sommeil	ES=0.29	[-0.31;0.89]	0.3507	1.0000 (I^2=0.00)	1	43
fluoxetine versus placebo						
FIQ	ES=-0.71	[-1.11;-0.31]	0.0000	0.5769 (I^2=0.00)	2	101
douleur	ES=-0.72	[-1.29;-0.15]	0.0126	0.1109 (I^2=0.55)	3	125
points douloureux (nombre)	ES=-0.46	[-1.12;0.20]	0.1744	1.0000 (I^2=0.00)	1	36
fatigue	ES=-0.34	[-0.69;0.02]	0.0635	0.4937 (I^2=0.00)	3	125
sommeil	ES=-0.21	[-0.71;0.28]	0.3989	0.5281 (I^2=0.00)	2	65
dpression	ES=-0.67	[-1.52;0.17]	0.1195	1.0000 (I^2=0.00)	1	24
anxit	ES=-0.47	[-1.31;0.36]	0.2668	1.0000 (I^2=0.00)	1	24
HAQ functional disability	ES=-0.17	[-1.00;0.66]	0.6896	1.0000 (I^2=0.00)	1	24
severit globale	ES=-0.56	[-1.07;-0.06]	0.0276	0.7454 (I^2=0.00)	2	65

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 17.1: *Forest's plot for FIQ*

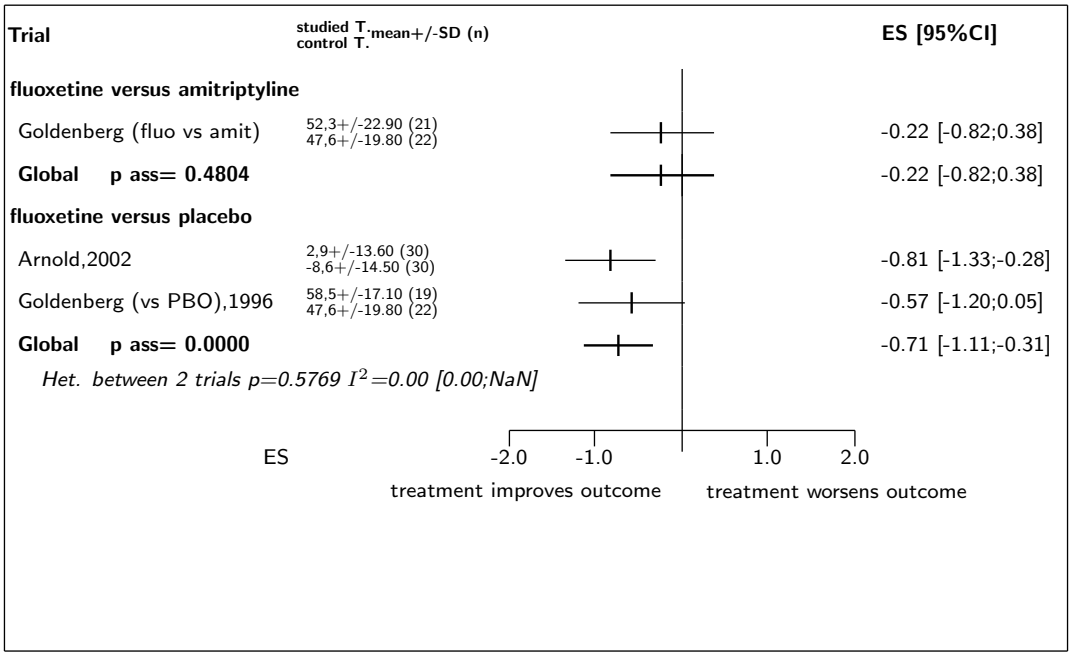


Figure 17.2: *Forest's plot for Douleur*

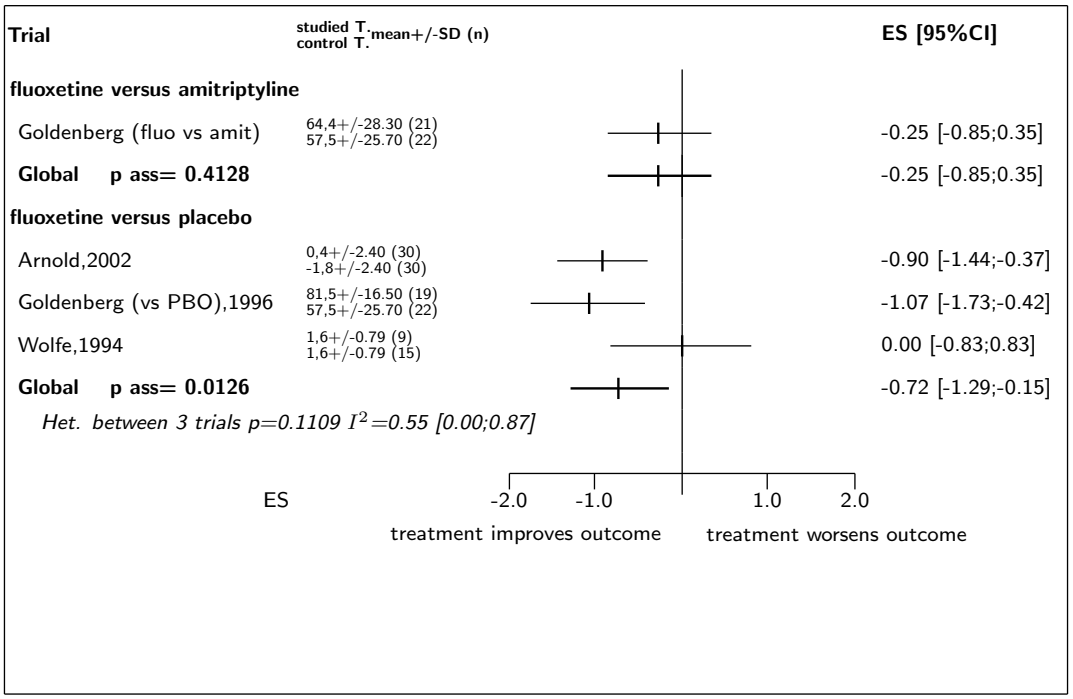


Figure 17.3: *Forest's plot for Points douloureux (nombre)*

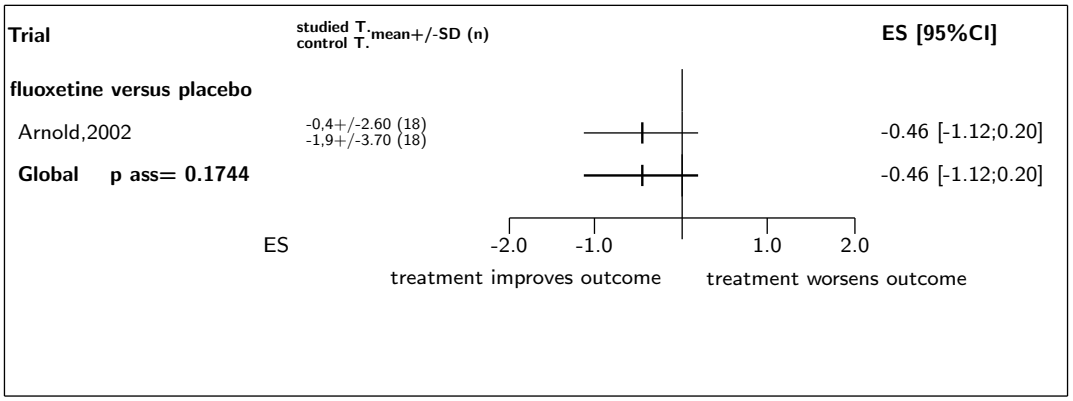


Figure 17.4: *Forest's plot for Fatigue*

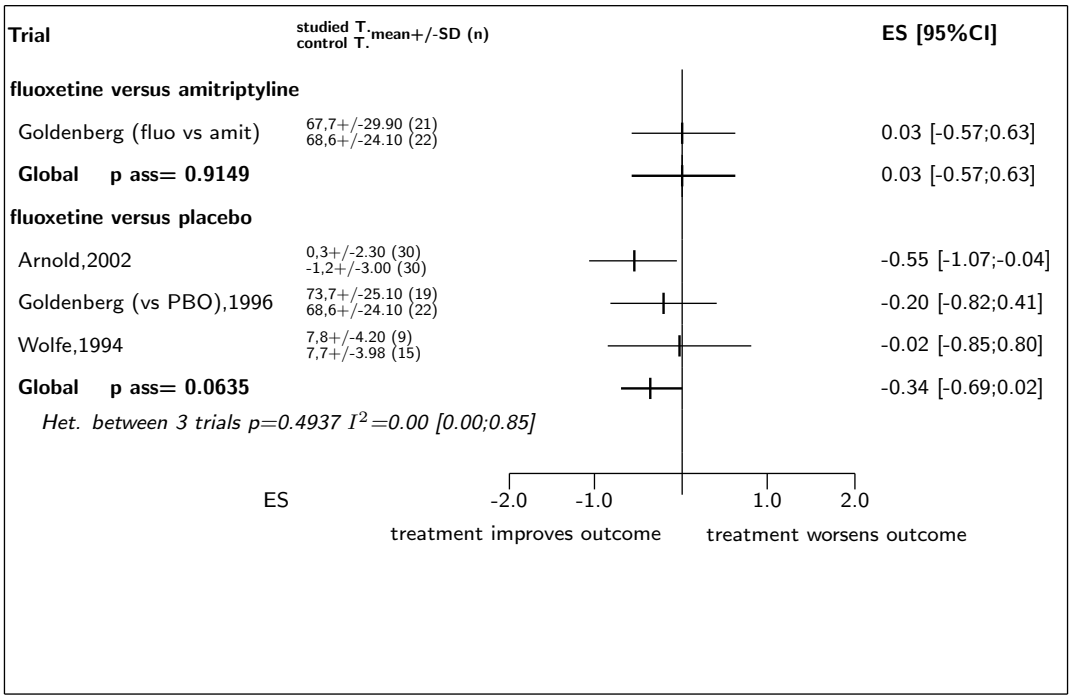


Figure 17.5: *Forest's plot for Sommeil*

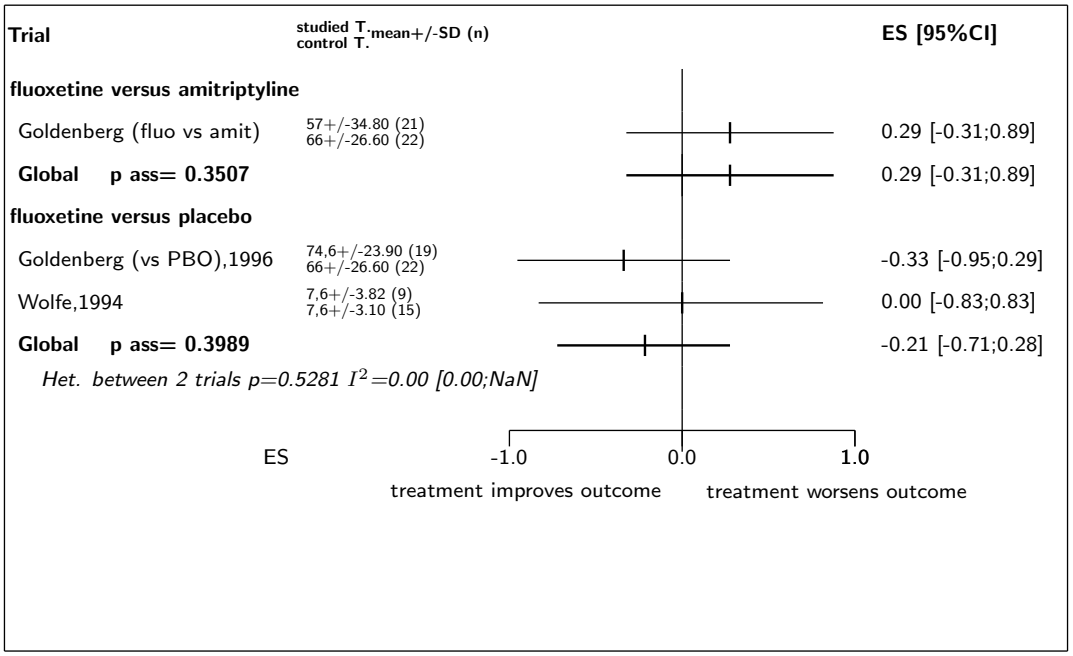


Figure 17.6: *Forest's plot for Dpression*

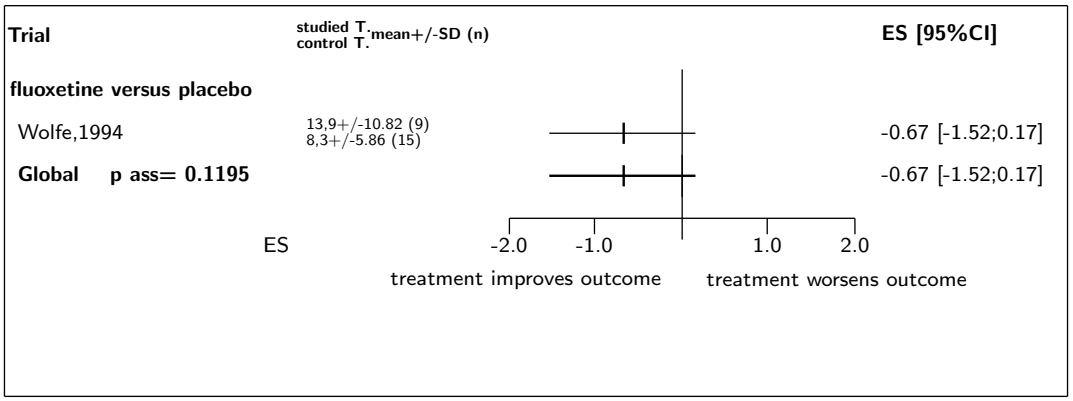


Figure 17.7: *Forest's plot for Anxit*

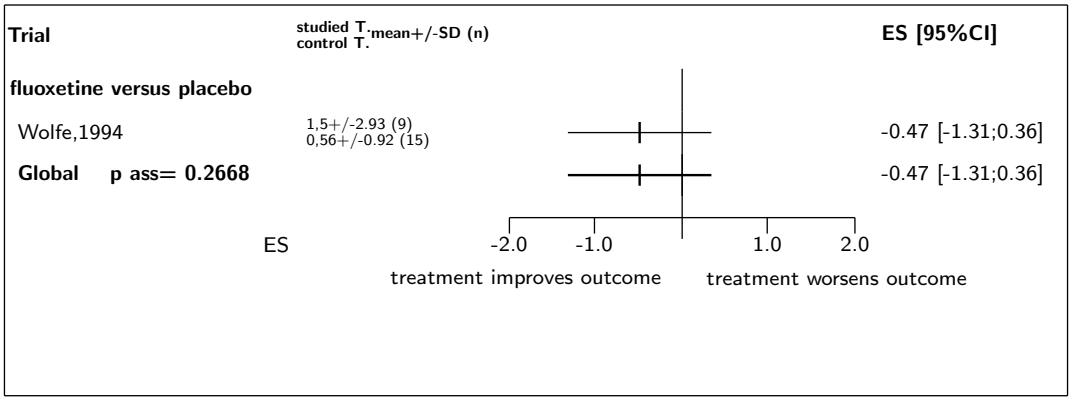


Figure 17.8: *Forest's plot for HAQ functional disability*

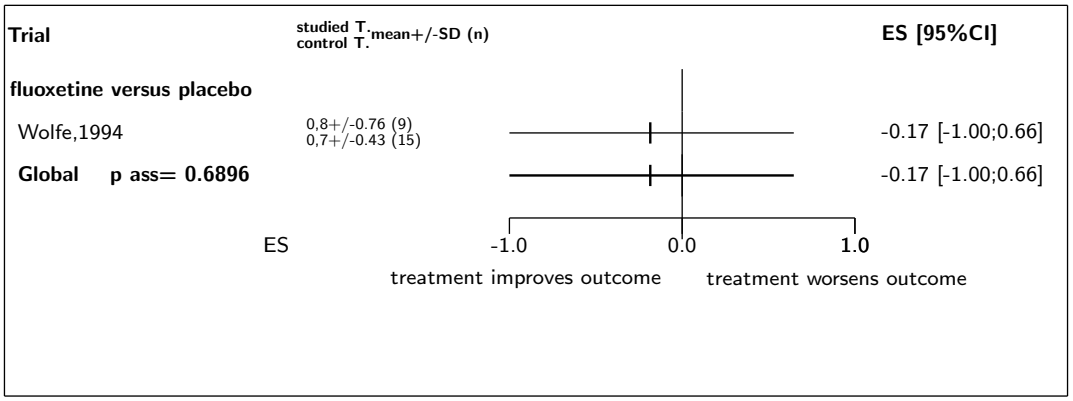
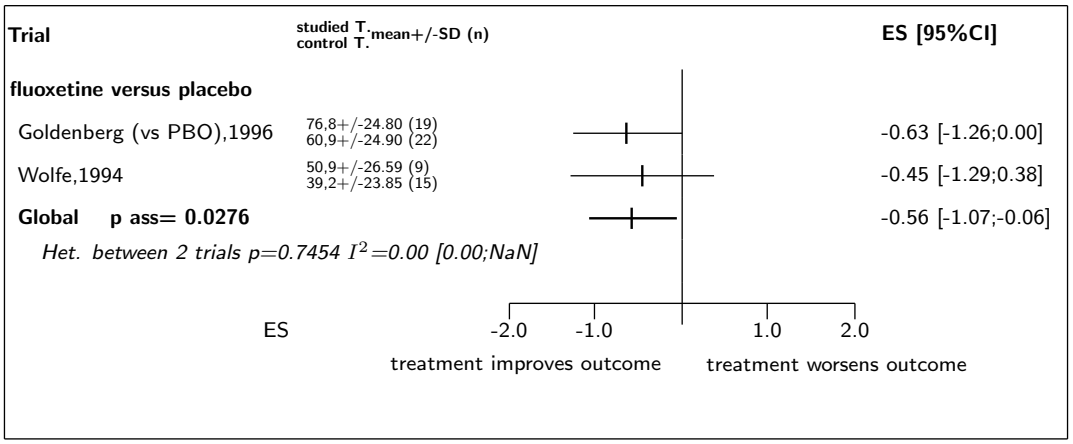


Figure 17.9: *Forest's plot for Severit globale*



References

[1] Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996 Nov;39:1852-9. [PMID=8912507]

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[4] Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996;39:1852-9. [PMID=8912507]

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18 Global meta-analysis: all fluoxetine

18.1 Global meta-analysis: all fluoxetine versus amitriptyline

Table 18.1: *All fluoxetineversus amitriptyline*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
FIQ	ES=-0.22	-0.82;0.38	0.4804	1.0000 (0.00)	1	43
douleur	ES=-0.25	-0.85;0.35	0.4128	1.0000 (0.00)	1	43
fatigue	ES=0.03	-0.57;0.63	0.9149	1.0000 (0.00)	1	43
sommeil	ES=0.29	-0.31;0.89	0.3507	1.0000 (0.00)	1	43

legend B

18.2 Global meta-analysis: all fluoxetine versus placebo

Table 18.2: *All fluoxetineversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
FIQ	ES=-0.71	-1.11;-0.31	0.0000	0.5769 (0.00)	2	101
douleur	ES=-0.72	-1.29;-0.15	0.0126	0.1109 (0.55)	3	125
points douloureux (nombre)	ES=-0.46	-1.12;0.20	0.1744	1.0000 (0.00)	1	36
fatigue	ES=-0.34	-0.69;0.02	0.0635	0.4937 (0.00)	3	125
sommeil	ES=-0.21	-0.71;0.28	0.3989	0.5281 (0.00)	2	65
dpression	ES=-0.67	-1.52;0.17	0.1195	1.0000 (0.00)	1	24
anxit	ES=-0.47	-1.31;0.36	0.2668	1.0000 (0.00)	1	24
HAQ functional disability	ES=-0.17	-1.00;0.66	0.6896	1.0000 (0.00)	1	24
severit globale	ES=-0.56	-1.07;-0.06	0.0276	0.7454 (0.00)	2	65

legend B

19 Ongoing studies of fluoxetine

No ongoing trial was identified.

20 Excluded studies for fluoxetine

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 20.1: *Excluded studies of fluoxetine*

Study	**Exclusion reason**
Cantini (1994) [**?**]	N'value pas la fluoxetine seule mais compare l'adjunction de fluoxetine la cyclobenzaprine par rapport la cyclobenzaprine seule
Ozerbil (fluo vs amitr) (2006) [**?**]	pas de critre clinique, etude purement physiopathologique

Part V

Milnacipran

21 Overview of milnacipran

21.1 Included trials

A total of 5 randomized comparisons which enrolled 2414 patients were identified. In all, 1 randomized comparison concerned milnacipran 100mg and 4 milnacipran 200mg.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for milnacipran 100mg and in section **??** (page **??**) for milnacipran 200mg.

The average study size was 482 patients (range 74 to 800). The first study was published in 2005, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We found 2 unpublished trials.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

21.2 Summary of meta-analysis results

The meta-analysis of the available trials about milnacipran provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

21.2.1 Milnacipran 100mg

Milnacipran 100mg was superior to **placebo** in terms of FIQ (ES=-0.23, 95% CI -0.37 to -0.09, p=0.0000, 1 trial)and HAQ functional disability (ES=-0.15, 95% CI -0.29 to -0.01, p=0.0343, 1 trial).
However, no significant difference was found on douleur (ES=-0.13, 95% CI -0.27 to 0.01, p=0.0698, 1 trial), fatigue (ES=-0.13, 95% CI -0.27 to 0.01, p=0.0598, 1 trial), sommeil (ES=-0.06, 95% CI -0.20 to 0.08, p=0.4039, 1 trial)and dpression (ES=-0.09, 95% CI -0.23 to 0.05, p=0.2166, 1 trial).

21.2.2 Milnacipran 200mg

Milnacipran 200mg was superior to **placebo** in terms of FIQ (ES=-0.17, 95% CI -0.31 to -0.03, p=0.0165, 1 trial), douleur (ES=-0.26, 95% CI -0.37 to -0.15, p=0.0000, 4 trials), dpression (ES=-0.16, 95% CI -0.30 to -0.02, p=0.0219, 1 trial), HAQ functional disability (ES=-0.18, 95% CI -0.32 to -0.04, p=0.0098, 1 trial)and patient Global Impression of Improvement (PGI-I) (ES=-0.43, 95% CI -0.64 to -0.22, p=0.0000, 1 trial).
However, no significant difference was found on fatigue (ES=-0.13, 95% CI -0.27 to 0.01, p=0.0598, 1 trial)and sommeil (ES=-0.03, 95% CI -0.17 to 0.11, p=0.6674, 1 trial).

Table 21.1: *Main study characteristics - milnacipran*

Trial	Patients	Treatments	Trial design and method
Milnacipran 100mg			
Milnacipran 100mg versus placebo			
Clauw 100mg (MLN MD 02), 2008 [**?**] n = 399 vs. 401	NA	milnacipran 100mg/j **versus** placebo	double blind parallel groups
Milnacipran 200mg			
Milnacipran 200mg versus placebo			
Mease 200mg/d (FMS 031), 2008 [**?**] n = 441 vs. 223	patients prsentant une FM	milnacipran 200mg/d **versus** placebo	double aveugle parallel groups 59 centres,
Clauw 200mg (MLN MD 02), 2008 [**?**] n = 396 vs. 401	NA	milnacipran 200mg/j **versus** placebo	double aveugle parallel groups
phase 2 Gendreau (once daily), 2005 [**?**, **?**] n = 46 vs. 28	critres ACR, douleur >10-20 sur une chelle logarithmique (echelle de Gracely),entre 18 et 70 ans	milnacipran jusqu' 200mg une fois par jour **versus** placebo	double blind Primary endpoint: changement score douleur 14 centres,US
phase 2 Gendreau (twice daily), 2005 [**?**, **?**, **?**] n = 51 vs. 28	critres ACR, douleur >10-20 sur une chelle logarithmique (echelle de Gracely)	milnacipran jusqu' 200mg 2 fois par jour **versus** placebo	double blind Primary endpoint: changement score douleur 14 centres,US

Table 21.2: *Summary of all results for milnacipran 100mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
milnacipran 100mg versus placebo						
FIQ	ES=-0.23	-0.37;-0.09	0.0000	1.0000 (1.00)	1	800
douleur	ES=-0.13	-0.27;0.01	0.0698	1.0000 (0.00)	1	800
fatigue	ES=-0.13	-0.27;0.01	0.0598	1.0000 (0.00)	1	800
sommeil	ES=-0.06	-0.20;0.08	0.4039	1.0000 (0.00)	1	800
dpression	ES=-0.09	-0.23;0.05	0.2166	1.0000 (0.00)	1	800
HAQ functional disability	ES=-0.15	-0.29;-0.01	0.0343	1.0000 (0.00)	1	800
amlioration globale (patient)	RR=1.21	1.08;1.35	0.0000	1.0000 (0.00)	1	792

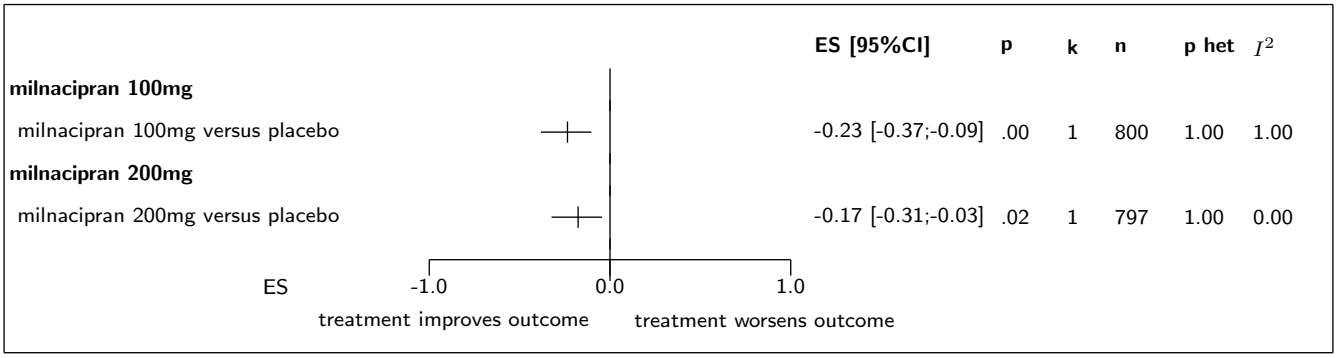
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 21.3: *Summary of all results for milnacipran 200mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
milnacipran 200mg versus placebo						
FIQ	ES=-0.17	-0.31;-0.03	0.0165	1.0000 (0.00)	1	797
douleur	ES=-0.26	-0.37;-0.15	0.0000	0.5606 (0.00)	4	1282
fatigue	ES=-0.13	-0.27;0.01	0.0598	1.0000 (0.00)	1	797
sommeil	ES=-0.03	-0.17;0.11	0.6674	1.0000 (0.00)	1	797
dpression	ES=-0.16	-0.30;-0.02	0.0219	1.0000 (0.00)	1	797
HAQ functional disability	ES=-0.18	-0.32;-0.04	0.0098	1.0000 (1.00)	1	797
patient Global Impression of Improvement (PGI-I)	ES=-0.43	-0.64;-0.22	0.0000	1.0000 (0.00)	1	384
amlioration globale (patient)	RR=1.21	1.07;1.35	0.0000	1.0000 (0.00)	1	786

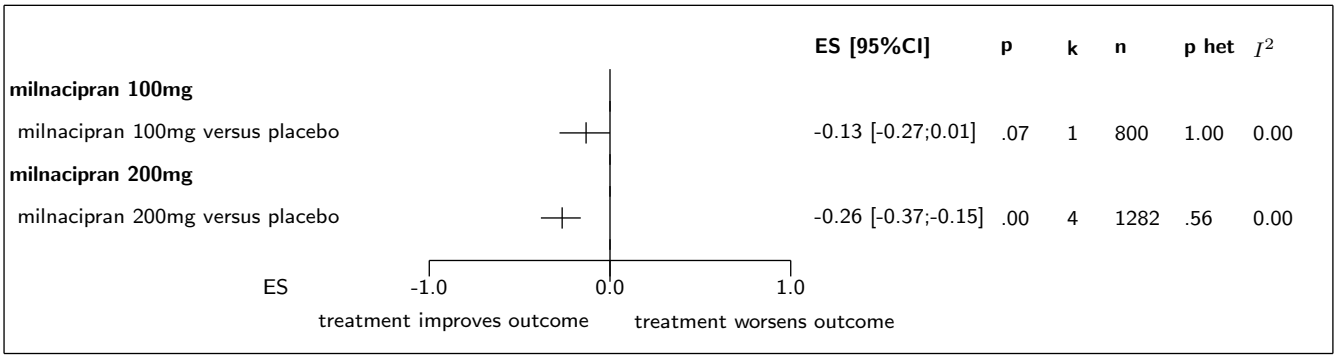
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 21.1: *Forest's plot for FIQ*



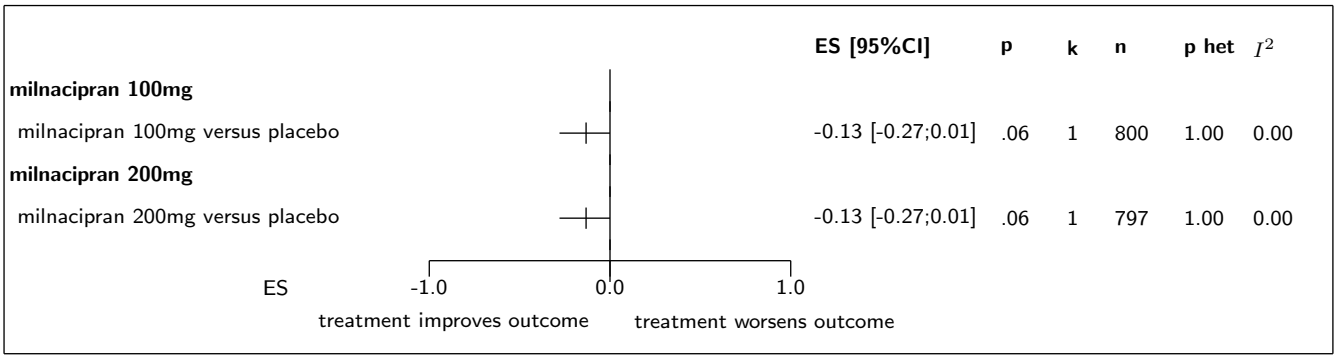
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.2: *Forest's plot for douleur*



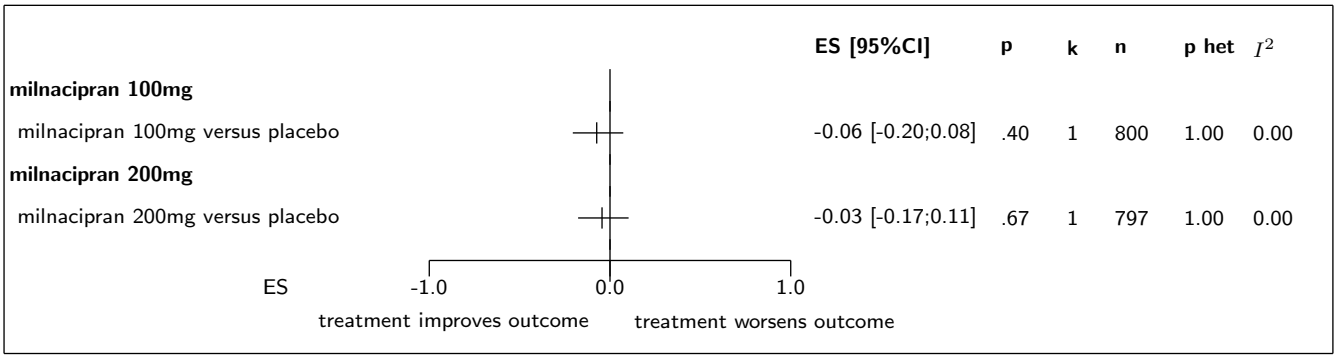
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.3: *Forest's plot for fatigue*



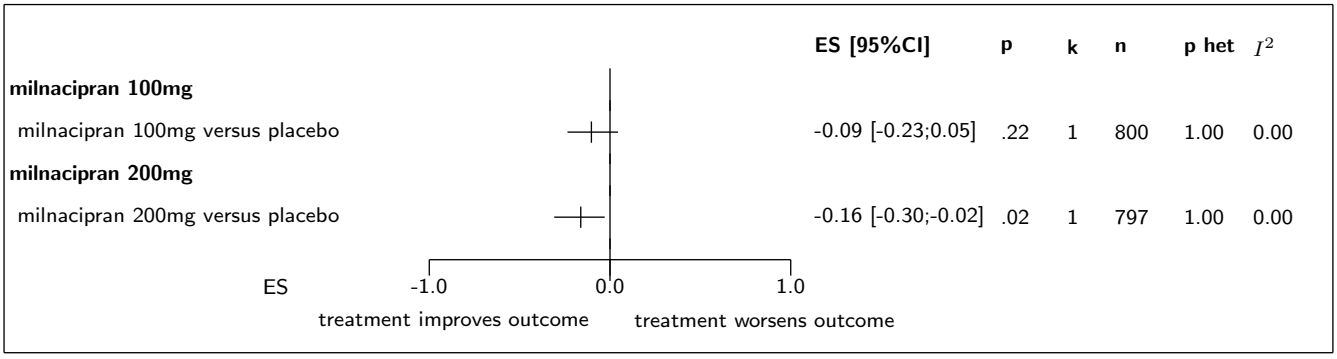
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.4: *Forest's plot for sommeil*



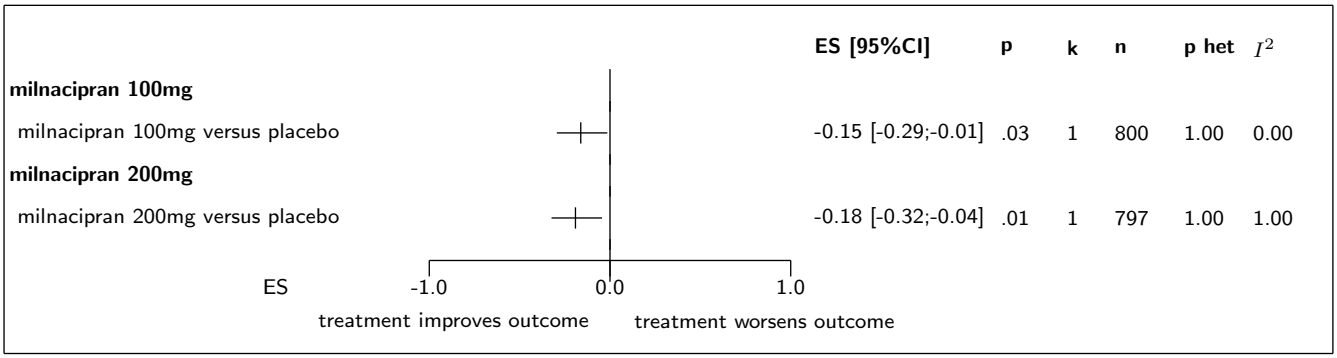
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.5: *Forest's plot for dpression*



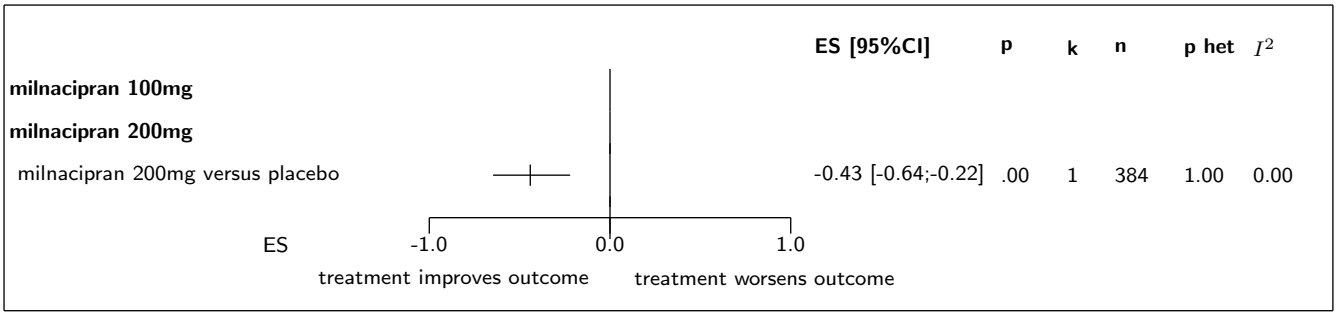
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.6: *Forest's plot for HAQ functional disability*



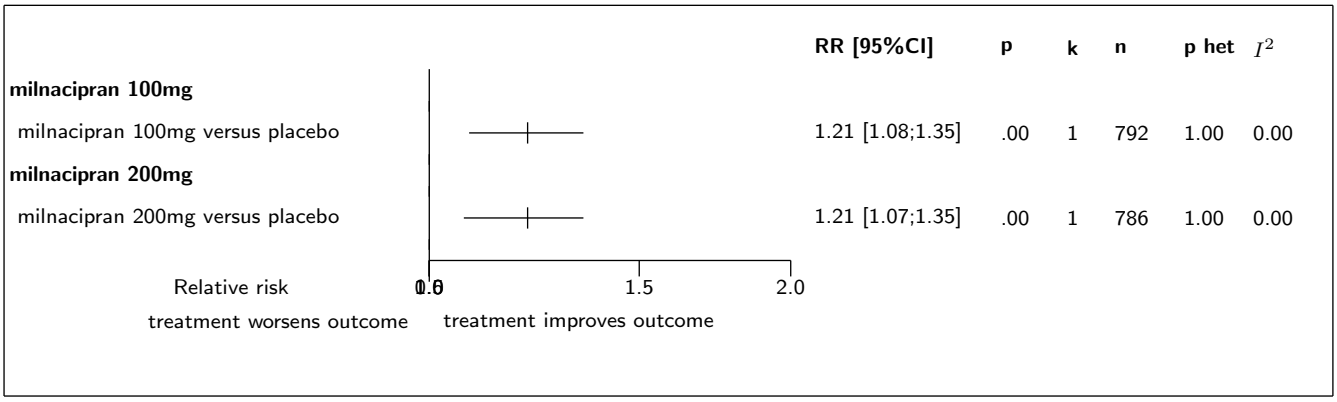
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.7: *Forest's plot for patient Global Impression of Improvement (PGI-I)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 21.8: *Forest's plot for amlioration globale (patient)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

22 Detailed results for milnacipran 100mg

22.1 Available trials

Only one trial which randomized 800 patients was identified: it compared milnacipran 100mg with placebo.
This trial included 800 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
This trial was unpublished.
HAQ functional disability data was reported in 1 trials; 1 trials reported data on sommeil; 1 trials reported data on fatigue; 1 trials reported data on douleur; 1 trials reported data on dpression; 1 trials reported data on amlioration globale (patient); and 1 trials reported data on FIQ.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of milnacipran 100mg.

Table 22.1: *Treatment description - milnacipran - milnacipran 100mg*

Trial	Studied treatment	Control treatment
Milnacipran 100mg versus placebo		
Clauw 100mg (MLN MD 02) (2008) [**?**] [a]	milnacipran 100mg/j	placebo

a) 3 bras : milnacipran 100mg (n=399), 200mg/d (n=396) et placebo (n=401)

Table 22.2: *Descriptions of participants - milnacipran - milnacipran 100mg*

Trial	Patients
Milnacipran 100mg versus placebo	
Clauw 100mg (MLN MD 02) (2008) [**?**]	NA

Table 22.3: *Main patients characteristics - milnacipran - milnacipran 100mg*

Trial	Characteristics
Milnacipran 100mg versus placebo	
Clauw 100mg (MLN MD 02), 2008 [**?**]	critres d'inclusion: NA

Table 22.4: *Design and methodological quality of trials - milnacipran - milnacipran 100mg*

Trial	Design	Duration	Centre	Primary endpoint
Milnacipran 100mg versus placebo				
Clauw 100mg (MLN MD 02), 2008 [**?**] n=800	Parallel groups double blind	15 semaines		

22.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Milnacipran 100mg versus placebo

The single study eligible for this comparison provided data on **FIQ**. The analysis detected a statistically significant difference in favor of milnacipran 100mg in FIQ, with a ES of -0.23 (95% CI -0.37 to -0.09, p=0.0000).
The single study eligible for this comparison provided data on **douleur**. No statistically significant difference between the groups was found in douleur, with a ES of -0.13 (95% CI -0.27 to 0.01, p=0.0698).
The single study eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of -0.13 (95% CI -0.27 to 0.01, p=0.0598).
The single study eligible for this comparison provided data on **sommeil**. No statistically significant difference between the groups was found in sommeil, with a ES of -0.06 (95% CI -0.20 to 0.08, p=0.4039).
The single study eligible for this comparison provided data on **dpression**. No statistically significant difference between the groups was found in dpression, with a ES of -0.09 (95% CI -0.23 to 0.05, p=0.2166).
The single study eligible for this comparison provided data on **HAQ functional disability**. The analysis detected a statistically significant difference in favor of milnacipran 100mg in HAQ functional disability, with a ES of -0.15 (95% CI -0.29 to -0.01, p=0.0343).
The single study eligible for this comparison provided data on **amlioration globale (patient)**. The analysis detected a statistically significant difference in favor of milnacipran 100mg in amlioration globale (patient), with a RR of 1.21 (95% CI 1.08 to 1.35, p=0.0000).

Table 22.5: *Results details - milnacipran - milnacipran 100mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
milnacipran 100mg versus placebo						
FIQ	ES=-0.23	[-0.37;-0.09]	0.0000	1.0000 (I^2=1.00)	1	800
douleur	ES=-0.13	[-0.27;0.01]	0.0698	1.0000 (I^2=0.00)	1	800
fatigue	ES=-0.13	[-0.27;0.01]	0.0598	1.0000 (I^2=0.00)	1	800
sommeil	ES=-0.06	[-0.20;0.08]	0.4039	1.0000 (I^2=0.00)	1	800
dpression	ES=-0.09	[-0.23;0.05]	0.2166	1.0000 (I^2=0.00)	1	800
HAQ functional disability	ES=-0.15	[-0.29;-0.01]	0.0343	1.0000 (I^2=0.00)	1	800
amlioration globale (patient)	RR=1.21	[1.08;1.35]	0.0000	1.0000 (I^2=0.00)	1	792

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 22.1: *Forest's plot for FIQ*

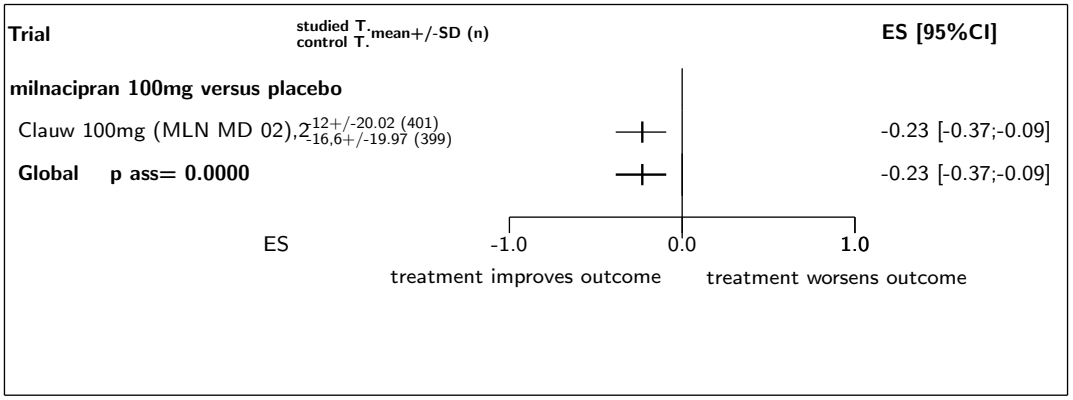


Figure 22.2: *Forest's plot for Douleur*

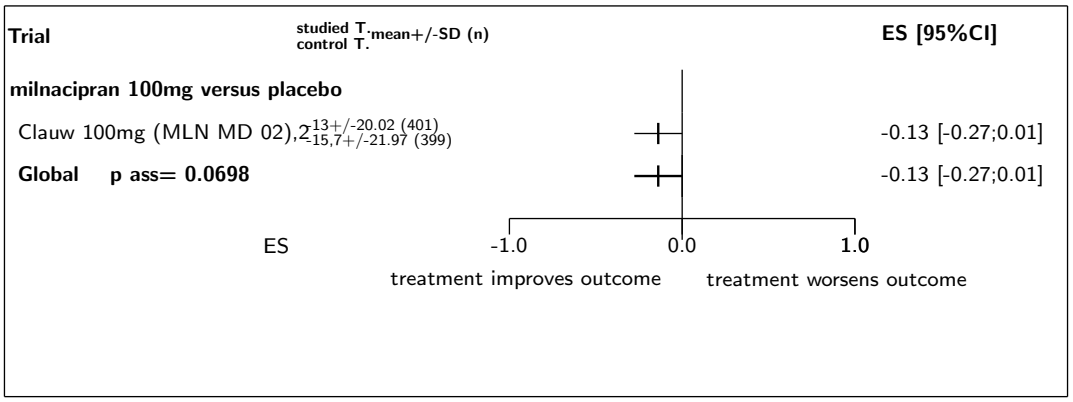


Figure 22.3: *Forest's plot for Fatigue*

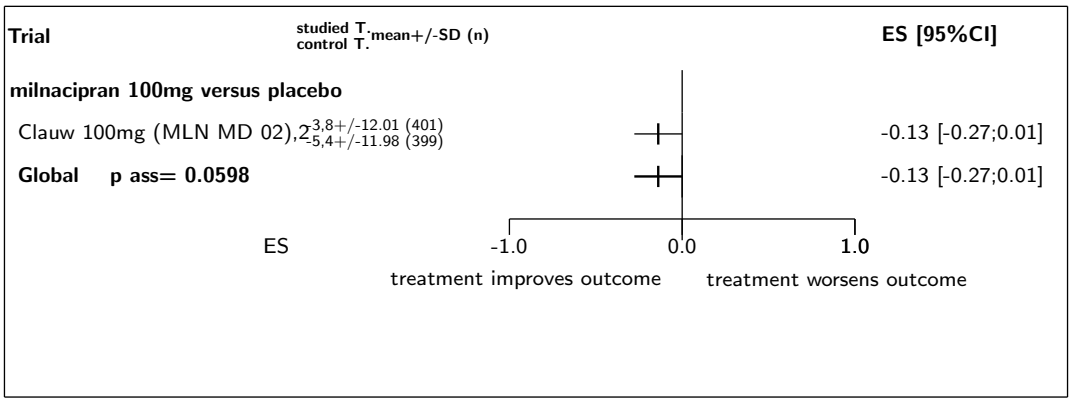


Figure 22.4: *Forest's plot for Sommeil*

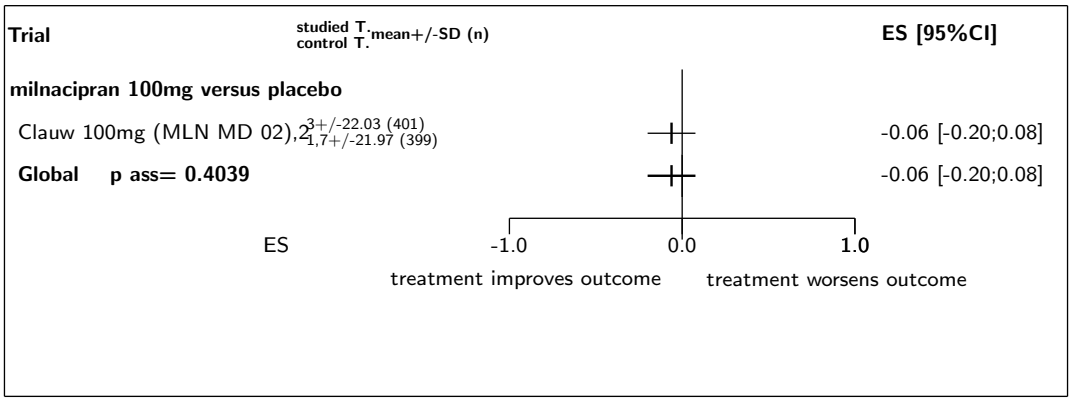


Figure 22.5: *Forest's plot for Dpression*

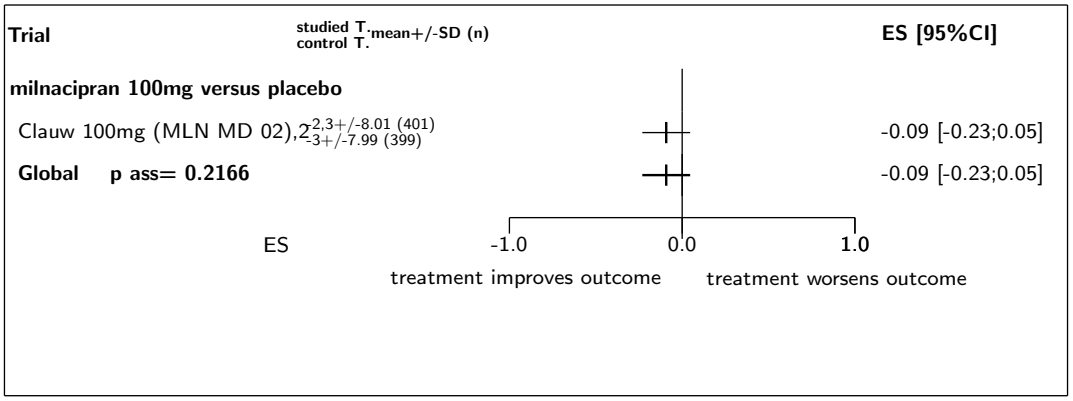


Figure 22.6: *Forest's plot for HAQ functional disability*

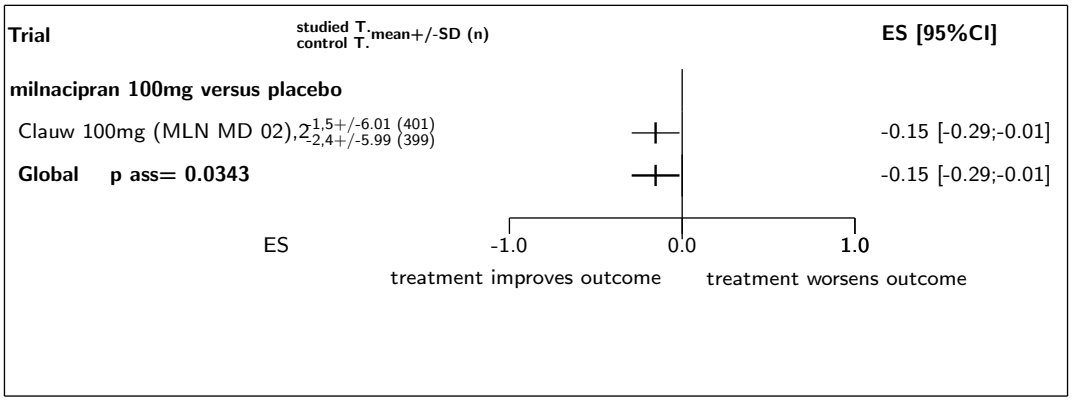
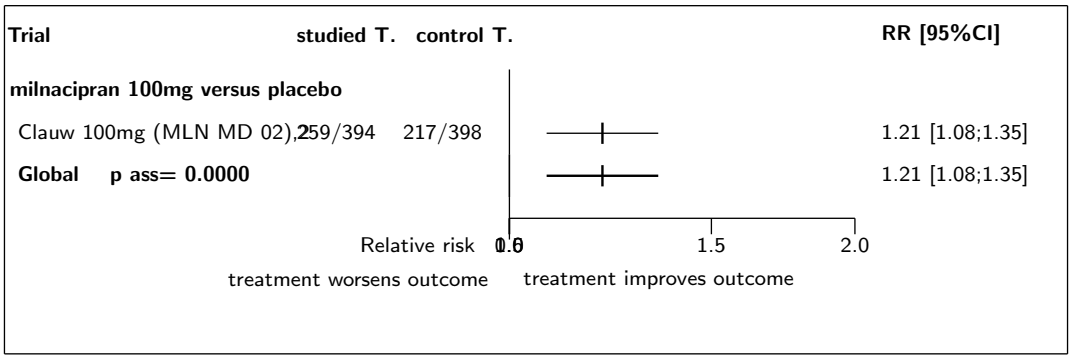


Figure 22.7: *Forest's plot for amlioration globale (patient)*



References

[1] Clauw DJ, Palmer RH, Thacker K et al. Milnacipran Efficacy in the Treatment of Fibromyalgia Syndrome: a 15 week, randomized, double blind placebo controlled trialACR/ARHP 2007. 2007; P517.

23 Detailed results for milnacipran 200mg

23.1 Available trials

A total of 4 RCTs which randomized 1614 patients were identified: all compared milnacipran 200mg with placebo.
The average study size was 403 patients (range 74 to 797). The first study was published in 2005, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We found one unpublished trial.
Douleur data was reported in 4 trials; 1 trials reported data on HAQ functional disability; 1 trials reported data on sommeil; 1 trials reported data on fatigue; 1 trials reported data on patient Global Impression of Improvement (PGI-I); 1 trials reported data on dpression; 1 trials reported data on amlioration globale (patient); and 1 trials reported data on FIQ.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of milnacipran 200mg.

Table 23.1: *Treatment description - milnacipran - milnacipran 200mg*

Trial	Studied treatment	Control treatment
Milnacipran 200mg versus placebo		
Mease 200mg/d (FMS 031) (2008) [**?**]	milnacipran 200mg/d	placebo
Clauw 200mg (MLN MD 02) (2008) [**?**] [b]	milnacipran 200mg/j	placebo
phase 2 Gendreau (once daily) (2005) [**?**, **?**] [c]	milnacipran jusqu' 200mg une fois par jour 4 semaine d'escalade de dose puis 8 semaine de dose fixe	placebo
phase 2 Gendreau (twice daily) (2005) [**?**, **?**, **?**] [d]	milnacipran jusqu' 200mg 2 fois par jour 4 semaine d'escalade de dose puis 8 semaine de dose fixe	placebo

b) 3 bras : milnacipran 100mg (n=399), 200mg/d (n=396) et placebo (n=401) c) 3e groupe recevant milnacipran 2 fois par jour d) 3e groupe recevant milnacipran une fois par jour

Table 23.2: *Descriptions of participants - milnacipran - milnacipran 200mg*

Trial	Patients
Milnacipran 200mg versus placebo	
Mease 200mg/d (FMS 031) (2008) [**?**]	Patients prsentant une FM
Clauw 200mg (MLN MD 02) (2008) [**?**]	NA
phase 2 Gendreau (once daily) (2005) [**?**, **?**]	Critres ACR, douleur >10-20 sur une chelle logarithmique (echelle de Gracely),entre 18 et 70 ans

continued...

Trial	Patients
phase 2 Gendreau (twice daily) (2005) [?, ?, ?]	Critres ACR, douleur >10-20 sur une chelle logarithmique (echelle de Gracely)

Table 23.3: *Main patients characteristics - milnacipran - milnacipran 200mg*

Trial	Characteristics
Milnacipran 200mg versus placebo	
Mease 200mg/d (FMS 031), 2008 [?]	age (mean), years: 49.3 ans femmes (%): 96% fibromyalgia Impact Questionnaire: 64.43 douleur: 69.03 (PED) fatigue: 67.5 (MFI) depression: 14.3 (BDI)
Clauw 200mg (MLN MD 02), 2008 [?]	critres d'inclusion: NA
phase 2 Gendreau (once daily), 2005 [?, ?]	age (mean), years: 47 ans femmes (%): 98% critres d'inclusion: ACR
phase 2 Gendreau (twice daily), 2005 [?, ?, ?]	age (mean), years: 47 ans femmes (%): 98% critres d'inclusion: ACR

Table 23.4: *Design and methodological quality of trials - milnacipran - milnacipran 200mg*

Trial	Design	Duration	Centre	Primary endpoint
Milnacipran 200mg versus placebo				
Mease 200mg/d (FMS 031), 2008 [?] n=664	Parallel groups double aveugle	27 semaines inclusion period: oct 2003 - jul 2005	59 centres	
Clauw 200mg (MLN MD 02), 2008 [?] n=797	Parallel groups double aveugle	15 semaines		
phase 2 Gendreau (once daily), 2005 [?, ?] n=74	double blind	3 mois	US 14 centres	changement score douleur
phase 2 Gendreau (twice daily), 2005 [?, ?, ?] n=79	double blind	3 mois	US 14 centres	changement score douleur

23.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Milnacipran 200mg versus placebo

Only one of the 4 studies eligible for this comparison provided data on **FIQ**. The analysis detected a statistically significant difference in favor of milnacipran 200mg in FIQ, with a ES of -0.17 (95% CI -0.31 to -0.03, p=0.0165).
All the 4 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of milnacipran 200mg in douleur, with a ES of -0.26 (95% CI -0.37 to -0.15, p=0.0000). No heterogeneity was detected (p = 0.5606, I^2 = 0.00%).
Only one of the 4 studies eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of -0.13 (95% CI -0.27 to 0.01, p=0.0598).
Only one of the 4 studies eligible for this comparison provided data on **sommeil**. No statistically significant difference between the groups was found in sommeil, with a ES of -0.03 (95% CI -0.17 to 0.11, p=0.6674).
Only one of the 4 studies eligible for this comparison provided data on **dpression**. The analysis detected a statistically significant difference in favor of milnacipran 200mg in dpression, with a ES of -0.16 (95% CI -0.30 to -0.02, p=0.0219).
Only one of the 4 studies eligible for this comparison provided data on **HAQ functional disability**. The analysis detected a statistically significant difference in favor of milnacipran 200mg in HAQ functional disability, with a ES of -0.18 (95% CI -0.32 to -0.04, p=0.0098).
Only one of the 4 studies eligible for this comparison provided data on **patient Global Impression of Improvement (PGI-I)**. The analysis detected a statistically significant difference in favor of milnacipran 200mg in patient Global Impression of Improvement (PGI-I), with a ES of -0.43 (95% CI -0.64 to -0.22, p=0.0000).
Only one of the 4 studies eligible for this comparison provided data on **amlioration globale (patient)**. The analysis detected a statistically significant difference in favor of milnacipran 200mg in amlioration globale (patient), with a RR of 1.21 (95% CI 1.07 to 1.35, p=0.0000).

Table 23.5: *Results details - milnacipran - milnacipran 200mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
milnacipran 200mg versus placebo						
FIQ	ES=-0.17	[-0.31;-0.03]	0.0165	1.0000 (I^2=0.00)	1	797
douleur	ES=-0.26	[-0.37;-0.15]	0.0000	0.5606 (I^2=0.00)	4	1282
fatigue	ES=-0.13	[-0.27;0.01]	0.0598	1.0000 (I^2=0.00)	1	797
sommeil	ES=-0.03	[-0.17;0.11]	0.6674	1.0000 (I^2=0.00)	1	797
dpression	ES=-0.16	[-0.30;-0.02]	0.0219	1.0000 (I^2=0.00)	1	797
HAQ functional disability	ES=-0.18	[-0.32;-0.04]	0.0098	1.0000 (I^2=1.00)	1	797
patient Global Impression of Improvement (PGI-I)	ES=-0.43	[-0.64;-0.22]	0.0000	1.0000 (I^2=0.00)	1	384
amlioration globale (patient)	RR=1.21	[1.07;1.35]	0.0000	1.0000 (I^2=0.00)	1	786

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 23.1: *Forest's plot for FIQ*

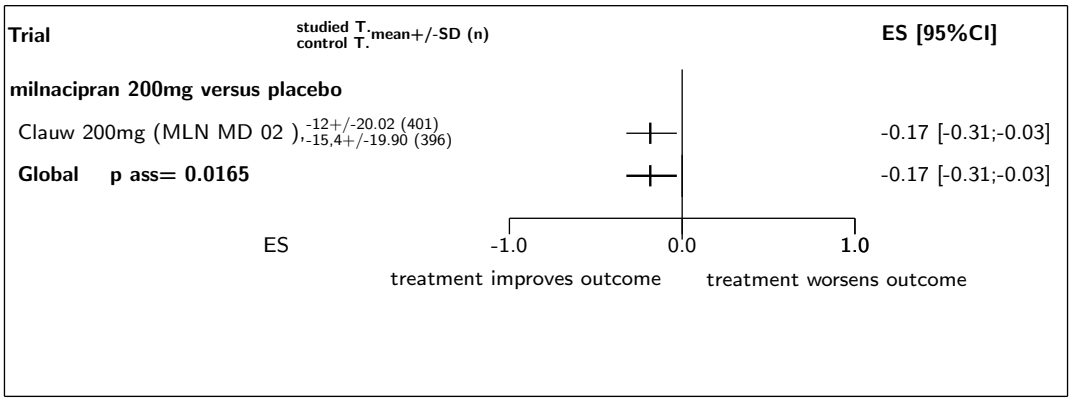


Figure 23.2: *Forest's plot for Douleur*

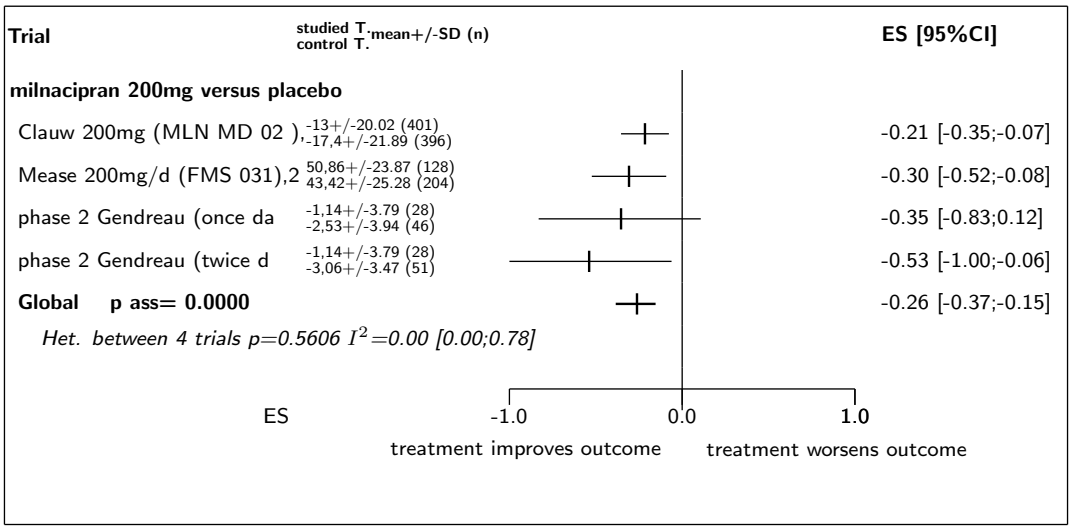


Figure 23.3: *Forest's plot for Fatigue*

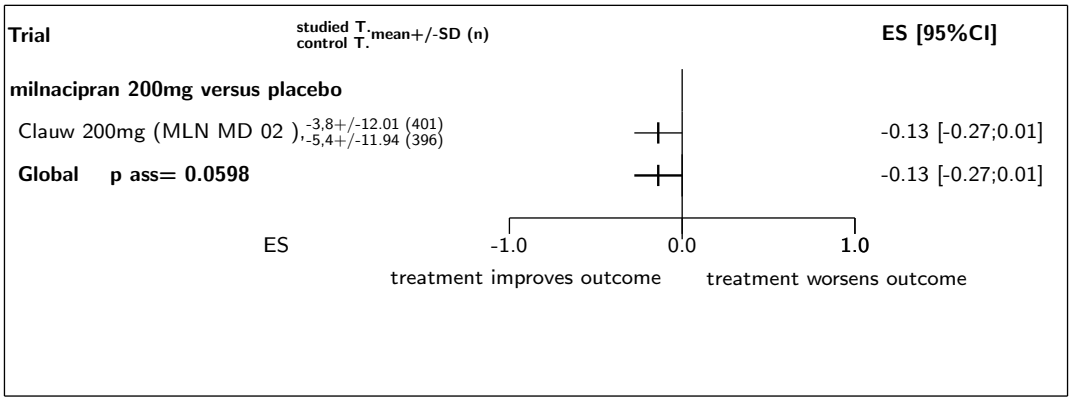


Figure 23.4: *Forest's plot for Sommeil*

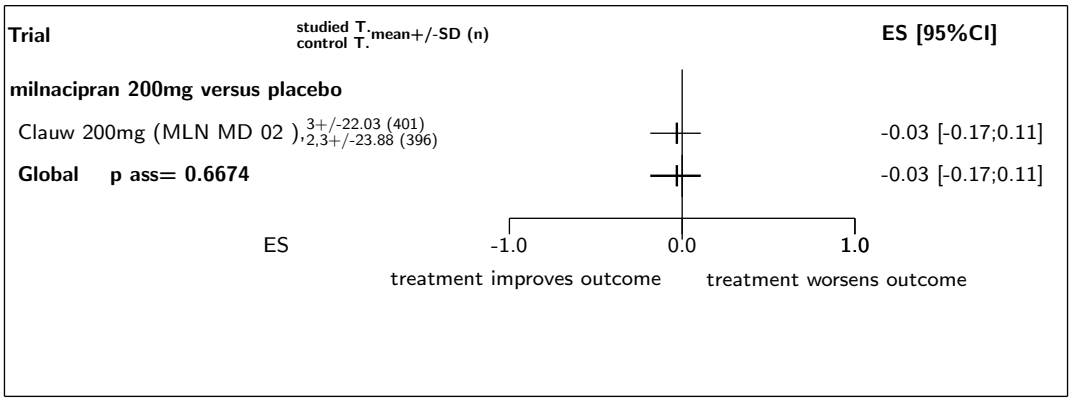


Figure 23.5: *Forest's plot for Dpression*

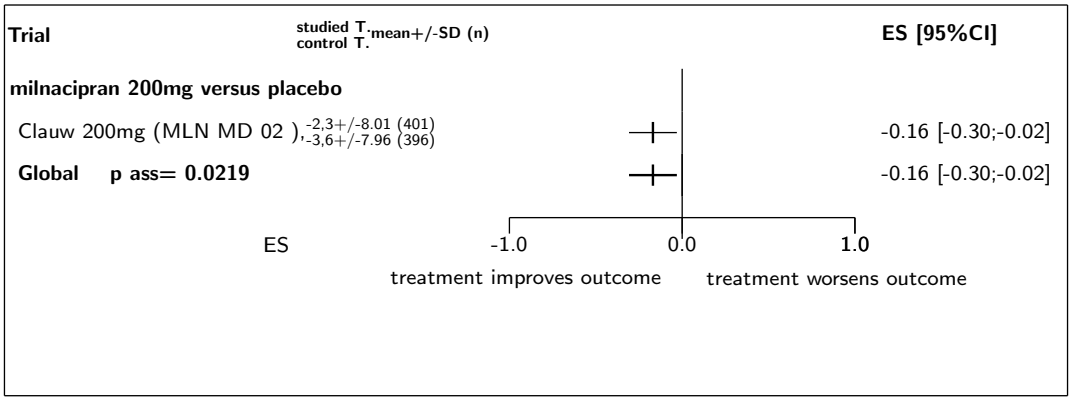


Figure 23.6: *Forest's plot for HAQ functional disability*

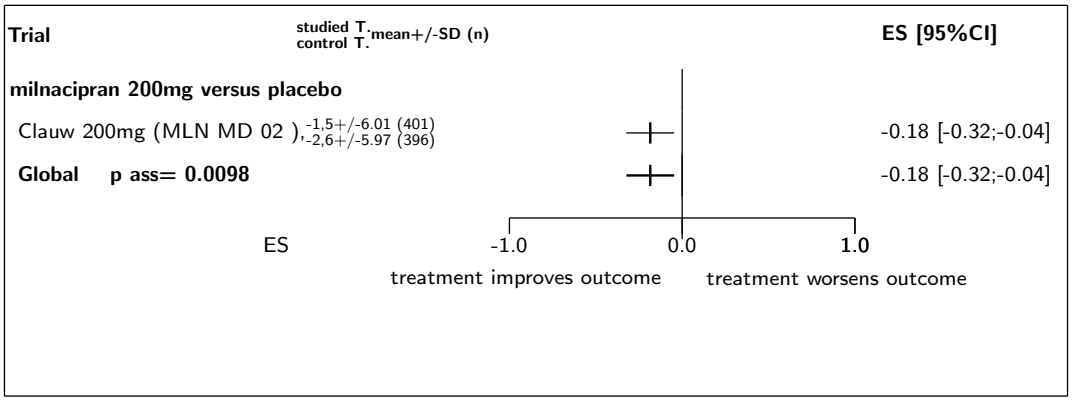


Figure 23.7: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*

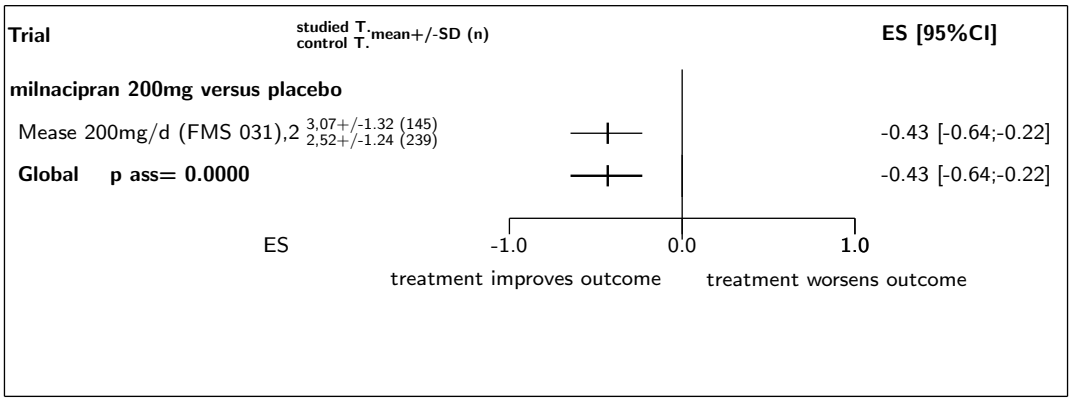
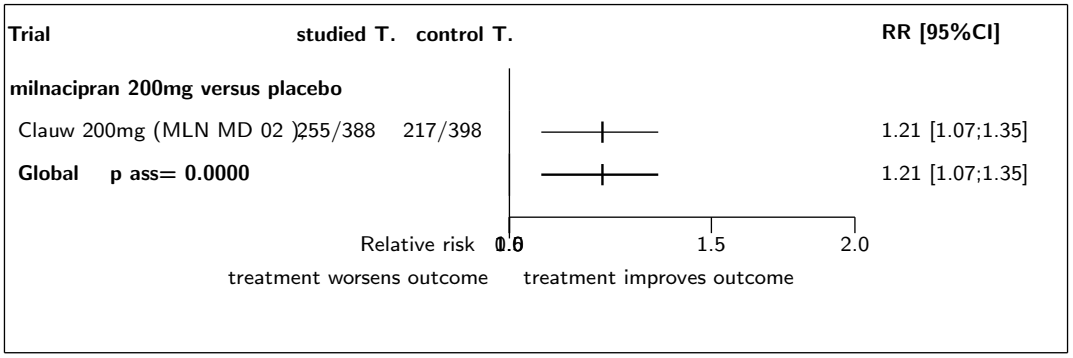


Figure 23.8: *Forest's plot for amlioration globale (patient)*



References

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24 Global meta-analysis: all milnacipran

24.1 Global meta-analysis: all milnacipran versus placebo

Table 24.1: *All milnacipranversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
FIQ	ES=-0.20	-0.30;-0.10	0.0000	0.5521 (0.00)	2	1597
douleur	ES=-0.21	-0.30;-0.12	0.0000	0.3914 (0.03)	5	2082
fatigue	ES=-0.13	-0.23;-0.04	0.0078	0.9983 (0.00)	2	1597
sommeil	ES=-0.04	-0.14;0.05	0.3711	0.7752 (0.00)	2	1597
dpression	ES=-0.12	-0.22;-0.03	0.0127	0.4528 (0.00)	2	1597
HAQ functional disability	ES=-0.17	-0.26;-0.07	0.0000	0.7375 (0.00)	2	1597
patient Global Impression of Improvement (PGI-I)	ES=-0.43	-0.64;-0.22	0.0000	1.0000 (0.00)	1	384
amlioration globale (patient)	RR=1.21	1.11;1.31	0.0000	0.9979 (0.00)	2	1578

legend B

25 Ongoing studies of milnacipran

A total of 4 ongoing studies were still ongoing at the date of this report. A list of these ongoing studies with a brief description is given table **??**.

Table 25.1: *Ongoing studies for milnacipran*

Study	**Description**
MLN MD 03 NCT00314249	Milnacipran **vs.** Placebo
FMS european [**?**] NCT00436033	milnacipran 200mg/j **vs.** placebo
NCT00757731 (European long term safety) NCT00757731	milnacipran 150mg et 200mg/j **vs.** milnacipran 100mg,
NCT00757679	milnacipran **vs.** placebo

26 Excluded studies for milnacipran

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 26.1: *Excluded studies of milnacipran*

Study	**Exclusion reason**
Goldenberg (0) [**?**]	extension de suivi non comparative
Gracely (0) [**?**]	etude de physiopathologie

Part VI

Muscle relaxant

27 Overview of muscle relaxant

No completed trial meeting the eligibility criteria was available.

28 Ongoing studies of Muscle relaxant

No ongoing trial was identified.

29 Excluded studies for Muscle relaxant

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 29.1: *Excluded studies of Muscle relaxant*

Study	Exclusion reason
Greene (1971) [**?**]	

Part VII

Pregabalin

30 Overview of pregabalin

30.1 Included trials

A total of 9 randomized comparisons which enrolled 3032 patients were identified. In all, 1 randomized comparison concerned pregabalin 150mg , 3 pregabalin 300mg , 3 pregabalin 450mg and two pregabalin 600mg.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for pregabalin 150mg, in section **??** (page **??**) for pregabalin 300mg, in section **??** (page **??**) for pregabalin 450mg and in section **??** (page **??**) for pregabalin 600mg.

The average study size was 336 patients (range 263 to 380). The first study was published in 2005, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

30.2 Summary of meta-analysis results

The meta-analysis of the available trials about pregabalin provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

30.2.1 Pregabalin 150mg

No significant difference was found between **pregabalin 150mg** and **placebo** in terms of douleur (ES=-0.10, 95% CI -0.35 to 0.14, p=0.4102, 1 trial), fatigue (ES=-0.20, 95% CI -0.45 to 0.05, p=0.1084, 1 trial), sommeil (ES=-0.18, 95% CI -0.42 to 0.06, p=0.1484, 1 trial), patient Global Impression of Improvement (PGI-I) (ES=-0.14, 95% CI -0.39 to 0.11, p=0.2810, 1 trial), amlioration globale (clinicien) (RR=1.21, 95% CI 0.95 to 1.53, p=0.1158, 1 trial)and amlioration globale (patient) (RR=1.14, 95% CI 0.92 to 1.43, p=0.2345, 1 trial).

30.2.2 Pregabalin 300mg

Pregabalin 300mg was superior to **placebo** in terms of douleur (ES=-0.27, 95% CI -0.40 to -0.15, p=0.0000, 3 trials), fatigue (ES=-0.18, 95% CI -0.31 to -0.06, p=0.0044, 3 trials), sommeil (ES=-0.29, 95% CI -0.41 to -0.16, p=0.0000, 3 trials)and patient Global Impression of Improvement (PGI-I) (ES=-0.33, 95% CI -0.58 to -0.08, p=0.0097, 1 trial).
However, no significant difference was found on FIQ (ES=-0.14, 95% CI -0.29 to 0.00, p=0.0506, 2 trials), dpression (ES=-0.06, 95% CI -0.27 to 0.14, p=0.5499, 2 trials), anxit (ES=-0.12, 95% CI -0.27 to 0.02, p=0.0960, 2 trials), sheehan disability scale (ES=-0.10, 95% CI -0.32 to 0.11, p=0.3516, 1 trial)and HAQ functional disability (ES=-0.07, 95% CI -0.28 to 0.13, p=0.4803, 1 trial).

30.2.3 Pregabalin 450mg

Pregabalin 450mg was superior to **placebo** in terms of FIQ (ES=-0.20, 95% CI -0.38 to -0.01, p=0.0353, 2 trials), douleur (ES=-0.39, 95% CI -0.57 to -0.21, p=0.0000, 3 trials), sommeil (ES=-0.48, 95% CI -0.66 to -0.29, p=0.0000, 3 trials), anxit (ES=-0.16, 95% CI -0.30 to -0.02,

p=0.0282, 2 trials)and patient Global Impression of Improvement (PGI-I) (ES=-0.48, 95% CI -0.73 to -0.23, p=0.0000, 1 trial).
However, no significant difference was found on fatigue (ES=-0.15, 95% CI -0.31 to 0.01, p=0.0690, 3 trials), dpression (ES=-0.13, 95% CI -0.27 to 0.02, p=0.0824, 2 trials), sheehan disability scale (ES=-0.12, 95% CI -0.33 to 0.10, p=0.2894, 1 trial)and HAQ functional disability (ES=-0.15, 95% CI -0.35 to 0.06, p=0.1596, 1 trial).

30.2.4 Pregabalin 600mg

Pregabalin 600mg was superior to **placebo** in terms of douleur (ES=-0.39, 95% CI -0.59 to -0.20, p=0.0000, 2 trials), sommeil (ES=-0.45, 95% CI -0.82 to -0.07, p=0.0187, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0106)(ES=-0.18, 95% CI -0.32 to -0.04, p=0.0131, 2 trials).
However, no significant difference was found on FIQ (ES=-0.18, 95% CI -0.40 to 0.05, p=0.1286, 2 trials), fatigue (ES=-0.11, 95% CI -0.26 to 0.03, p=0.1275, 2 trials), dpression (ES=-0.12, 95% CI -0.26 to 0.02, p=0.1011, 2 trials), sheehan disability scale (ES=-0.13, 95% CI -0.35 to 0.09, p=0.2479, 1 trial)and HAQ functional disability (ES=-0.10, 95% CI -0.30 to 0.10, p=0.3435, 1 trial).

Table 30.1: *Main study characteristics - pregabalin*

Trial	Patients	Treatments	Trial design and method
Pregabalin 150mg			
Pregabalin 150mg versus placebo			
Crofford 150mg, 2005 [**?**, **?**] n = 132 vs. 131	critres ACR, douleur >=40mm sur une EVA de 100mm, score moyen de douleur >=4 (/10) sur 4 mesure dans la semaine prcdent l'inclusion	pregabalin 150mg/j **versus** placebo	double blind parallel groups Primary endpoint: score de douleur 40 centres,USA
Pregabalin 300mg			
Pregabalin 300mg versus placebo			
Arnold 300mg, 2008 [**?**, **?**] n = 183 vs. 184	critres ACR; EVA douleur >=40 mm (/100mm); >= 18 ans	pregabalin 300mg **versus** placebo	double blind parallel groups Primary endpoint: score de douleur, PGIC, FIQ US
Crofford 300mg, 2005 [**?**] n = 134 vs. 131	critres ACR, douleur >=40mm sur une EVA de 100mm, score moyen de douleur >=4 (/10) sur 4 mesure dans la semaine prcdent l'inclusion	pregabalin 300mg/j **versus** placebo	double blind Primary endpoint: score de douleur 40 centres,USA
Mease (300mg), 2008 [**?**] n = 185 vs. 190	critres ACR, >=18 ans, score douleur NRS >=4 /11 et VAS >=40mm (/100)	pregabalin 300mg mg (deux prise par jour) **versus** placebo	double blind parallel groups Primary endpoint: score douleur NSR 79 centres,USA
Pregabalin 450mg			
Pregabalin 450mg versus placebo			
Arnold 450mg, 2008 [**?**, **?**] n = 190 vs. 184	critres ACR; EVA douleur >=40 mm (/100mm); >= 18 ans	pregabalin 450mg **versus** placebo	double blind parallel groups Primary endpoint: score de douleur, PGIC, FIQ 84 centres,US

continued...

Trial	Patients	Treatments	Trial design and method
Crofford 450mg, 2005 [**?**] n = 132 vs. 131	critres ACR, douleur >=40mm sur une EVA de 100mm, score moyen de douleur >=4 (/10) sur 4 mesure dans la semaine prcdent l'inclusion	pregabalin 450mg/j **versus** placebo	double blind Primary endpoint: score de douleur 40 centres,USA
Mease (450 mg), 2008 [**?**] n = 183 vs. 190	critres ACR, >=18 ans, score douleur NRS >=4 /11 et VAS >=40mm (/100)	pregabalin 450 mg (deux prise par jour) **versus** placebo	double blind Primary endpoint: score douleur NSR 79 centres,US
Pregabalin 600mg			
Pregabalin 600mg versus placebo			
Arnold 600mg, 2008 [**?**, **?**] n = 188 vs. 184	critres ACR; EVA douleur >=40 mm (/100mm); >= 18 ans	pregabalin 600mg **versus** placebo	double blind parallel groups Primary endpoint: score de douleur 84 centres,US
Mease (600mg), 2008 [**?**] n = 190 vs. 190	critres ACR, >=18 ans, score douleur NRS >=4 /11 et VAS >=40mm (/100)	pregabalin 600mg mg (deux prise par jour) **versus** placebo	double blind Primary endpoint: score douleur NSR 79 centres,US

Table 30.2: *Summary of all results for pregabalin 150mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pregabalin 150mg versus placebo						
douleur	ES=-0.10	-0.35;0.14	0.4102	1.0000 (0.00)	1	260
fatigue	ES=-0.20	-0.45;0.05	0.1084	1.0000 (0.00)	1	247
sommeil	ES=-0.18	-0.42;0.06	0.1484	1.0000 (0.00)	1	260
patient Global Impression of Improvement (PGI-I)	ES=-0.14	-0.39;0.11	0.2810	1.0000 (1.00)	1	247
amlioration globale (clinicien)	RR=1.21	0.95;1.53	0.1158	1.0000 (0.00)	1	249
amlioration globale (patient)	RR=1.14	0.92;1.43	0.2345	1.0000 (0.00)	1	247

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 30.3: *Summary of all results for pregabalin 300mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pregabalin 300mg versus placebo						
FIQ	ES=-0.14	-0.29;0.00	0.0506	0.7974 (0.00)	2	741
douleur	ES=-0.27	-0.40;-0.15	0.0000	0.6638 (0.00)	3	1005
fatigue	ES=-0.18	-0.31;-0.06	0.0044	0.3706 (0.00)	3	982
sommeil	ES=-0.29	-0.41;-0.16	0.0000	0.7841 (0.00)	3	1003
dpression	ES=-0.06	-0.27;0.14	0.5499	0.1516 (0.51)	2	741
anxit	ES=-0.12	-0.27;0.02	0.0960	0.3343 (0.00)	2	741
sheehan disability scale	ES=-0.10	-0.32;0.11	0.3516	1.0000 (1.00)	1	333
HAQ functional disability	ES=-0.07	-0.28;0.13	0.4803	1.0000 (0.00)	1	374
patient Global Impression of Improvement (PGI-I)	ES=-0.33	-0.58;-0.08	0.0097	1.0000 (0.00)	1	247
amlioration globale (clinicien)	RR=1.30	1.03;1.62	0.0248	1.0000 (0.00)	1	250
amlioration globale (patient)	RR=0.94 [1]	0.66;1.35	0.7550	0.0087 (0.85) †	2	600

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 30.4: *Summary of all results for pregabalin 450mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pregabalin 450mg versus placebo						
FIQ	ES=-0.20	-0.38;-0.01	0.0353	0.2054 (0.38)	2	746
douleur	ES=-0.39	-0.57;-0.21	0.0000	0.1245 (0.52)	3	1004
fatigue	ES=-0.15	-0.31;0.01	0.0690	0.1889 (0.40)	3	985
sommeil	ES=-0.48	-0.66;-0.29	0.0000	0.1246 (0.52)	3	1001
dpression	ES=-0.13	-0.27;0.02	0.0824	0.6832 (0.00)	2	745
anxit	ES=-0.16	-0.30;-0.02	0.0282	0.9412 (0.00)	2	745
sheehan disability scale	ES=-0.12	-0.33;0.10	0.2894	1.0000 (0.00)	1	326
HAQ functional disability	ES=-0.15	-0.35;0.06	0.1596	1.0000 (0.00)	1	372
patient Global Impression of Improvement (PGI-I)	ES=-0.48	-0.73;-0.23	0.0000	1.0000 (0.00)	1	248
amlioration globale (clinicien)	RR=1.56	1.27;1.92	0.0000	1.0000 (0.00)	1	250
amlioration globale (patient)	RR=1.34	1.18;1.51	0.0000	0.4371 (0.00)	2	599

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.90 95% CI 0.79;1.02

Endpoint	Effect	95% CI	p ass	p het	k	n

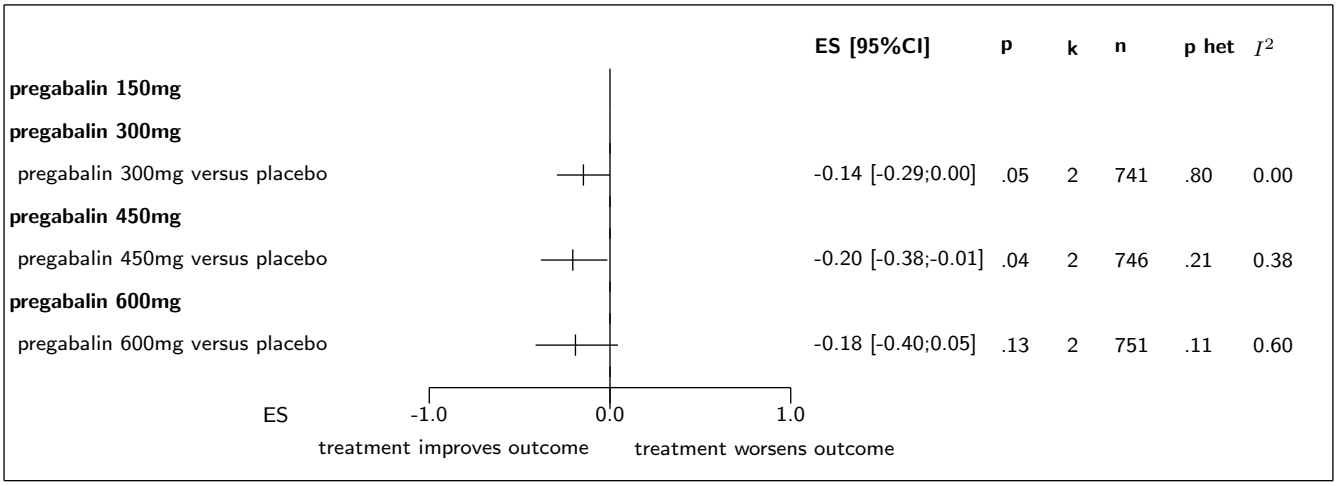
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 30.5: *Summary of all results for pregabalin 600mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pregabalin 600mg versus placebo						
FIQ	ES=-0.18	-0.40;0.05	0.1286	0.1132 (0.60)	2	751
douleur	ES=-0.39	-0.59;-0.20	0.0000	0.1863 (0.43)	2	752
fatigue	ES=-0.11	-0.26;0.03	0.1275	0.5473 (0.00)	2	744
sommeil	ES=-0.45 [2]	-0.82;-0.07	0.0187	0.0106 (0.85) †	2	746
dpression	ES=-0.12	-0.26;0.02	0.1011	0.6422 (0.00)	2	751
anxit	ES=-0.18	-0.32;-0.04	0.0131	0.4053 (0.00)	2	751
sheehan disability scale	ES=-0.13	-0.35;0.09	0.2479	1.0000 (1.00)	1	326
HAQ functional disability	ES=-0.10	-0.30;0.10	0.3435	1.0000 (0.00)	1	379
amlioration globale (patient)	RR=1.22	1.04;1.44	0.0172	1.0000 (0.00)	1	353

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

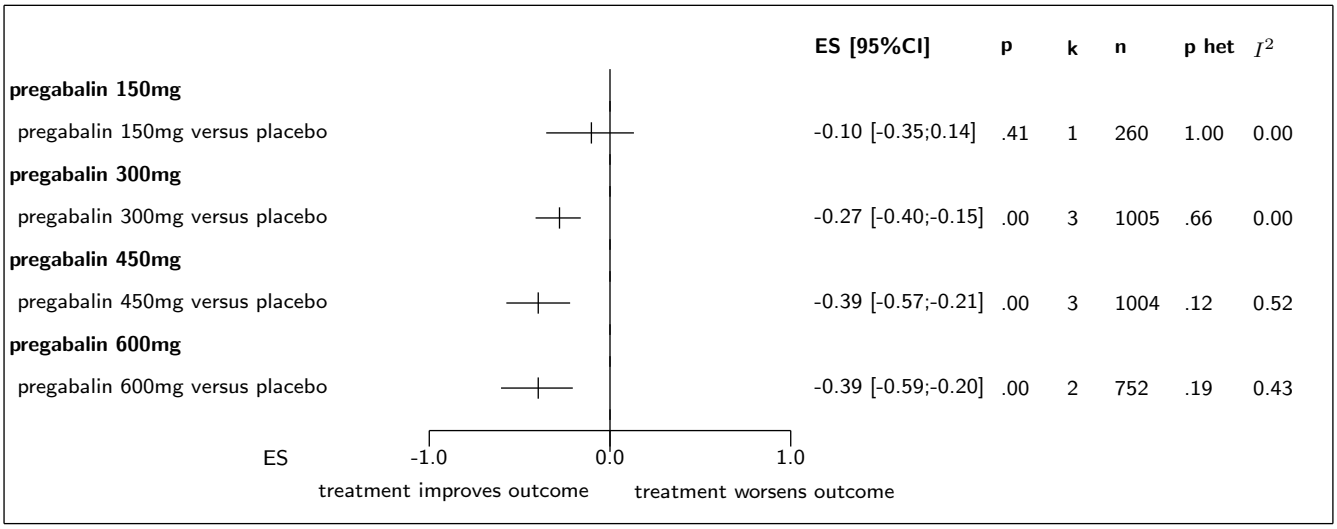
Figure 30.1: *Forest's plot for FIQ*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; [r]: random effect model used

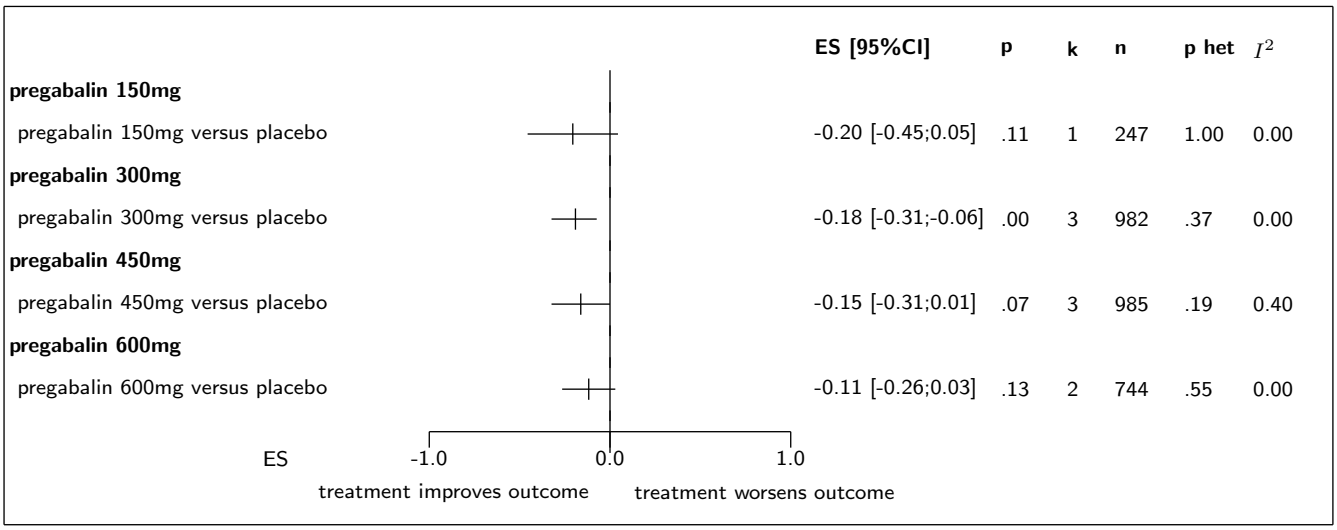
[2] with a random model ($\tau^2 = 0.061$). The results with a fixed effect model was RRFE=-0.44 95% CI -0.59;-0.30

Figure 30.2: *Forest's plot for douleur*



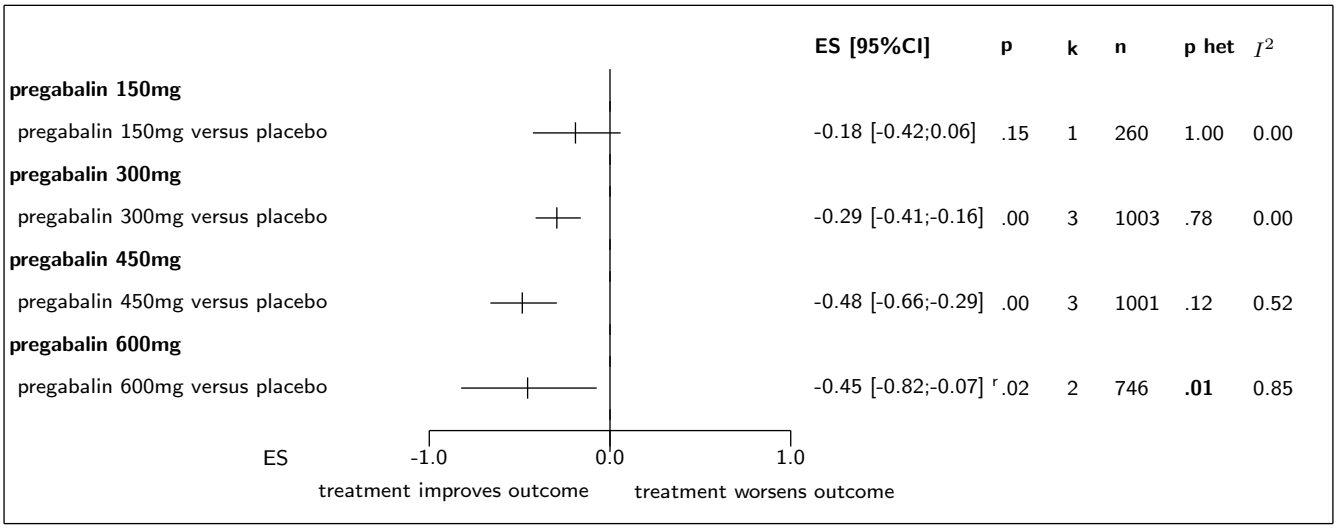
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.3: *Forest's plot for fatigue*



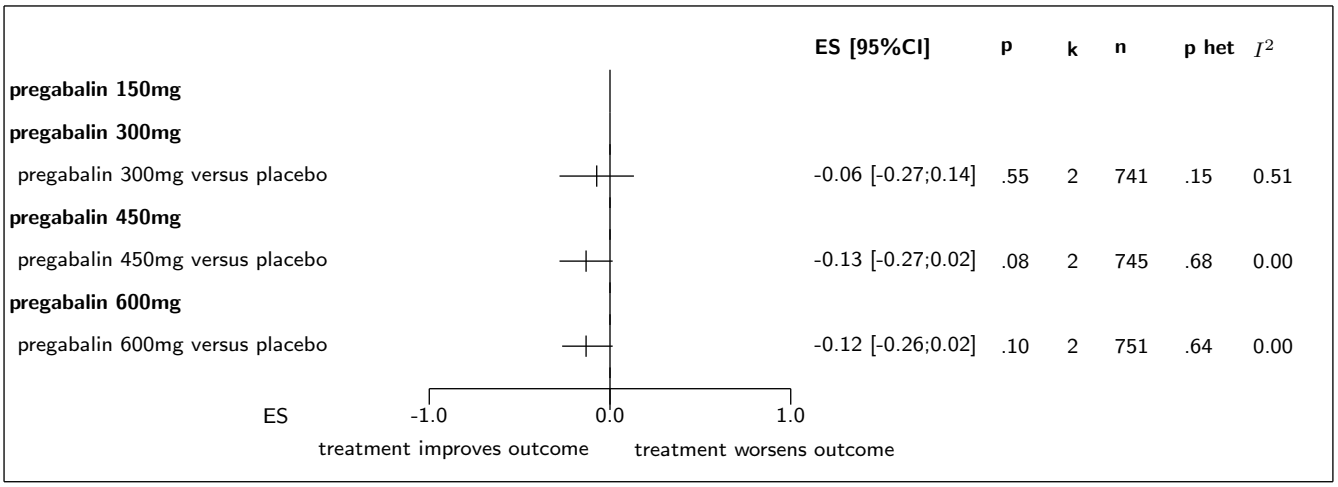
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.4: *Forest's plot for sommeil*



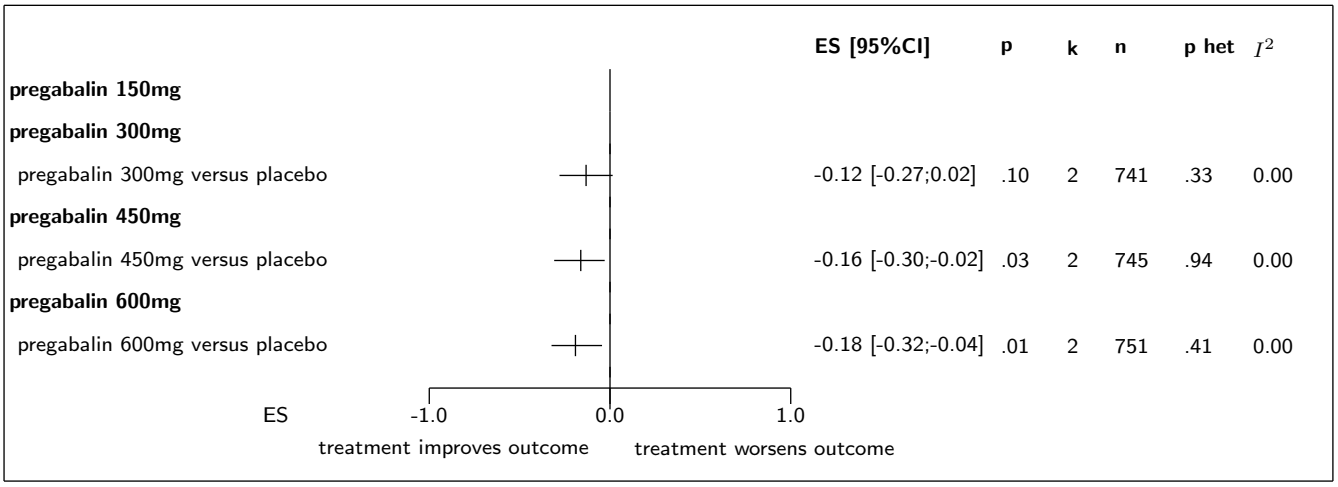
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.5: *Forest's plot for dpression*



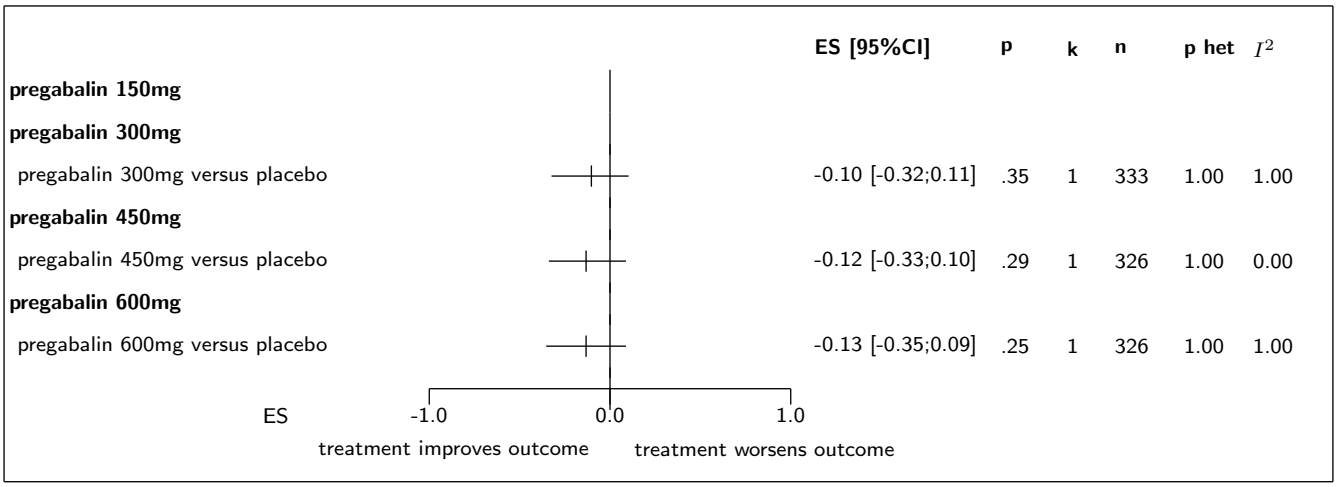
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.6: *Forest's plot for anxit*



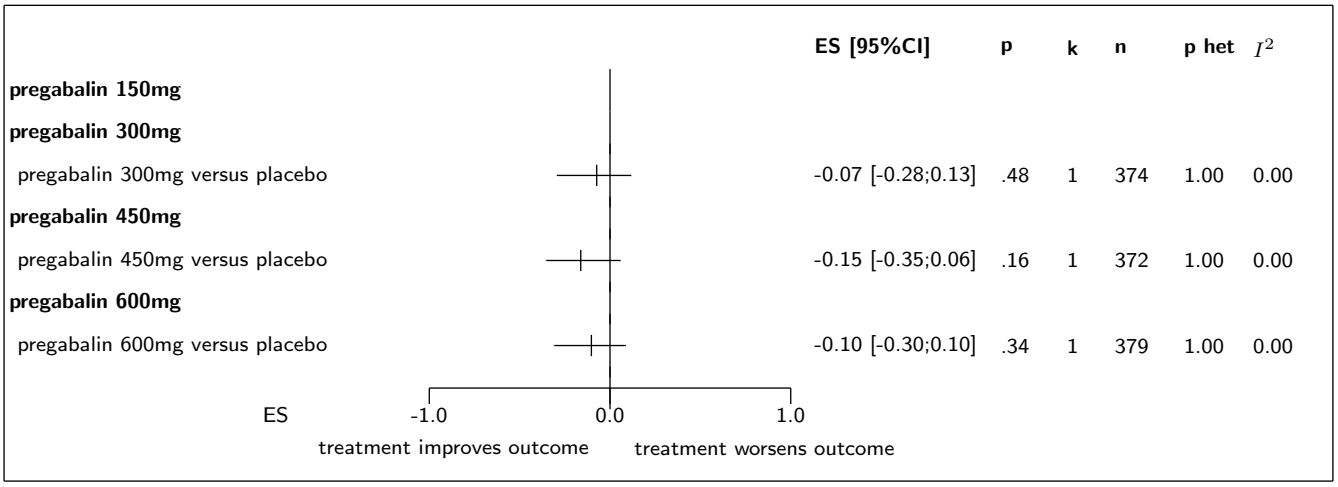
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.7: *Forest's plot for sheehan disability scale*



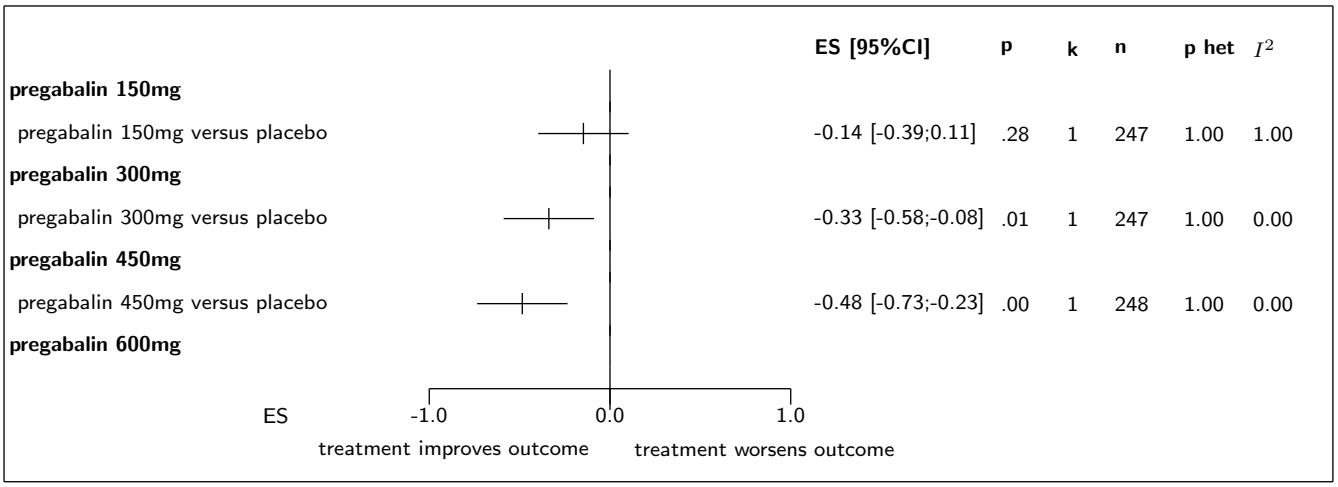
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.8: *Forest's plot for HAQ functional disability*



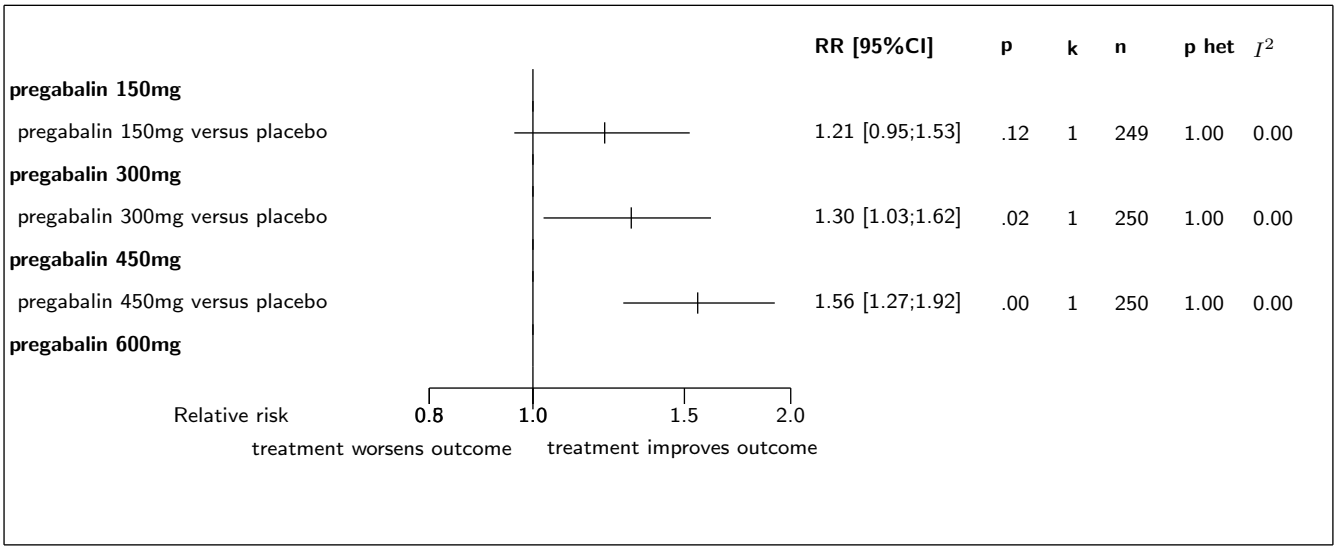
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.9: *Forest's plot for patient Global Impression of Improvement (PGI-I)*



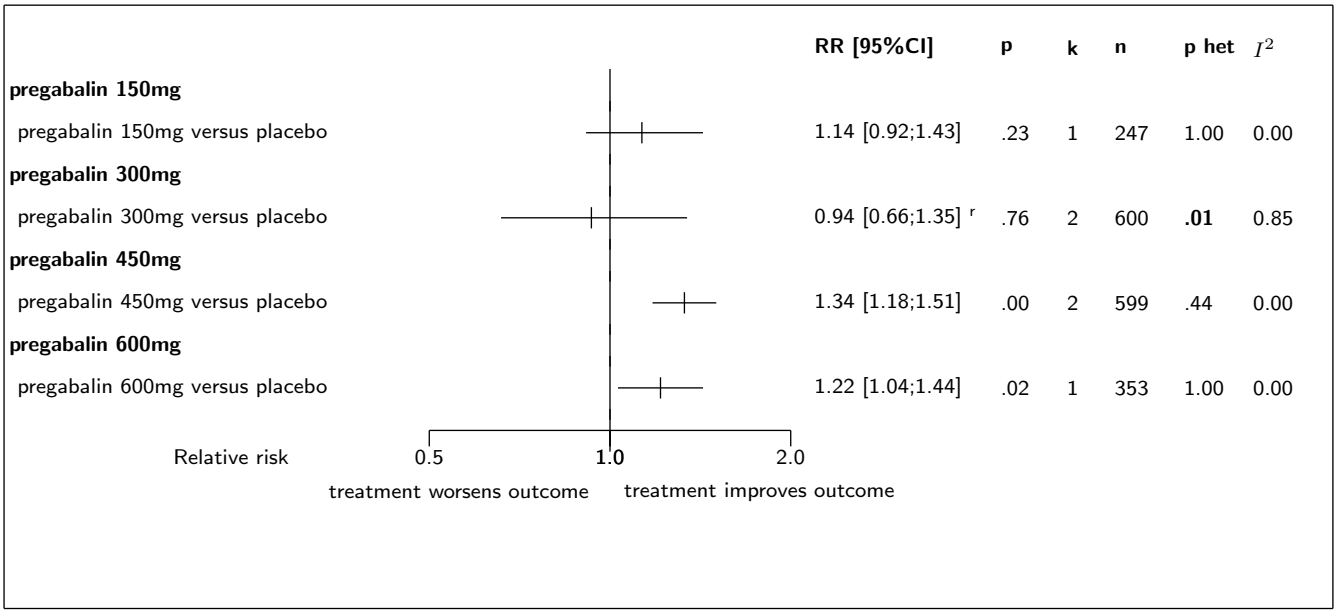
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 30.10: *Forest's plot for amlioration globale (clinicien)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 30.11: *Forest's plot for amlioration globale (patient)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

31 Detailed results for pregabalin 150mg

31.1 Available trials

Only one trial which randomized 263 patients was identified: it compared pregabalin 150mg with placebo.
This trial included 263 patients and was published in 2005.
This trial was double blind in design.
It was reported in English language.
Amlioration globale (clinicien) data was reported in 1 trials; 1 trials reported data on fatigue; 1 trials reported data on patient Global Impression of Improvement (PGI-I); 1 trials reported data on sommeil; 1 trials reported data on amlioration globale (patient); and 1 trials reported data on douleur.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of pregabalin 150mg.

Table 31.1: *Treatment description - pregabalin - pregabalin 150mg*

Trial	Studied treatment	Control treatment
Pregabalin 150mg versus placebo		
Crofford 150mg (2005) [**?**, **?**] [a]	Pregabalin 150mg/j	placebo

a) 4 bras: pregabalin 150, 300, 450 mg/j, placebo

Table 31.2: *Descriptions of participants - pregabalin - pregabalin 150mg*

Trial	Patients
Pregabalin 150mg versus placebo	
Crofford 150mg (2005) [**?**, **?**]	Critres ACR, douleur >=40mm sur une EVA de 100mm, score moyen de douleur >=4 (/10) sur 4 mesure dans la semaine prcdent l'inclusion

Table 31.3: *Main patients characteristics - pregabalin - pregabalin 150mg*

Trial	Characteristics
Pregabalin 150mg versus placebo	
Crofford 150mg, 2005 [**?**, **?**]	age (mean), years: 48.8 ans femmes (%): 93% critres d'inclusion: ACR douleur: 7 (/10) fatigue: 38.8 (MAF fatigue index global) depression: 8.5 (HADS depression) anxit: 10.1 (HADS anxit)

Table 31.4: *Design and methodological quality of trials - pregabalin - pregabalin 150mg*

Trial	Design	Duration	Centre	Primary endpoint
Pregabalin 150mg versus placebo				
Crofford 150mg, 2005 [?, ?] n=263	Parallel groups double blind	8 semaines inclusion period: sept 1999 - apr 2000	USA 40 centres	score de douleur

31.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Pregabalin 150mg versus placebo

The single study eligible for this comparison provided data on **douleur**. No statistically significant difference between the groups was found in douleur, with a ES of -0.10 (95% CI -0.35 to 0.14, p=0.4102).
The single study eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of -0.20 (95% CI -0.45 to 0.05, p=0.1084).
The single study eligible for this comparison provided data on **sommeil**. No statistically significant difference between the groups was found in sommeil, with a ES of -0.18 (95% CI -0.42 to 0.06, p=0.1484).
The single study eligible for this comparison provided data on **patient Global Impression of Improvement (PGI-I)**. No statistically significant difference between the groups was found in patient Global Impression of Improvement (PGI-I), with a ES of -0.14 (95% CI -0.39 to 0.11, p=0.2810).
The single study eligible for this comparison provided data on **amlioration globale (clinicien)**. No statistically significant difference between the groups was found in amlioration globale (clinicien), with a RR of 1.21 (95% CI 0.95 to 1.53, p=0.1158).
The single study eligible for this comparison provided data on **amlioration globale (patient)**. No statistically significant difference between the groups was found in amlioration globale (patient), with a RR of 1.14 (95% CI 0.92 to 1.43, p=0.2345).

Table 31.5: *Results details - pregabalin - pregabalin 150mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pregabalin 150mg versus placebo						
douleur	ES=-0.10	[-0.35;0.14]	0.4102	1.0000 (I^2=0.00)	1	260
fatigue	ES=-0.20	[-0.45;0.05]	0.1084	1.0000 (I^2=0.00)	1	247
sommeil	ES=-0.18	[-0.42;0.06]	0.1484	1.0000 (I^2=0.00)	1	260
patient Global Impression of Improvement (PGI-I)	ES=-0.14	[-0.39;0.11]	0.2810	1.0000 (I^2=1.00)	1	247
amlioration globale (clinicien)	RR=1.21	[0.95;1.53]	0.1158	1.0000 (I^2=0.00)	1	249
amlioration globale (patient)	RR=1.14	[0.92;1.43]	0.2345	1.0000 (I^2=0.00)	1	247

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 31.1: *Forest's plot for Douleur*

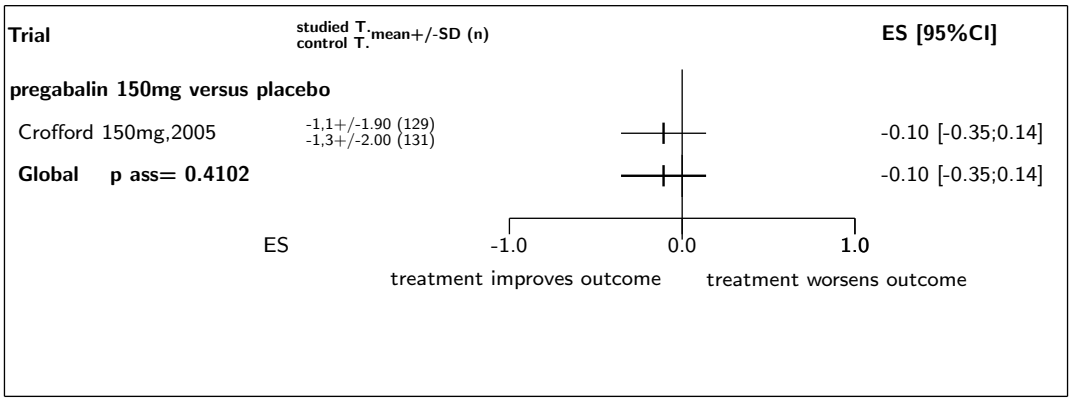


Figure 31.2: *Forest's plot for Fatigue*

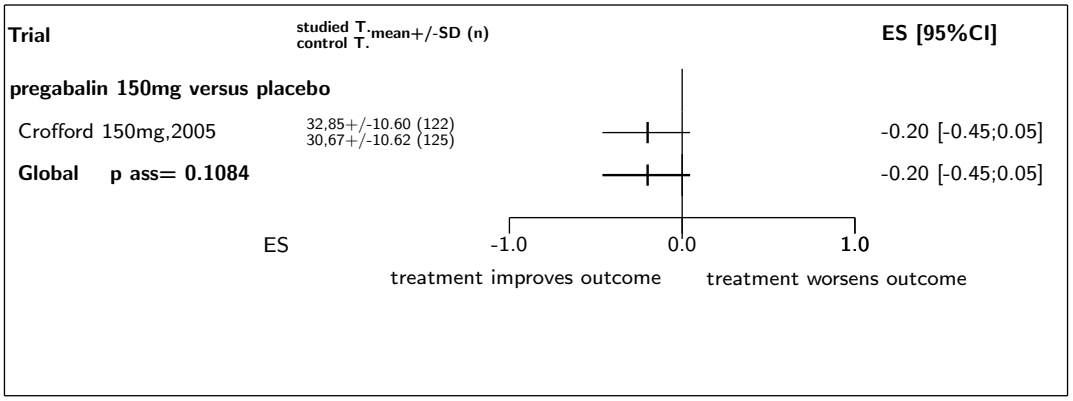


Figure 31.3: *Forest's plot for Sommeil*

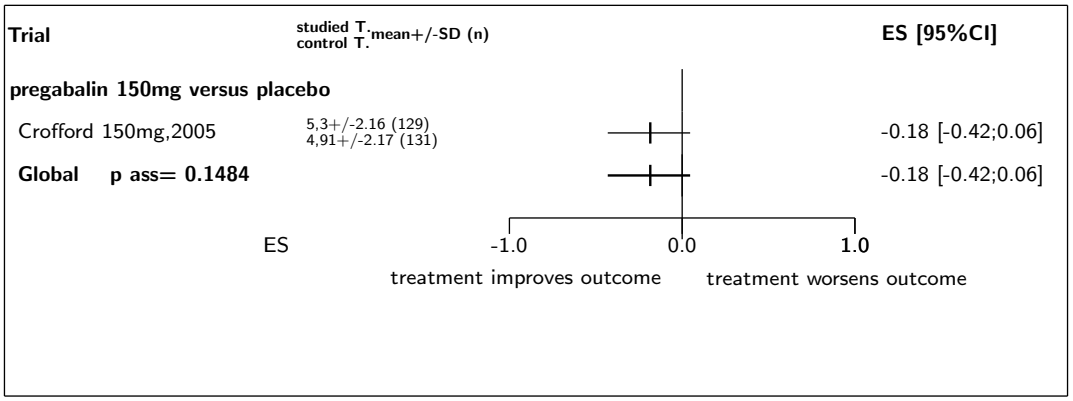


Figure 31.4: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*

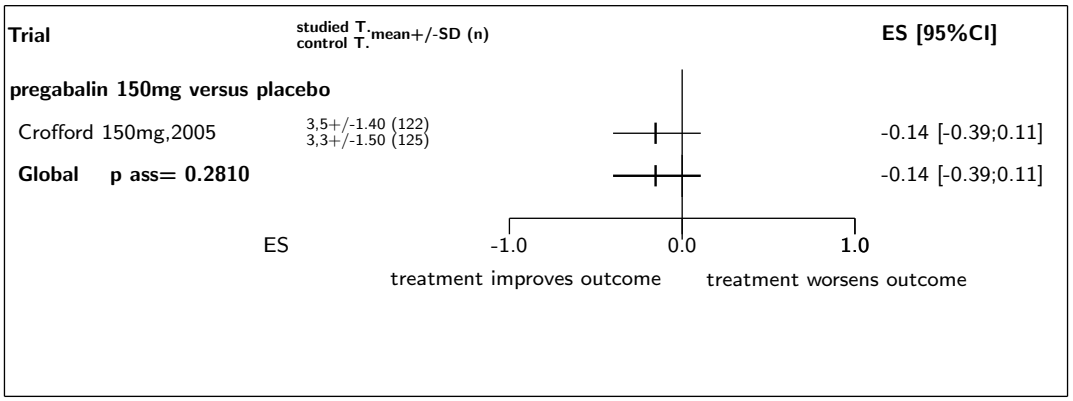


Figure 31.5: *Forest's plot for amlioration globale (clinicien)*

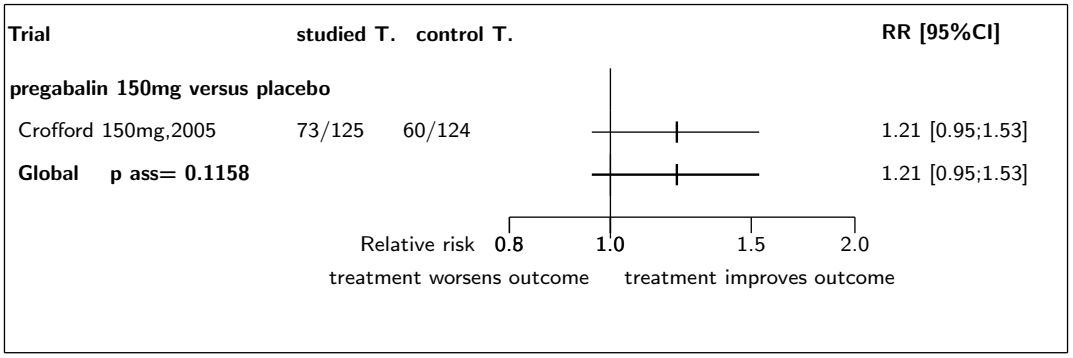
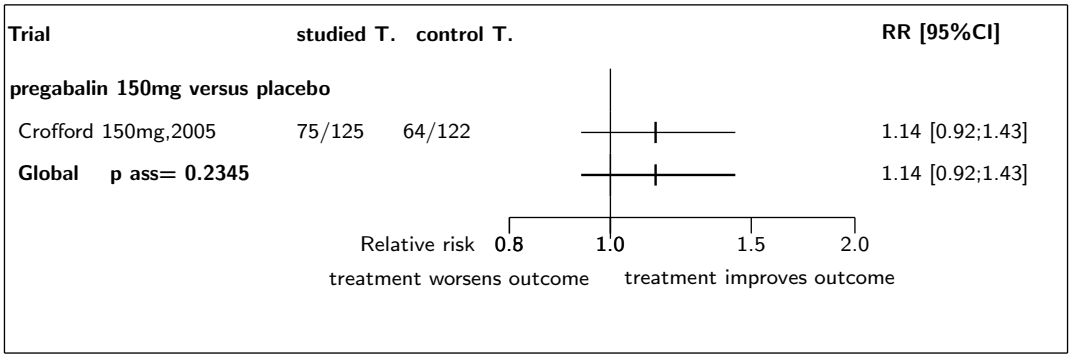


Figure 31.6: *Forest's plot for amlioration globale (patient)*



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32 Detailed results for pregabalin 300mg

32.1 Available trials

A total of 3 RCTs which randomized 1007 patients were identified: all compared pregabalin 300mg with placebo.
The average study size was 335 patients (range 265 to 375). The first study was published in 2005, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Sommeil data was reported in 3 trials; 3 trials reported data on fatigue; 3 trials reported data on douleur; 2 trials reported data on dpression; 2 trials reported data on amlioration globale (patient); 2 trials reported data on FIQ; 2 trials reported data on anxit; 1 trials reported data on amlioration globale (clinicien); 1 trials reported data on HAQ functional disability; 1 trials reported data on sheehan disability scale; and 1 trials reported data on patient Global Impression of Improvement (PGI-I).
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of pregabalin 300mg.

Table 32.1: *Treatment description - pregabalin - pregabalin 300mg*

Trial	Studied treatment	Control treatment
Pregabalin 300mg versus placebo		
Arnold 300mg (2008) [**?**, **?**] [a]	pregabalin 300mg	placebo
Crofford 300mg (2005) [**?**] [b]	Pregabalin 300mg/j	placebo
Mease (300mg) (2008) [**?**]	pregabalin 300mg mg (deux prise par jour)	placebo

a) 4 bras : pregabalin 300 mg/j, 450 mg/j et 600 mg/j b) 4 bras: pregabalin 150, 300, 450 mg/j, placebo

Table 32.2: *Descriptions of participants - pregabalin - pregabalin 300mg*

Trial	Patients
Pregabalin 300mg versus placebo	
Arnold 300mg (2008) [**?**, **?**]	Critres ACR; EVA douleur >=40 mm (/100mm); >= 18 ans
Crofford 300mg (2005) [**?**]	Critres ACR, douleur >=40mm sur une EVA de 100mm, score moyen de douleur >=4 (/10) sur 4 mesure dans la semaine prcdent l'inclusion
Mease (300mg) (2008) [**?**]	Critres ACR, >=18 ans, score douleur NRS >=4 /11 et VAS >=40mm (/100)

Table 32.3: *Main patients characteristics - pregabalin - pregabalin 300mg*

Trial	Characteristics
Pregabalin 300mg versus placebo	
Arnold 300mg, 2008 [?, ?]	age (mean), years: 50 ans femmes (%): 93.5% critres d'inclusion: ACR nombre de points douloureux: 16.9 fibromyalgia Impact Questionnaire: 59.7 douleur: 6.65 (NRS 0-10) fatigue: 35.8 (MAF) depression: 7 (HADS depression) anxit: 8.7 (HADS anxit)
Crofford 300mg, 2005 [?]	age (mean), years: 48.8 ans femmes (%): 93% critres d'inclusion: ACR douleur: 7 (/10) fatigue: 38.8 (MAF fatigue index global) depression: 8.5 (HADS depression) anxit: 10.1 (HADS anxit)
Mease (300mg), 2008 [?]	age (mean), years: 49.3 ans femmes (%): 95.2% critres d'inclusion: ACR nombre de points douloureux: 17 (/18) fibromyalgia Impact Questionnaire: 64.3 (0-100) douleur: 7.15 (0-10) fatigue: 8.3 (0-10, FIG fatigue) depression: 8.3 (0-21, HADS) anxit: 9.5 (0-21, HADS)

Table 32.4: *Design and methodological quality of trials - pregabalin - pregabalin 300mg*

Trial	Design	Duration	Centre	Primary endpoint
Pregabalin 300mg versus placebo				
Arnold 300mg, 2008 [?, ?] n=367	Parallel groups double blind	14 weeks inclusion period: oct 2005-jul 2006	US	score de douleur, PGIC, FIQ
Crofford 300mg, 2005 [?] n=265	double blind	8 semaines inclusion period: sept 1999 - apr 2000	USA 40 centres	score de douleur
Mease (300mg), 2008 [?] n=375	Parallel groups double blind	14 semaines	USA 79 centres	score douleur NSR

32.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Pregabalin 300mg versus placebo

A total of 2 of the 3 studies eligible for this comparison provided data on **FIQ**. When pooled together, there was no statistically significant difference between the groups in FIQ, with a ES of -0.14 (95% CI -0.29 to 0.00, p=0.0506). No heterogeneity was detected (p = 0.7974, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of pregabalin 300mg in douleur, with a ES of -0.27 (95% CI -0.40 to -0.15, p=0.0000). No heterogeneity was detected (p = 0.6638, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **fatigue**. The analysis detected a statistically significant difference in favor of pregabalin 300mg in fatigue, with a ES of -0.18 (95% CI -0.31 to -0.06, p=0.0044). No heterogeneity was detected (p = 0.3706, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **sommeil**. The analysis detected a statistically significant difference in favor of pregabalin 300mg in sommeil, with a ES of -0.29 (95% CI -0.41 to -0.16, p=0.0000). No heterogeneity was detected (p = 0.7841, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **dpression**. When pooled together, there was no statistically significant difference between the groups in dpression, with a ES of -0.06 (95% CI -0.27 to 0.14, p=0.5499). No heterogeneity was detected (p = 0.1516, I^2 = 0.51%).
A total of 2 of the 3 studies eligible for this comparison provided data on **anxit**. When pooled together, there was no statistically significant difference between the groups in anxit, with a ES of -0.12 (95% CI -0.27 to 0.02, p=0.0960). No heterogeneity was detected (p = 0.3343, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **sheehan disability scale**. No statistically significant difference between the groups was found in sheehan disability scale, with a ES of -0.10 (95% CI -0.32 to 0.11, p=0.3516).
Only one of the 3 studies eligible for this comparison provided data on **HAQ functional disability**. No statistically significant difference between the groups was found in HAQ functional disability, with a ES of -0.07 (95% CI -0.28 to 0.13, p=0.4803).
Only one of the 3 studies eligible for this comparison provided data on **patient Global Impression of Improvement (PGI-I)**. The analysis detected a statistically significant difference in favor of pregabalin 300mg in patient Global Impression of Improvement (PGI-I), with a ES of -0.33 (95% CI -0.58 to -0.08, p=0.0097).
Only one of the 3 studies eligible for this comparison provided data on **amlioration globale (clinicien)**. The analysis detected a statistically significant difference in favor of pregabalin 300mg in amlioration globale (clinicien), with a RR of 1.30 (95% CI 1.03 to 1.62, p=0.0248).
A total of 2 of the 3 studies eligible for this comparison provided data on **amlioration globale (patient)**. When pooled together, there was no statistically significant difference between the groups in amlioration globale (patient), with a RR of 0.94 (95% CI 0.66 to 1.35, p=0.7550). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0087, I^2 = 0.85%).

Table 32.5: *Results details - pregabalin - pregabalin 300mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pregabalin 300mg versus placebo						
FIQ	ES=-0.14	[-0.29;0.00]	0.0506	0.7974 (I^2=0.00)	2	741
douleur	ES=-0.27	[-0.40;-0.15]	0.0000	0.6638 (I^2=0.00)	3	1005
fatigue	ES=-0.18	[-0.31;-0.06]	0.0044	0.3706 (I^2=0.00)	3	982

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
sommeil	ES=-0.29	[-0.41;-0.16]	0.0000	0.7841 (I^2=0.00)	3	1003
dpression	ES=-0.06	[-0.27;0.14]	0.5499	0.1516 (I^2=0.51)	2	741
anxit	ES=-0.12	[-0.27;0.02]	0.0960	0.3343 (I^2=0.00)	2	741
sheehan disability scale	ES=-0.10	[-0.32;0.11]	0.3516	1.0000 (I^2=1.00)	1	333
HAQ functional disability	ES=-0.07	[-0.28;0.13]	0.4803	1.0000 (I^2=0.00)	1	374
patient Global Impression of Improvement (PGI-I)	ES=-0.33	[-0.58;-0.08]	0.0097	1.0000 (I^2=0.00)	1	247
amlioration globale (clinicien)	RR=1.30	[1.03;1.62]	0.0248	1.0000 (I^2=0.00)	1	250
amlioration globale (patient)	RR=0.94	[0.66;1.35]	0.7550	0.0087 (I^2=0.85)	2	600

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 32.1: *Forest's plot for FIQ*

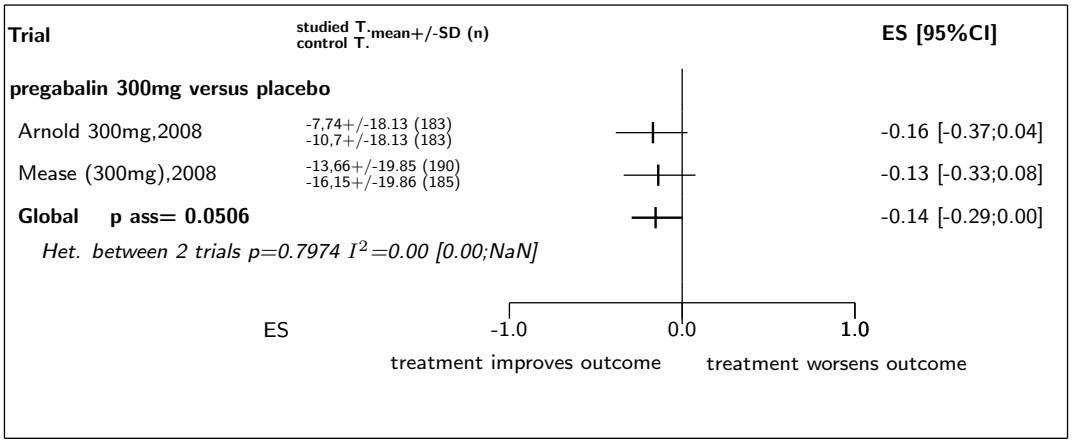


Figure 32.2: *Forest's plot for Douleur*

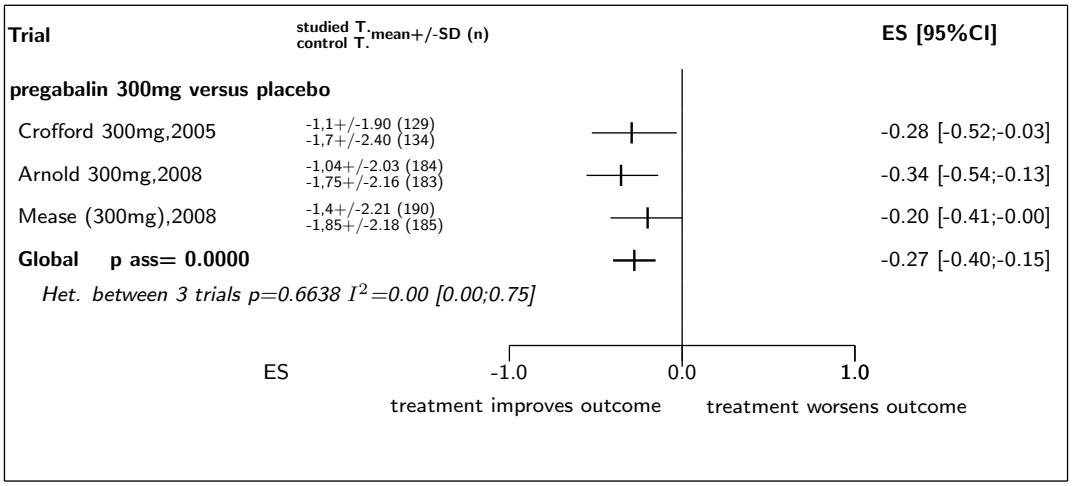


Figure 32.3: *Forest's plot for Fatigue*

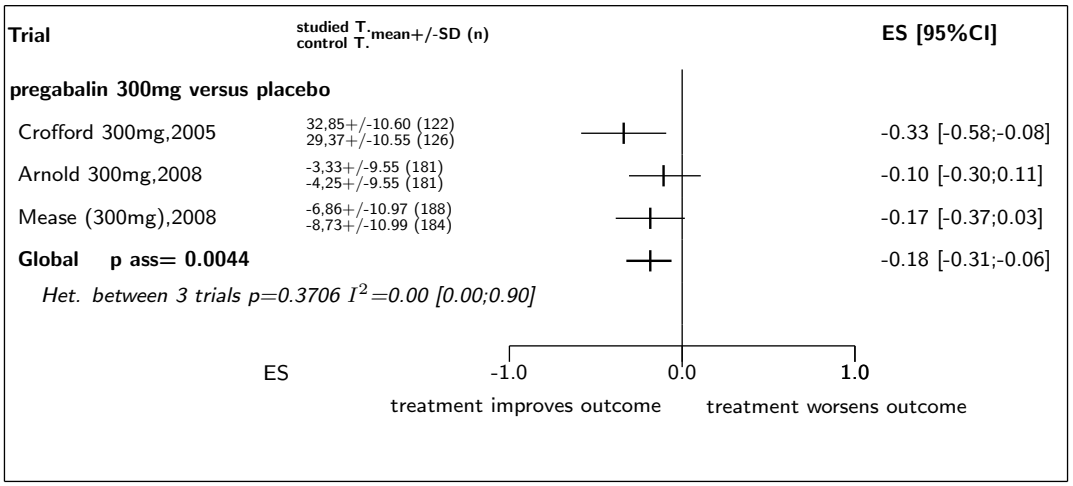


Figure 32.4: *Forest's plot for Sommeil*

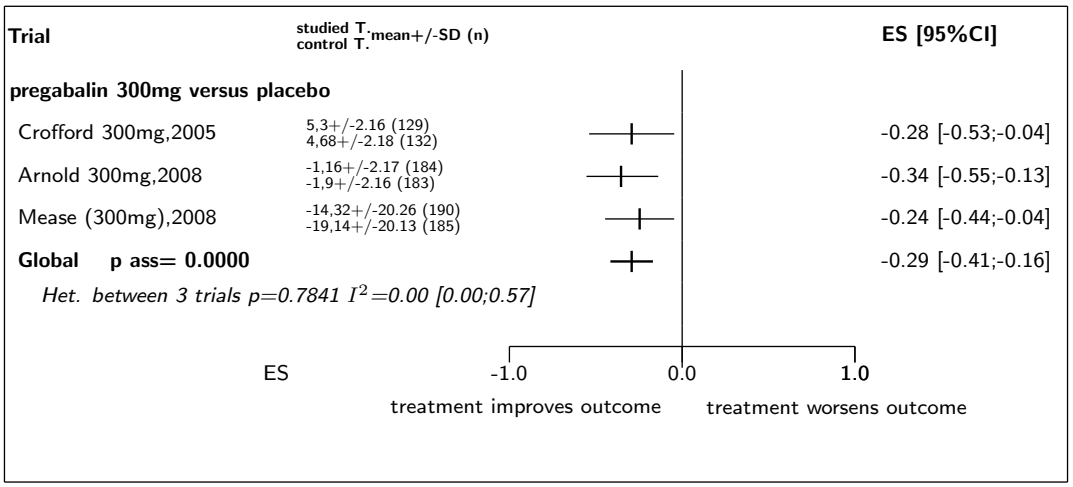


Figure 32.5: *Forest's plot for Dpression*

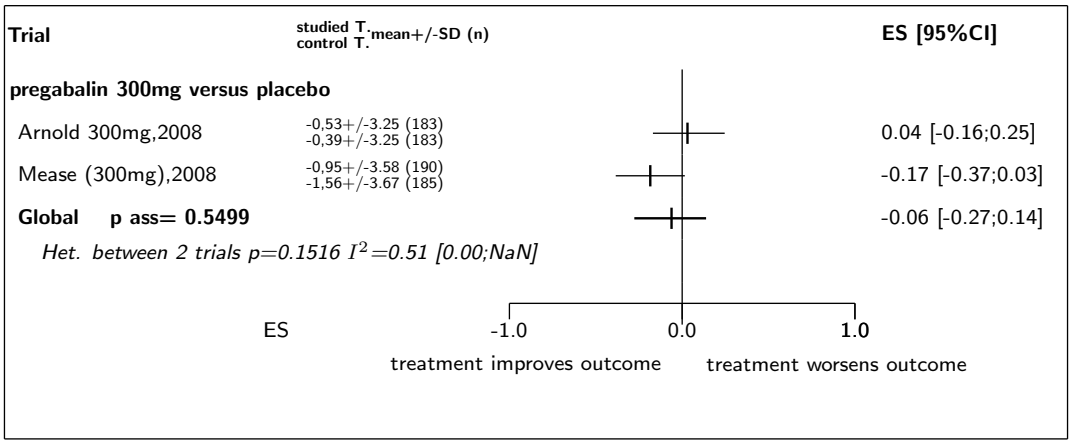


Figure 32.6: *Forest's plot for Anxit*

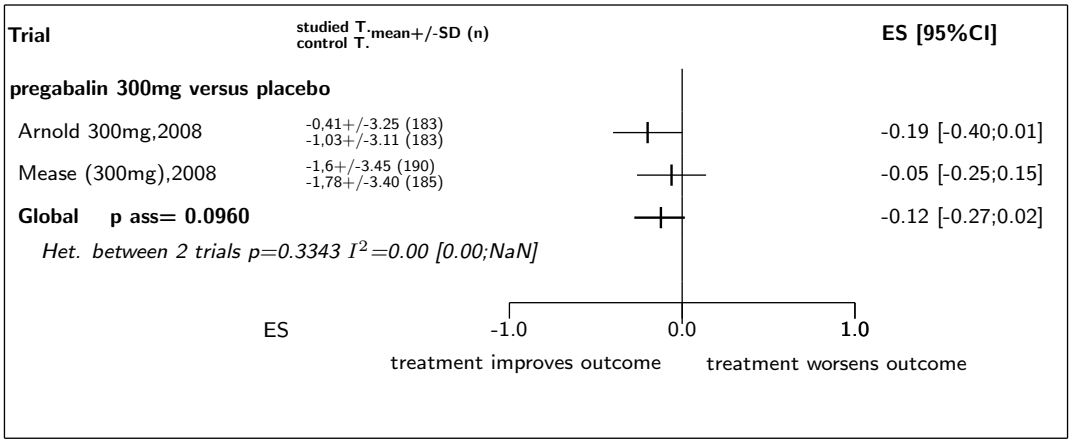


Figure 32.7: *Forest's plot for Sheehan disability scale*

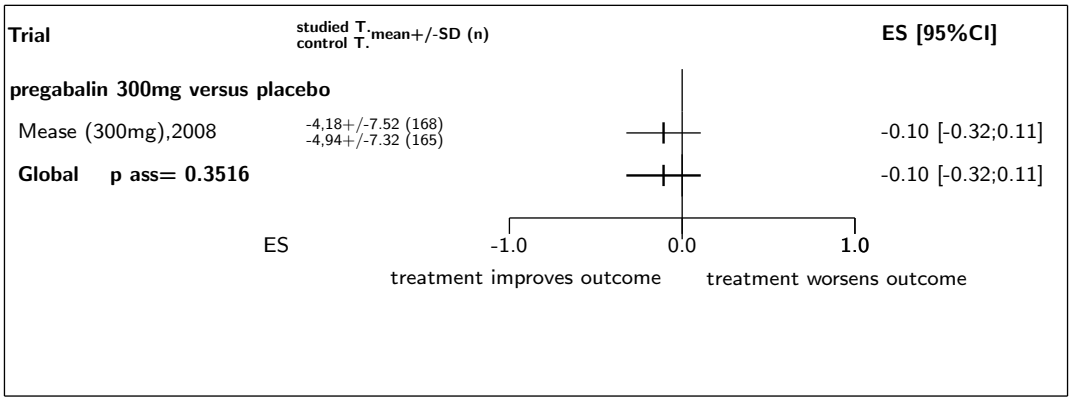


Figure 32.8: *Forest's plot for HAQ functional disability*

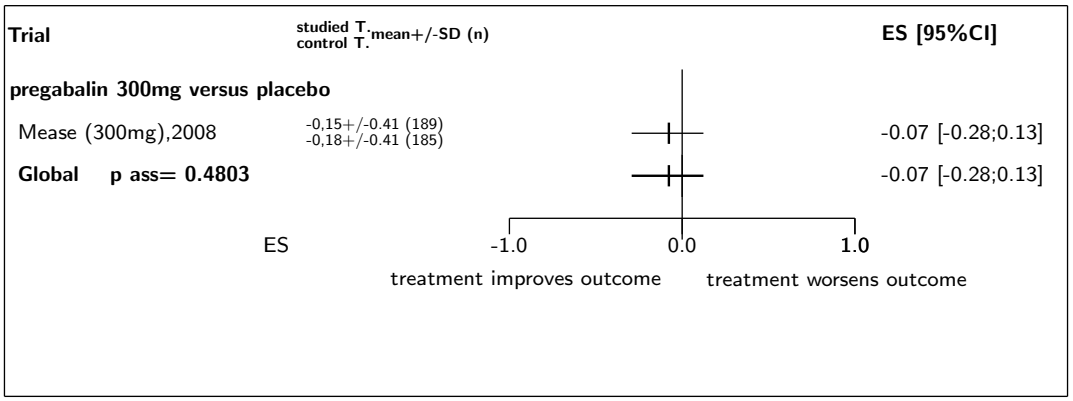


Figure 32.9: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*

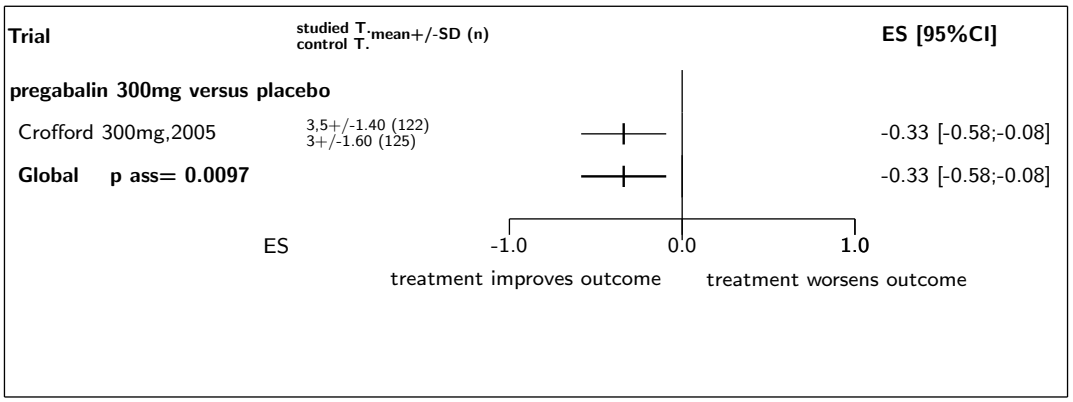


Figure 32.10: *Forest's plot for amlioration globale (clinicien)*

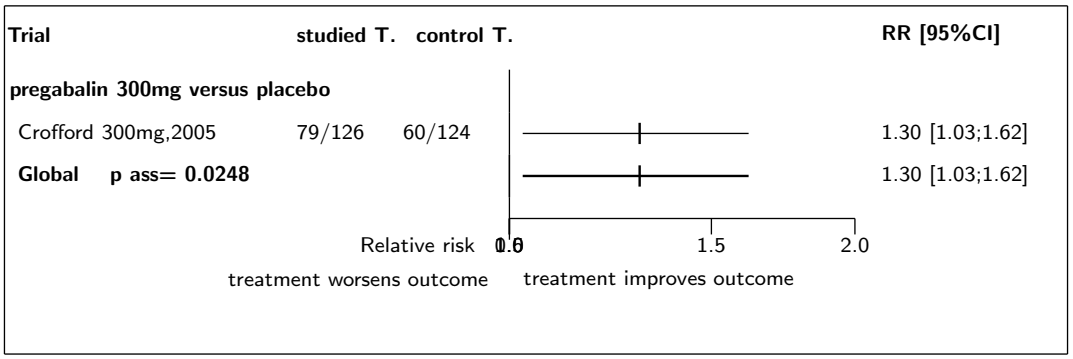
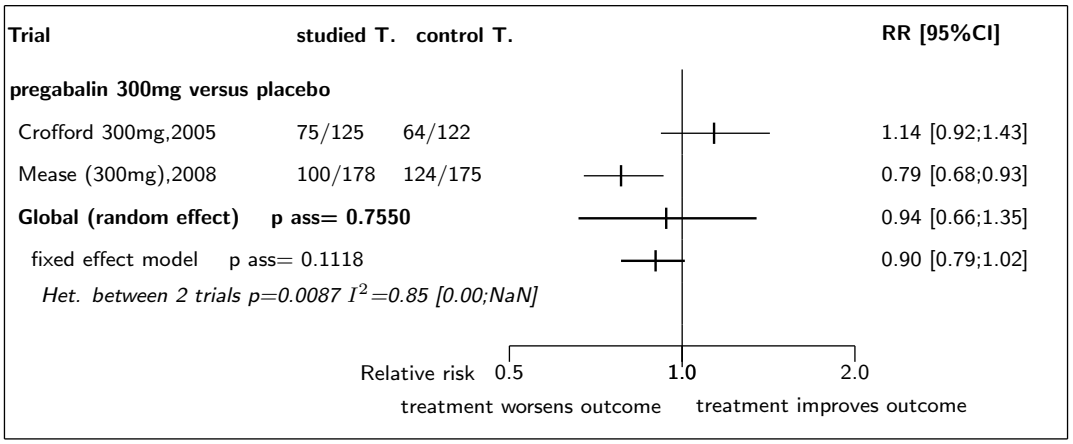


Figure 32.11: *Forest's plot for amlioration globale (patient)*



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33 Detailed results for pregabalin 450mg

33.1 Available trials

A total of 3 RCTs which randomized 1010 patients were identified: all compared pregabalin 450mg with placebo.
The average study size was 336 patients (range 263 to 374). The first study was published in 2005, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Sommeil data was reported in 3 trials; 3 trials reported data on fatigue; 3 trials reported data on douleur; 2 trials reported data on dpression; 2 trials reported data on amlioration globale (patient); 2 trials reported data on FIQ; 2 trials reported data on anxit; 1 trials reported data on amlioration globale (clinicien); 1 trials reported data on HAQ functional disability; 1 trials reported data on sheehan disability scale; and 1 trials reported data on patient Global Impression of Improvement (PGI-I).
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of pregabalin 450mg.

Table 33.1: *Treatment description - pregabalin - pregabalin 450mg*

Trial	Studied treatment	Control treatment
Pregabalin 450mg versus placebo		
Arnold 450mg (2008) [**?**, **?**] [a]	pregabalin 450mg	placebo
Crofford 450mg (2005) [**?**] [b]	Pregabalin 450mg/j	placebo
Mease (450 mg) (2008) [**?**]	pregabalin 450 mg (deux prise par jour)	placebo

a) 4 bras : pregabalin 300 mg/j, 450 mg/j et 600 mg/j b) 4 bras: pregabalin 150, 300, 450 mg/j, placebo

Table 33.2: *Descriptions of participants - pregabalin - pregabalin 450mg*

Trial	Patients
Pregabalin 450mg versus placebo	
Arnold 450mg (2008) [**?**, **?**]	Critres ACR; EVA douleur >=40 mm (/100mm); >= 18 ans
Crofford 450mg (2005) [**?**]	Critres ACR, douleur >=40mm sur une EVA de 100mm, score moyen de douleur >=4 (/10) sur 4 mesure dans la semaine prcdent l'inclusion
Mease (450 mg) (2008) [**?**]	Critres ACR, >=18 ans, score douleur NRS >=4 /11 et VAS >=40mm (/100)

Table 33.3: *Main patients characteristics - pregabalin - pregabalin 450mg*

Trial	Characteristics
Pregabalin 450mg versus placebo	
Arnold 450mg, 2008 [?, ?]	age (mean), years: 50 ans femmes (%): 93.5% critres d'inclusion: ACR nombre de points douloureux: 16.9 fibromyalgia Impact Questionnaire: 59.7 douleur: 6.65 (NRS 0-10) fatigue: 35.8 (MAF) depression: 7 (HADS depression) anxit: 8.7 (HADS anxit)
Crofford 450mg, 2005 [?]	age (mean), years: 48.8 ans femmes (%): 93% critres d'inclusion: ACR douleur: 7 (/10) fatigue: 38.8 (MAF fatigue index global) depression: 8.5 (HADS depression) anxit: 10.1 (HADS anxit)
Mease (450 mg), 2008 [?]	age (mean), years: 49.3 ans femmes (%): 95.2% critres d'inclusion: ACR nombre de points douloureux: 17 (/18) fibromyalgia Impact Questionnaire: 64.3 (0-100) douleur: 7.15 (0-10) fatigue: 8.3 (0-10, FIG fatigue) depression: 8.3 (0-21, HADS) anxit: 9.5 (0-21, HADS)

Table 33.4: *Design and methodological quality of trials - pregabalin - pregabalin 450mg*

Trial	Design	Duration	Centre	Primary endpoint
Pregabalin 450mg versus placebo				
Arnold 450mg, 2008 [?, ?] n=374	Parallel groups double blind	14 semaines inclusion period: oct 2005-jul 2006	US 84 centres	score de douleur, PGIC, FIQ
Crofford 450mg, 2005 [?] n=263	double blind	8 semaines inclusion period: sept 1999 - apr 2000	USA 40 centres	score de douleur
Mease (450 mg), 2008 [?] n=373	double blind	14 semaines	US 79 centres	score douleur NSR

33.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Pregabalin 450mg versus placebo

A total of 2 of the 3 studies eligible for this comparison provided data on **FIQ**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in FIQ, with a ES of -0.20 (95% CI -0.38 to -0.01, p=0.0353). No heterogeneity was detected (p = 0.2054, I^2 = 0.38%).
All the 3 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in douleur, with a ES of -0.39 (95% CI -0.57 to -0.21, p=0.0000). No heterogeneity was detected (p = 0.1245, I^2 = 0.52%).
All the 3 studies had extractable data about the number of participants with **fatigue**. When pooled together, there was no statistically significant difference between the groups in fatigue, with a ES of -0.15 (95% CI -0.31 to 0.01, p=0.0690). No heterogeneity was detected (p = 0.1889, I^2 = 0.40%).
All the 3 studies had extractable data about the number of participants with **sommeil**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in sommeil, with a ES of -0.48 (95% CI -0.66 to -0.29, p=0.0000). No heterogeneity was detected (p = 0.1246, I^2 = 0.52%).
A total of 2 of the 3 studies eligible for this comparison provided data on **dpression**. When pooled together, there was no statistically significant difference between the groups in dpression, with a ES of -0.13 (95% CI -0.27 to 0.02, p=0.0824). No heterogeneity was detected (p = 0.6832, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **anxit**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in anxit, with a ES of -0.16 (95% CI -0.30 to -0.02, p=0.0282). No heterogeneity was detected (p = 0.9412, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **sheehan disability scale**. No statistically significant difference between the groups was found in sheehan disability scale, with a ES of -0.12 (95% CI -0.33 to 0.10, p=0.2894).
Only one of the 3 studies eligible for this comparison provided data on **HAQ functional disability**. No statistically significant difference between the groups was found in HAQ functional disability, with a ES of -0.15 (95% CI -0.35 to 0.06, p=0.1596).
Only one of the 3 studies eligible for this comparison provided data on **patient Global Impression of Improvement (PGI-I)**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in patient Global Impression of Improvement (PGI-I), with a ES of -0.48 (95% CI -0.73 to -0.23, p=0.0000).
Only one of the 3 studies eligible for this comparison provided data on **amlioration globale (clinicien)**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in amlioration globale (clinicien), with a RR of 1.56 (95% CI 1.27 to 1.92, p=0.0000).
A total of 2 of the 3 studies eligible for this comparison provided data on **amlioration globale (patient)**. The analysis detected a statistically significant difference in favor of pregabalin 450mg in amlioration globale (patient), with a RR of 1.34 (95% CI 1.18 to 1.51, p=0.0000). No heterogeneity was detected (p = 0.4371, I^2 = 0.00%).

Table 33.5: *Results details - pregabalin - pregabalin 450mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pregabalin 450mg versus placebo						
FIQ	ES=-0.20	[-0.38;-0.01]	0.0353	0.2054 (I^2=0.38)	2	746
douleur	ES=-0.39	[-0.57;-0.21]	0.0000	0.1245 (I^2=0.52)	3	1004
fatigue	ES=-0.15	[-0.31;0.01]	0.0690	0.1889 (I^2=0.40)	3	985
sommeil	ES=-0.48	[-0.66;-0.29]	0.0000	0.1246 (I^2=0.52)	3	1001

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dpression	ES=-0.13	[-0.27;0.02]	0.0824	0.6832 (I^2=0.00)	2	745
anxit	ES=-0.16	[-0.30;-0.02]	0.0282	0.9412 (I^2=0.00)	2	745
sheehan disability scale	ES=-0.12	[-0.33;0.10]	0.2894	1.0000 (I^2=0.00)	1	326
HAQ functional disability	ES=-0.15	[-0.35;0.06]	0.1596	1.0000 (I^2=0.00)	1	372
patient Global Impression of Improvement (PGI-I)	ES=-0.48	[-0.73;-0.23]	0.0000	1.0000 (I^2=0.00)	1	248
amlioration globale (clinicien)	RR=1.56	[1.27;1.92]	0.0000	1.0000 (I^2=0.00)	1	250
amlioration globale (patient)	RR=1.34	[1.18;1.51]	0.0000	0.4371 (I^2=0.00)	2	599

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 33.1: *Forest's plot for FIQ*

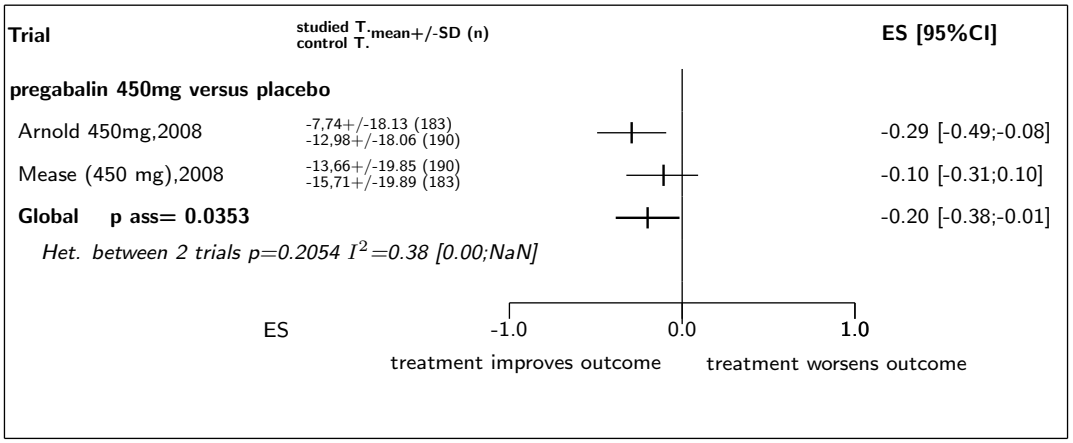


Figure 33.2: *Forest's plot for Douleur*

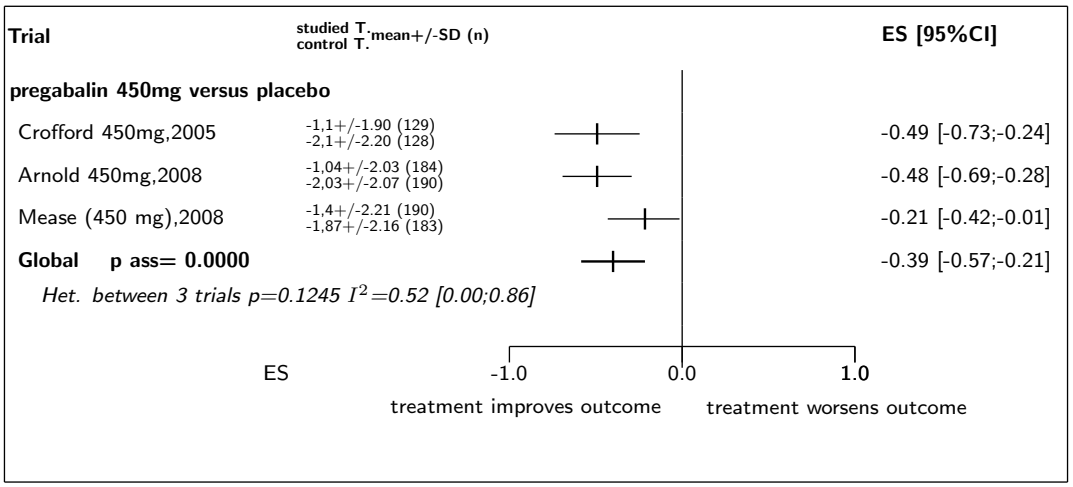


Figure 33.3: *Forest's plot for Fatigue*

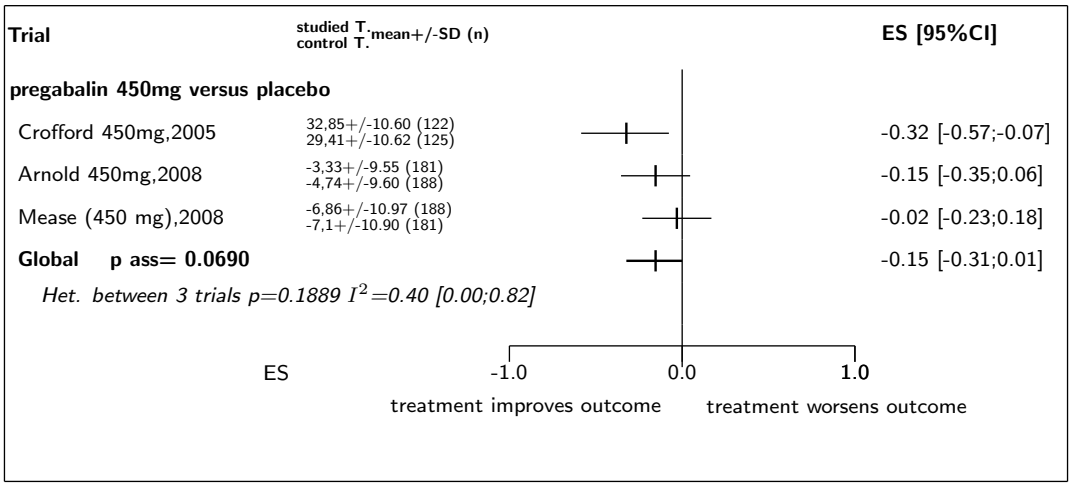


Figure 33.4: *Forest's plot for Sommeil*

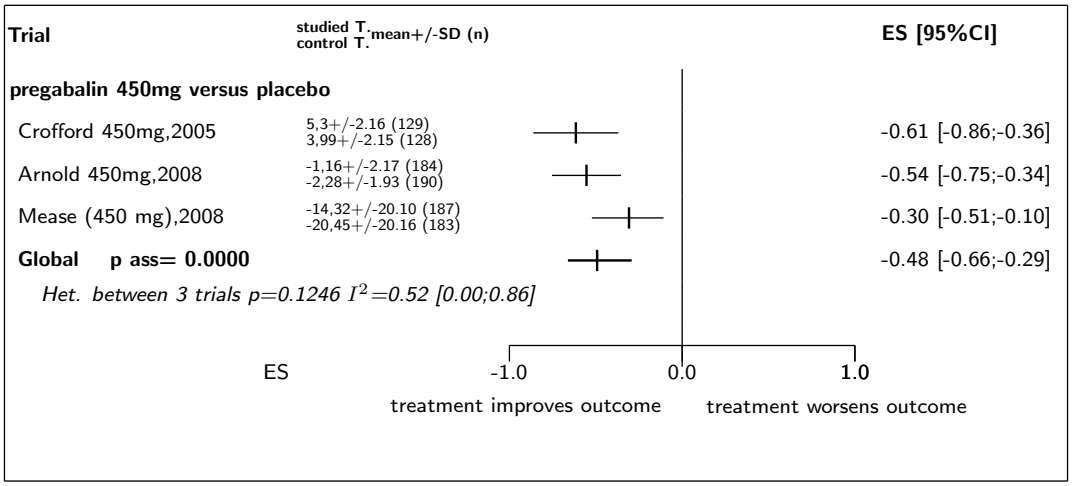


Figure 33.5: *Forest's plot for Dpression*

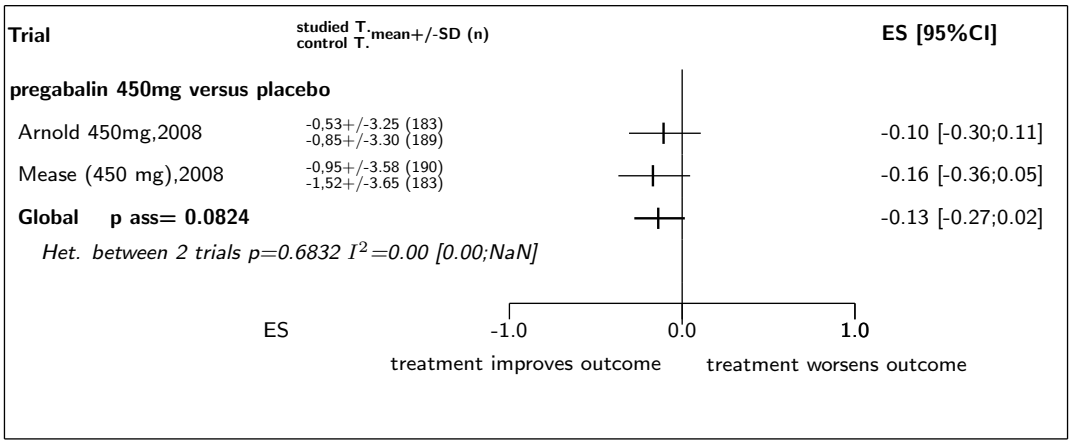


Figure 33.6: *Forest's plot for Anxit*

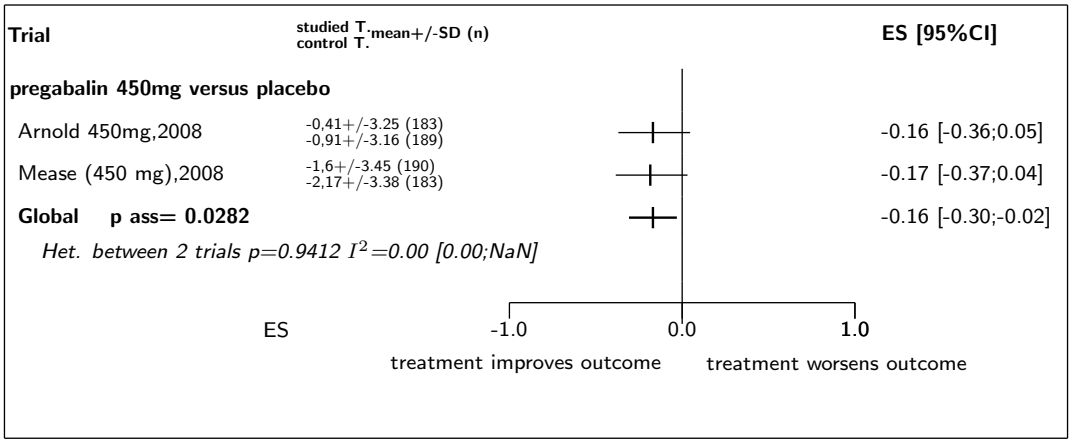


Figure 33.7: *Forest's plot for Sheehan disability scale*

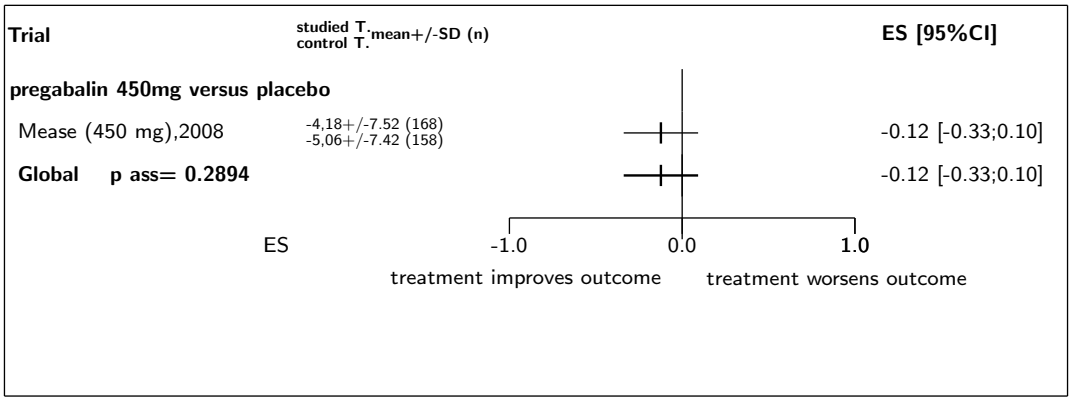


Figure 33.8: *Forest's plot for HAQ functional disability*

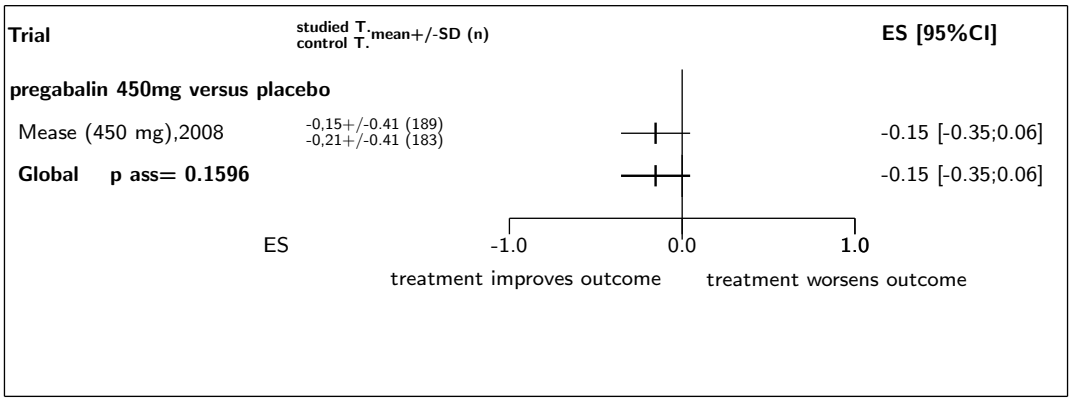


Figure 33.9: *Forest's plot for Patient Global Impression of Improvement (PGI-I)*

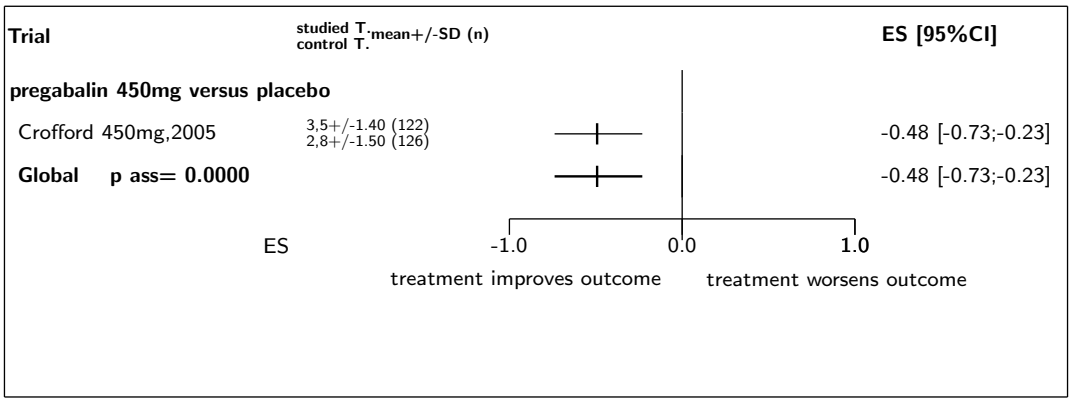


Figure 33.10: *Forest's plot for amlioration globale (clinicien)*

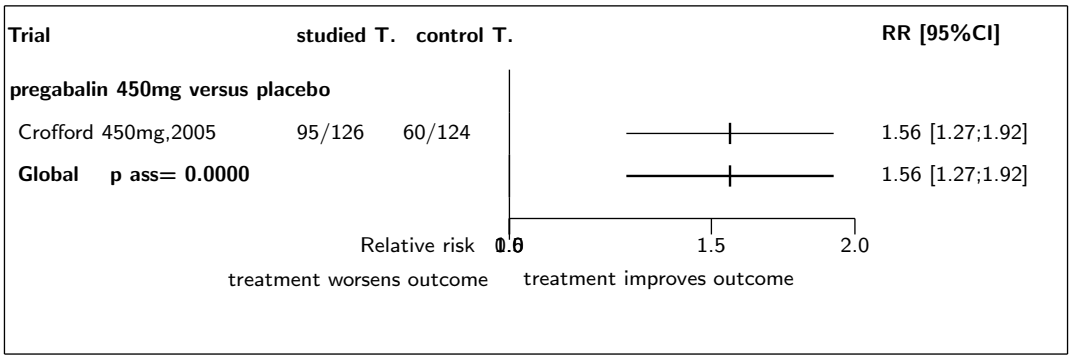
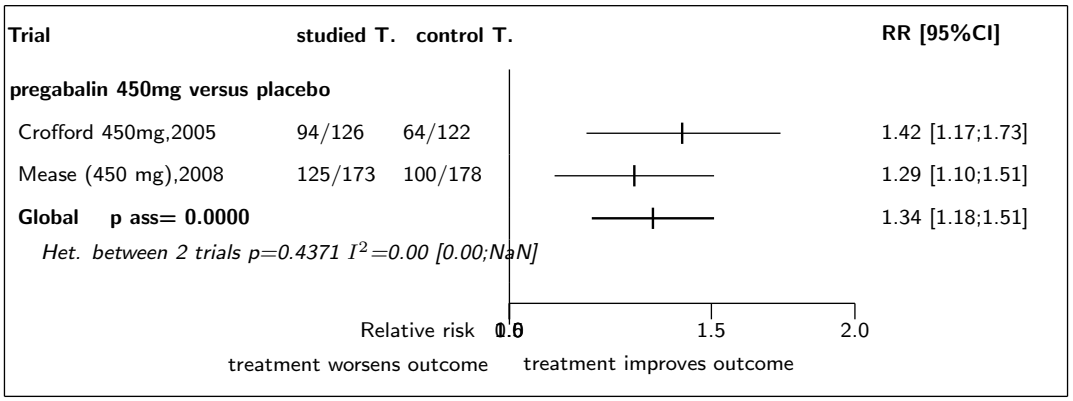


Figure 33.11: *Forest's plot for amlioration globale (patient)*



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[3] Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr, LaMoreaux LK, Martin SA, Sharma U. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264-73. [PMID=15818684]

[4] Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP Jr, Martin SA, Sharma U. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35:502-14. [PMID=18278830]

34 Detailed results for pregabalin 600mg

34.1 Available trials

A total of 2 RCTs which randomized 752 patients were identified: all compared pregabalin 600mg with placebo.
The average study size was 376 patients (range 372 to 380). The first study was published in 2008, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language.
We did not found any unpublished trial.
Dpression data was reported in 2 trials; 2 trials reported data on fatigue; 2 trials reported data on douleur; 2 trials reported data on anxit; 2 trials reported data on sommeil; 2 trials reported data on FIQ; 1 trials reported data on HAQ functional disability; 1 trials reported data on sheehan disability scale; and 1 trials reported data on amlioration globale (patient).
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of pregabalin 600mg.

Table 34.1: *Treatment description - pregabalin - pregabalin 600mg*

Trial	Studied treatment	Control treatment
Pregabalin 600mg versus placebo		
Arnold 600mg (2008) [**?**, **?**] [a]	pregabalin 600mg	placebo
Mease (600mg) (2008) [**?**]	pregabalin 600mg mg (deux prise par jour)	placebo

a) 4 bras : pregabalin 300 mg/j, 450 mg/j et 600 mg/j

Table 34.2: *Descriptions of participants - pregabalin - pregabalin 600mg*

Trial	Patients
Pregabalin 600mg versus placebo	
Arnold 600mg (2008) [**?**, **?**]	Critres ACR; EVA douleur >=40 mm (/100mm); >= 18 ans
Mease (600mg) (2008) [**?**]	Critres ACR, >=18 ans, score douleur NRS >=4 /11 et VAS >=40mm (/100)

Table 34.3: *Main patients characteristics - pregabalin - pregabalin 600mg*

Trial	Characteristics
Pregabalin 600mg versus placebo	
Arnold 600mg, 2008 [?, ?]	age (mean), years: 50 ans femmes (%): 93.5% critres d'inclusion: ACR nombre de points douloureux: 16.9 fibromyalgia Impact Questionnaire: 59.7 douleur: 6.65 (NRS 0-10) fatigue: 35.8 (MAF) depression: 7 (HADS depression) anxit: 8.7 (HADS anxit)
Mease (600mg), 2008 [?]	age (mean), years: 49.3 ans femmes (%): 95.2% critres d'inclusion: ACR nombre de points douloureux: 17 (/18) fibromyalgia Impact Questionnaire: 64.3 (0-100) douleur: 7.15 (0-10) fatigue: 8.3 (0-10, FIG fatigue) depression: 8.3 (0-21, HADS) anxit: 9.5 (0-21, HADS)

Table 34.4: *Design and methodological quality of trials - pregabalin - pregabalin 600mg*

Trial	Design	Duration	Centre	Primary endpoint
Pregabalin 600mg versus placebo				
Arnold 600mg, 2008 [?, ?] n=372	Parallel groups double blind confirmatory trial at low risk of bias	14 weeks inclusion period: oct 2005-jul 2006	US 84 centres	score de douleur
Mease (600mg), 2008 [?] n=380	double blind	14 semaines	US 79 centres	score douleur NSR

34.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Pregabalin 600mg versus placebo

All the 2 studies had extractable data about the number of participants with **FIQ**. When pooled together, there was no statistically significant difference between the groups in FIQ, with a ES of -0.18 (95% CI -0.40 to 0.05, p=0.1286). No heterogeneity was detected (p = 0.1132, I^2 = 0.60%).
All the 2 studies had extractable data about the number of participants with **douleur**. The analysis detected a statistically significant difference in favor of pregabalin 600mg in douleur, with a ES of -0.39 (95% CI -0.59 to -0.20, p=0.0000). No heterogeneity was detected (p = 0.1863, I^2 = 0.43%).

All the 2 studies had extractable data about the number of participants with **fatigue**. When pooled together, there was no statistically significant difference between the groups in fatigue, with a ES of -0.11 (95% CI -0.26 to 0.03, p=0.1275). No heterogeneity was detected (p = 0.5473, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **sommeil**. The analysis detected a statistically significant difference in favor of pregabalin 600mg in sommeil, with a ES of -0.45 (95% CI -0.82 to -0.07, p=0.0187). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0106, I^2 = 0.85%).
All the 2 studies had extractable data about the number of participants with **dpression**. When pooled together, there was no statistically significant difference between the groups in dpression, with a ES of -0.12 (95% CI -0.26 to 0.02, p=0.1011). No heterogeneity was detected (p = 0.6422, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **anxit**. The analysis detected a statistically significant difference in favor of pregabalin 600mg in anxit, with a ES of -0.18 (95% CI -0.32 to -0.04, p=0.0131). No heterogeneity was detected (p = 0.4053, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **sheehan disability scale**. No statistically significant difference between the groups was found in sheehan disability scale, with a ES of -0.13 (95% CI -0.35 to 0.09, p=0.2479).
Only one of the 2 studies eligible for this comparison provided data on **HAQ functional disability**. No statistically significant difference between the groups was found in HAQ functional disability, with a ES of -0.10 (95% CI -0.30 to 0.10, p=0.3435).
Only one of the 2 studies eligible for this comparison provided data on **amlioration globale (patient)**. The analysis detected a statistically significant difference in favor of pregabalin 600mg in amlioration globale (patient), with a RR of 1.22 (95% CI 1.04 to 1.44, p=0.0172).

Table 34.5: *Results details - pregabalin - pregabalin 600mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pregabalin 600mg versus placebo						
FIQ	ES=-0.18	[-0.40;0.05]	0.1286	0.1132 (I^2=0.60)	2	751
douleur	ES=-0.39	[-0.59;-0.20]	0.0000	0.1863 (I^2=0.43)	2	752
fatigue	ES=-0.11	[-0.26;0.03]	0.1275	0.5473 (I^2=0.00)	2	744
sommeil	ES=-0.45	[-0.82;-0.07]	0.0187	0.0106 (I^2=0.85)	2	746
dpression	ES=-0.12	[-0.26;0.02]	0.1011	0.6422 (I^2=0.00)	2	751
anxit	ES=-0.18	[-0.32;-0.04]	0.0131	0.4053 (I^2=0.00)	2	751
sheehan disability scale	ES=-0.13	[-0.35;0.09]	0.2479	1.0000 (I^2=1.00)	1	326
HAQ functional disability	ES=-0.10	[-0.30;0.10]	0.3435	1.0000 (I^2=0.00)	1	379
amlioration globale (patient)	RR=1.22	[1.04;1.44]	0.0172	1.0000 (I^2=0.00)	1	353

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 34.1: *Forest's plot for FIQ*

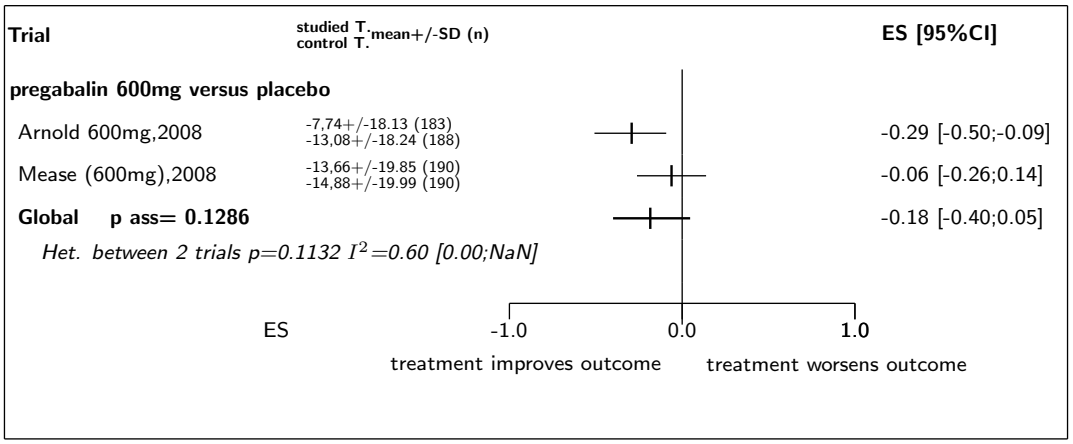


Figure 34.2: *Forest's plot for Douleur*

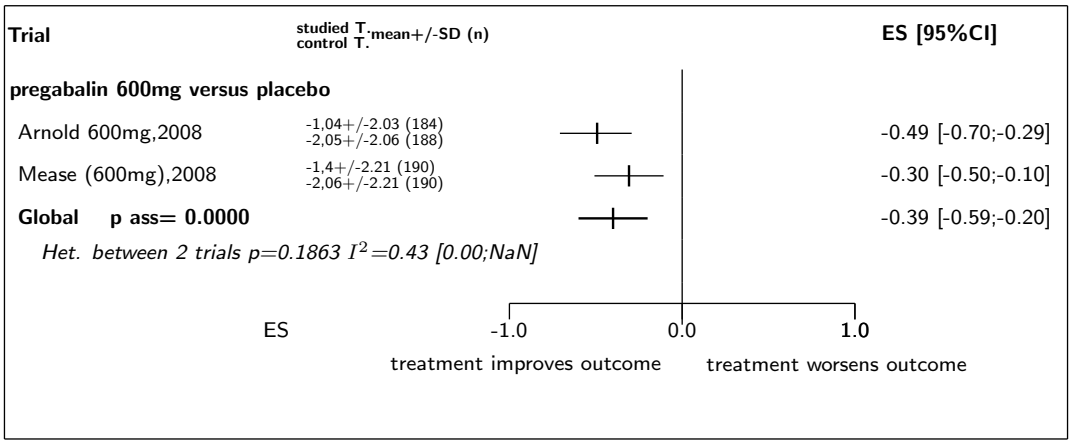


Figure 34.3: *Forest's plot for Fatigue*

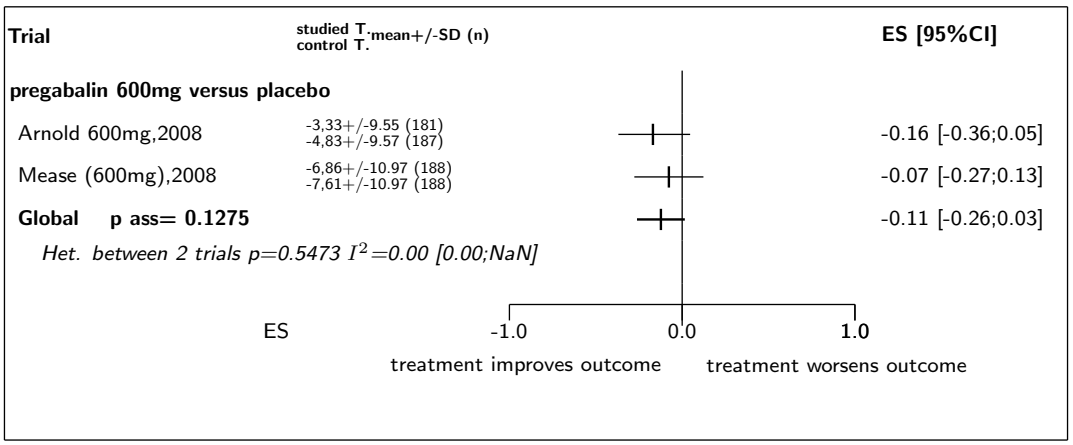


Figure 34.4: *Forest's plot for Sommeil*

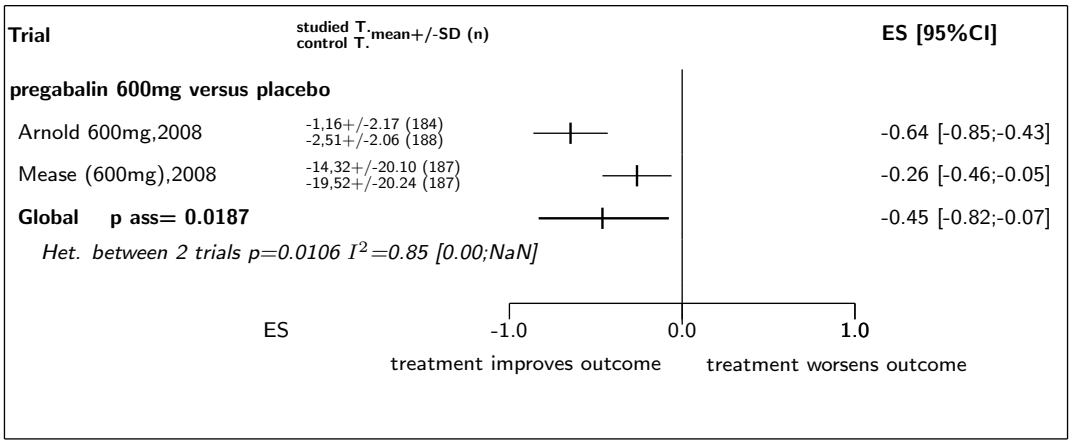


Figure 34.5: *Forest's plot for Dpression*

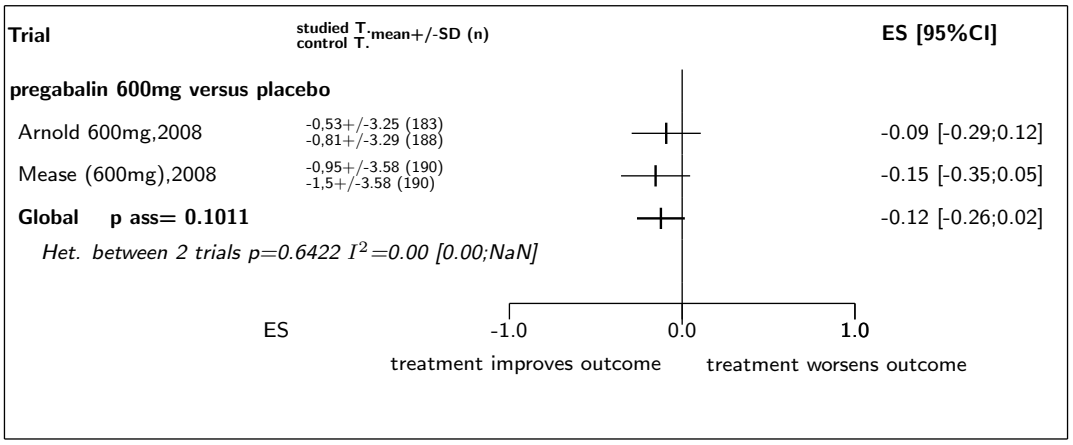


Figure 34.6: *Forest's plot for Anxit*

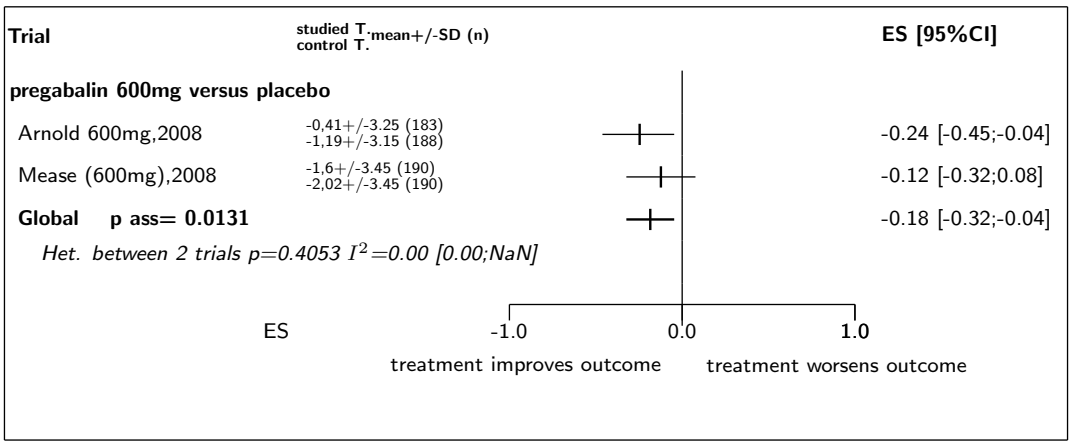


Figure 34.7: *Forest's plot for Sheehan disability scale*

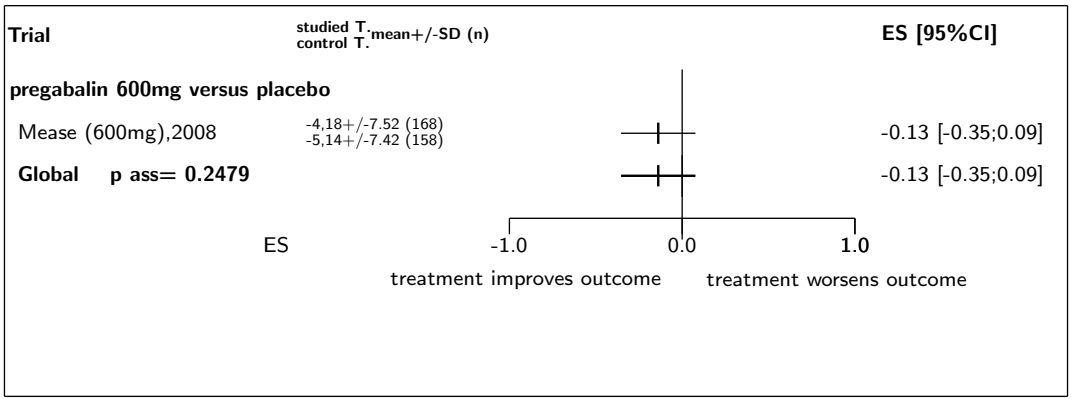


Figure 34.8: *Forest's plot for HAQ functional disability*

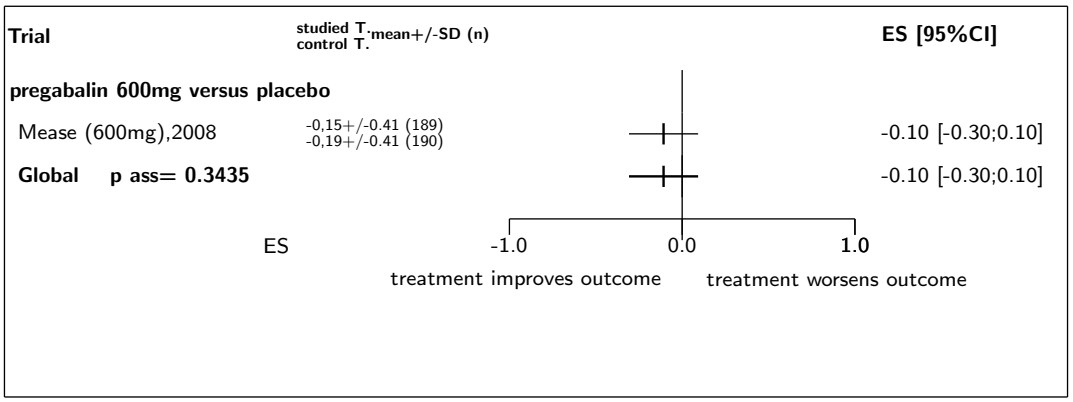
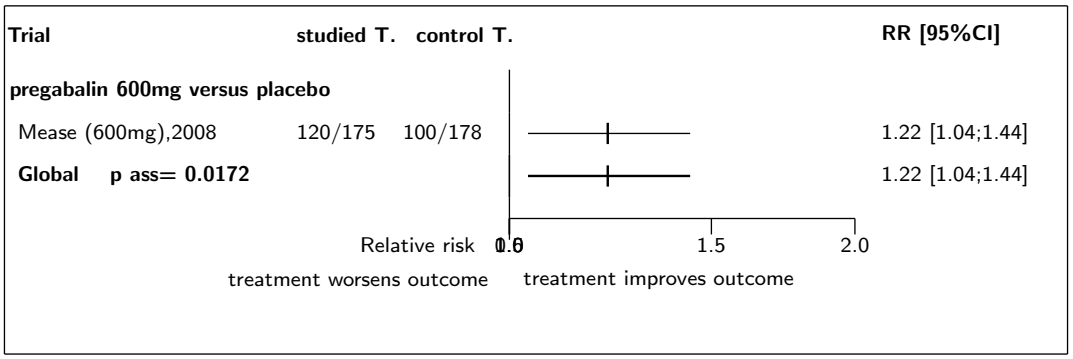


Figure 34.9: *Forest's plot for amlioration globale (patient)*



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[1] Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP Jr, Sharma U, Martin SA, Barrett JA, Haig G. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain 2008;9:792-805. [PMID=18524684]

[2] Duan R, Diri E, Young JP, et al. Efficacy of pregablin monotherapy for relief of pain associated with fibromyalgia: time course and durability of pain results of a 14-week, double-blind, placebo-controlled trial. ACR/ARHP 2007 meeting, Boston.

[3] Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP Jr, Martin SA, Sharma U. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35:502-14. [PMID=18278830]

35 Global meta-analysis: all pregabalin

35.1 Global meta-analysis: all pregabalin versus placebo

Table 35.1: *All pregabalinversus placebo*

Endpoint	**Effect**	**95% CI**	**p ass**	**p het (I^2)**	**k**	**n**
FIQ	ES=-0.17	-0.25;-0.09	0.0000	0.4892 (0.00)	6	2238
douleur	ES=-0.32	-0.41;-0.23	0.0000	0.1374 (0.35)	9	3021
fatigue	ES=-0.15	-0.23;-0.08	0.0000	0.6037 (0.00)	9	2958
sommeil	ES=-0.38 [1]	-0.49;-0.27	0.0000	0.0175 (0.57) †	9	3010
dpression	ES=-0.10	-0.19;-0.02	0.0143	0.7170 (0.00)	6	2237
anxit	ES=-0.16	-0.24;-0.07	0.0000	0.8541 (0.00)	6	2237
sheehan disability scale	ES=-0.12	-0.24;0.01	0.0694	0.9860 (0.00)	3	985
HAQ functional disability	ES=-0.11	-0.22;0.01	0.0775	0.8793 (0.00)	3	1125
patient Global Impression of Improvement (PGI-I)	ES=-0.32	-0.51;-0.12	0.0000	0.1641 (0.45)	3	742
amlioration globale (clinicien)	RR=1.36	1.16;1.58	0.0000	0.2434 (0.29)	3	749
amlioration globale (patient)	RR=1.15 [2]	0.96;1.37	0.1242	0.0001 (0.82) †	6	1799

legend B

[1] with a random model ($\tau^2 = 0.016$). The results with a fixed effect model was RRFE=-0.38 95% CI -0.45;-0.30
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.13 95% CI 1.05;1.22

36 Ongoing studies of pregabalin

A total of 2 ongoing studies were still ongoing at the date of this report. A list of these ongoing studies with a brief description is given table **??**.

Table 36.1: *Ongoing studies for pregabalin*

Study	**Description**
Pauer (non US study) [**?**, **?**, **?**]	pregabalin 300mg **vs.** placebo ACR 1990; EVA douleur >=40mm (0-100mm)
Abeles [**?**]	pregabalin **vs.** traitement standard (suivant les prfrence habituelles du mdecin) NA

37 Excluded studies for pregabalin

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 37.1: *Excluded studies of pregabalin*

Study	**Exclusion reason**
FREEDOM (Crofford) 300mg (2008) [**?**, **?**, **?**]	essai au design spcifique non comparable et non agrgeable aux autres essais. Les mesures n'ont t faites que durant la priode avant l'chappement thrapeutique. Les rsultats obtenus sur les scores et chelles ne sont donc pas comparable ceux des autres tudes mesurs pour tous les patients en fin d'essai.

Part VIII

Sedative hypnotics

38 Overview of sedative hypnotics

No completed trial meeting the eligibility criteria was available.

39 Ongoing studies of Sedative hypnotics

No ongoing trial was identified.

40 Excluded studies for Sedative hypnotics

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 40.1: *Excluded studies of Sedative hypnotics*

Study	Exclusion reason
Gronblad (1993) [**?**]	

Part IX

Tramadol

41 Overview of tramadol

41.1 Included trials

A total of 3 randomized comparisons which enrolled 422 patients were identified. In all, 2 randomized comparisons concerned tramadol and one tramadol/acetaminophen.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for tramadol and in section **??** (page **??**) for tramadol/acetaminophen.

The average study size was 140 patients (range 40 to 313). The first study was published in 2000, and the last study was published in 2006.
All trials were double blind in design. All included studies were reported in English language. We found one unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

41.2 Summary of meta-analysis results

The meta-analysis of the available trials about tramadol provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

41.2.1 Tramadol

Tramadol was superior to **placebo** in terms of douleur (ES=-0.49, 95% CI -0.97 to -0.01, p=0.0454, 1 trial).
However, no significant difference was found on FIQ (ES=-0.15, 95% CI -0.62 to 0.32, p=0.5280, 1 trial).

41.2.2 Tramadol/acetaminophen

Tramadol/acetaminophen was superior to **placebo** in terms of FIQ (ES=-0.37, 95% CI -0.60 to -0.15, p=0.0000, 1 trial), douleur (ES=-0.39, 95% CI -0.62 to -0.17, p=0.0000, 1 trial)and anxit (ES=-0.27, 95% CI -0.49 to -0.04, p=0.0191, 1 trial).
However, no significant difference was found on points douloureux (nombre) (ES=-0.22, 95% CI -0.44 to 0.01, p=0.0562, 1 trial), fatigue (ES=-0.12, 95% CI -0.35 to 0.10, p=0.2705, 1 trial), sommeil (ES=0.00, 95% CI -0.22 to 0.22, p=1.0000, 1 trial)and dpression (ES=-0.13, 95% CI -0.35 to 0.09, p=0.2477, 1 trial).

Table 41.1: *Main study characteristics - tramadol*

Trial	Patients	Treatments	Trial design and method
Tramadol			
Tramadol versus placebo			
Gur, 2006 [**?**] n = 20 vs. 20	femmes	tramadol faible dose (100mg/j) **versus** placebo	simple aveugle parallel groups Turquie
Russell, 2000 [**?**] n = 35 vs. 34	ACR 1990	tramadol 50-400mg **versus** placebo	double blind parallel groups Primary endpoint: time to exit because inadequate pain relief 5 centres,USA
Tramadol/acetaminophen			
Tramadol/acetaminophen versus placebo			
Bennett, 2003 [**?**, **?**] n = 156 vs. 157	critres ACR, VAS douleur >=40mm (/100)	association tramadol 37.5 mg acetaminophen 325 mg **versus** placebo	double blind parallel groups 27 centres,

Table 41.2: *Summary of all results for tramadol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
tramadol versus placebo						
FIQ	ES=-0.15	-0.62;0.32	0.5280	1.0000 (0.00)	1	69
douleur	ES=-0.49	-0.97;-0.01	0.0454	1.0000 (0.00)	1	69
amlioration globale (patient)	RR=2.02	1.27;3.21	0.0030	1.0000 (0.00)	1	69

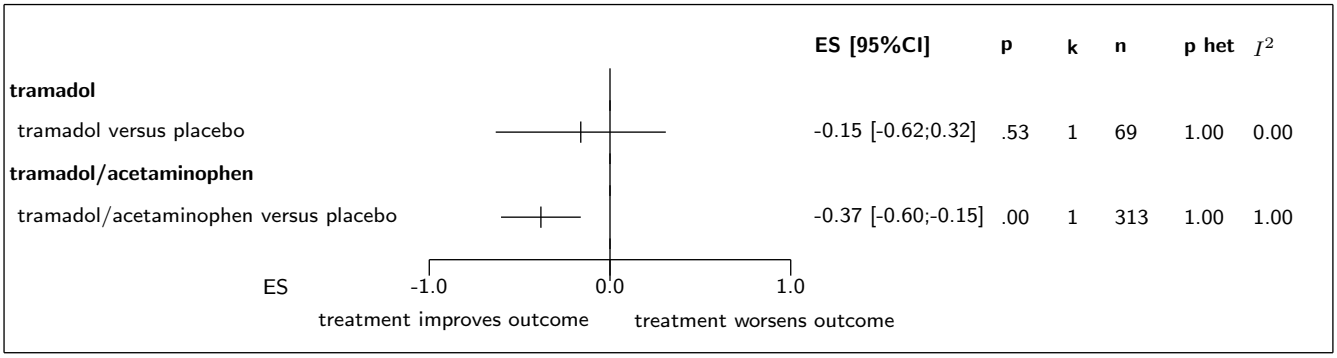
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 41.3: *Summary of all results for tramadol/acetaminophen*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
tramadol/acetaminophen versus placebo						
FIQ	ES=-0.37	-0.60;-0.15	0.0000	1.0000 (1.00)	1	313
douleur	ES=-0.39	-0.62;-0.17	0.0000	1.0000 (0.00)	1	313
points douloureux (nombre)	ES=-0.22	-0.44;0.01	0.0562	1.0000 (1.00)	1	313
fatigue	ES=-0.12	-0.35;0.10	0.2705	1.0000 (0.00)	1	313
sommeil	ES=0.00	-0.22;0.22	1.0000	1.0000 (0.00)	1	313
dpression	ES=-0.13	-0.35;0.09	0.2477	1.0000 (0.00)	1	313
anxit	ES=-0.27	-0.49;-0.04	0.0191	1.0000 (0.00)	1	313

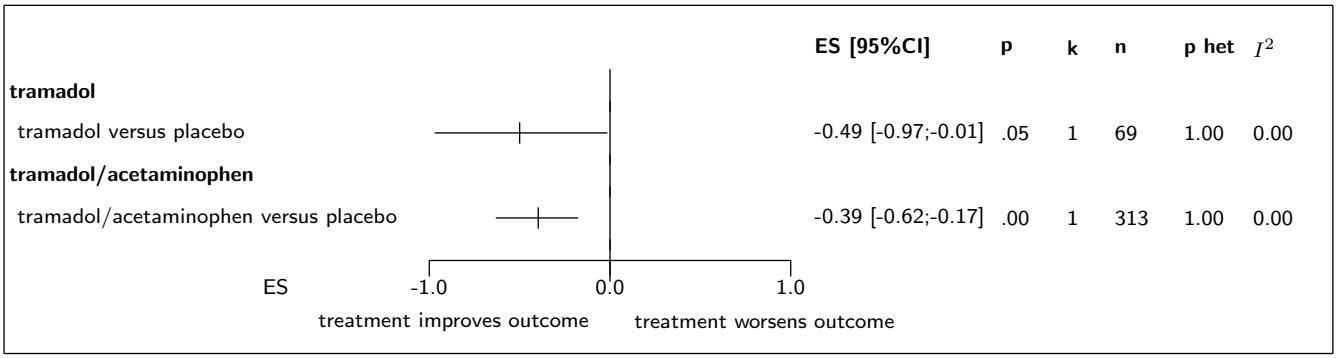
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 41.1: *Forest's plot for FIQ*



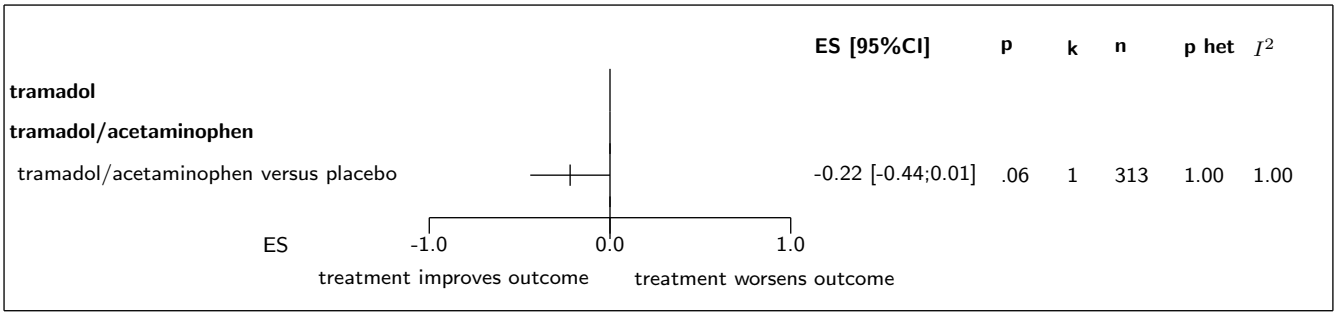
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.2: *Forest's plot for douleur*



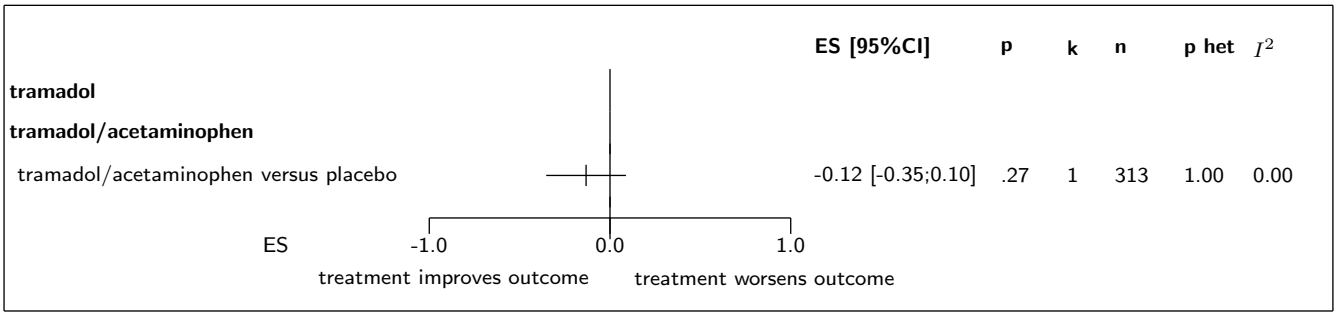
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.3: *Forest's plot for points douloureux (nombre)*



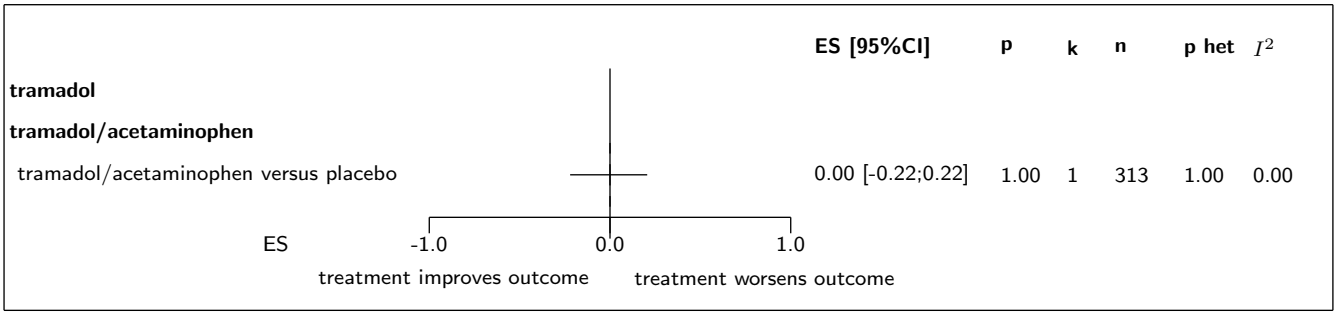
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.4: *Forest's plot for fatigue*



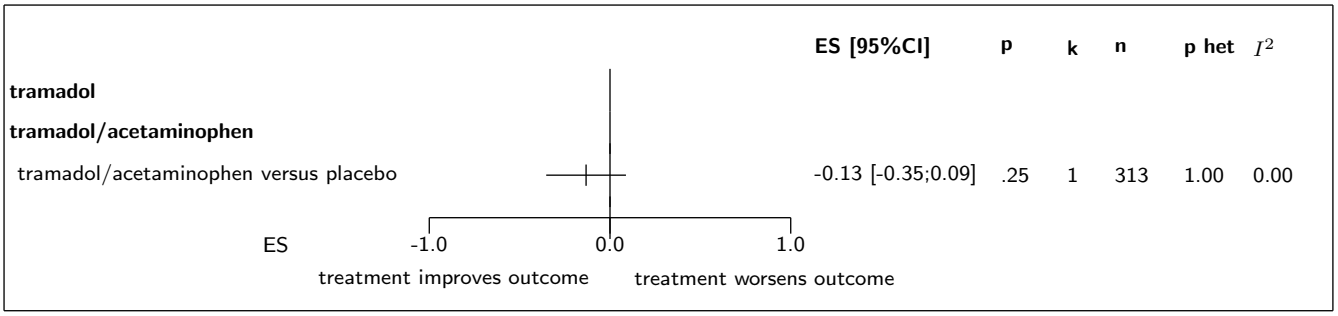
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.5: *Forest's plot for sommeil*



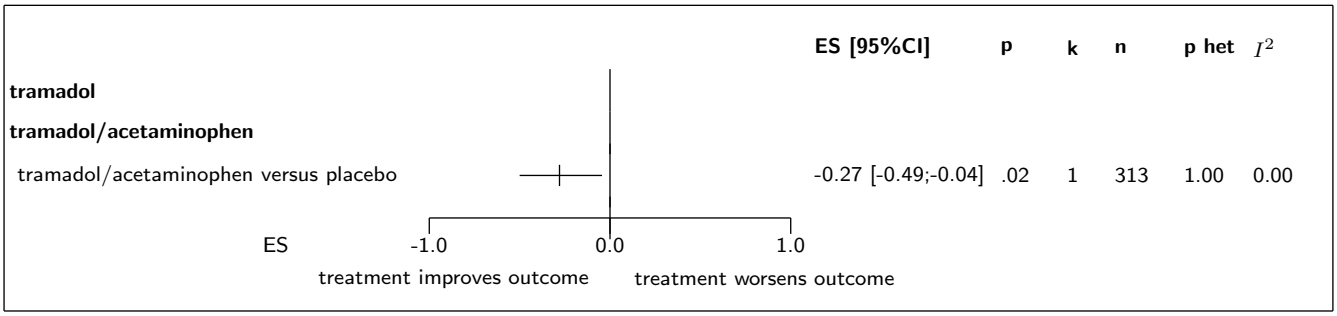
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.6: *Forest's plot for dpression*



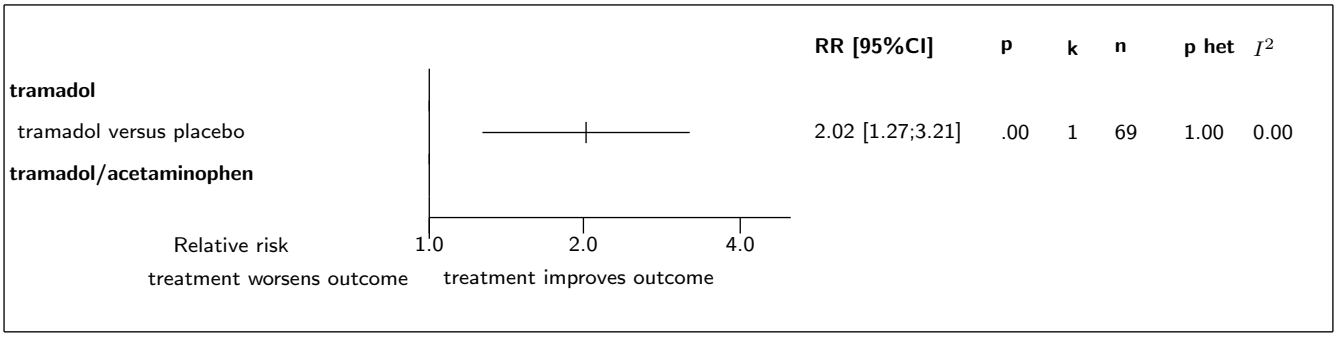
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.7: *Forest's plot for anxit*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 41.8: *Forest's plot for amlioration globale (patient)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

42 Detailed results for tramadol

42.1 Available trials

A total of 2 RCTs which randomized 109 patients were identified: all compared tramadol with placebo.
The average study size was 54 patients (range 40 to 69). The first study was published in 2000, and the last study was published in 2006.
This trial was double blind in design.
All included studies were reported in English language. We found one unpublished trial.
Amlioration globale (patient) data was reported in 1 trials; 1 trials reported data on douleur; and 1 trials reported data on FIQ.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of tramadol.

Table 42.1: *Treatment description - tramadol - tramadol*

Trial	Studied treatment	Control treatment
Tramadol versus placebo		
Gur (2006) [**?**]	tramadol faible dose (100mg/j)	placebo
Russell (2000) [**?**]	tramadol 50-400mg	placebo

Table 42.2: *Descriptions of participants - tramadol - tramadol*

Trial	Patients
Tramadol versus placebo	
Gur (2006) [**?**]	Femmes
Russell (2000) [**?**]	ACR 1990

Table 42.3: *Main patients characteristics - tramadol - tramadol*

Trial	Characteristics
Tramadol versus placebo	
Gur, 2006 [**?**]	femmes (%): 100% critres d'inclusion: ND
Russell, 2000 [**?**]	age (mean), years: 48.8y femmes (%): 94.2% critres d'inclusion: ACR 1990 nombre de points douloureux: 15.1 fibromyalgia Impact Questionnaire: 34.7 douleur: 4 (/10)

Table 42.4: *Design and methodological quality of trials - tramadol - tramadol*

Trial	Design	Duration	Centre	Primary endpoint
Tramadol versus placebo				
Gur, 2006 [**?**] n=40	Parallel groups simple aveugle	3 mois	Turquie	
Russell, 2000 [**?**] n=69	Parallel groups double blind	6 semaines	USA 5 centres	time to exit because inadequate pain relief

42.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Tramadol versus placebo

Only one of the 2 studies eligible for this comparison provided data on **FIQ**. No statistically significant difference between the groups was found in FIQ, with a ES of -0.15 (95% CI -0.62 to 0.32, p=0.5280).
Only one of the 2 studies eligible for this comparison provided data on **douleur**. The analysis detected a statistically significant difference in favor of tramadol in douleur, with a ES of -0.49 (95% CI -0.97 to -0.01, p=0.0454).
Only one of the 2 studies eligible for this comparison provided data on **amlioration globale (patient)**. The analysis detected a statistically significant difference in favor of tramadol in amlioration globale (patient), with a RR of 2.02 (95% CI 1.27 to 3.21, p=0.0030).

Table 42.5: *Results details - tramadol - tramadol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
tramadol versus placebo						
FIQ	ES=-0.15	[-0.62;0.32]	0.5280	1.0000 (I^2=0.00)	1	69
douleur	ES=-0.49	[-0.97;-0.01]	0.0454	1.0000 (I^2=0.00)	1	69
amlioration globale (patient)	RR=2.02	[1.27;3.21]	0.0030	1.0000 (I^2=0.00)	1	69

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 42.1: *Forest's plot for FIQ*

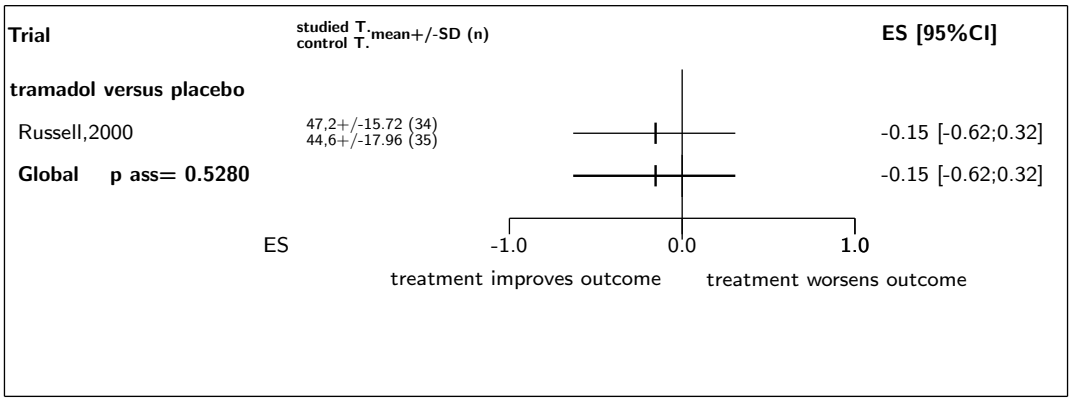


Figure 42.2: *Forest's plot for Douleur*

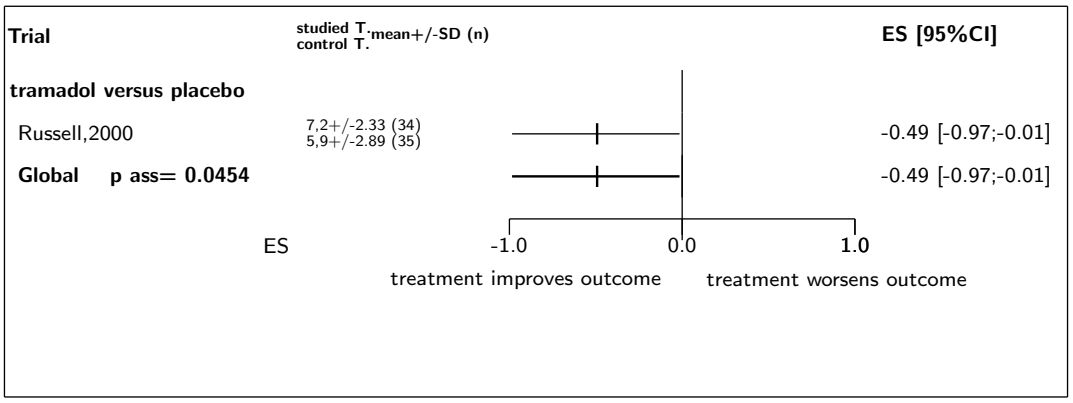
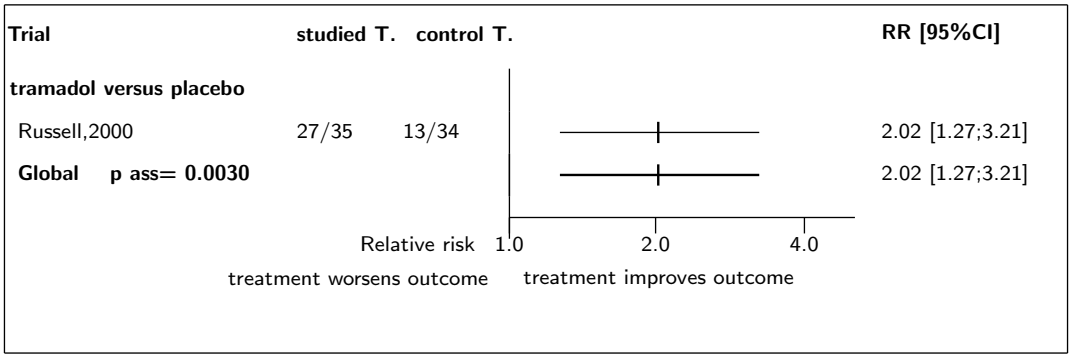


Figure 42.3: *Forest's plot for amlioration globale (patient)*



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[1] Gur A, Calgan N, Nas K, Cevik R, Sarac AJ. Low dose of tramadol in the treatment of fibromyalgia syndrome: a controlled clinical trial versus placebo.European League against Rheumatism; Amsterdam; 2006. Ann Rheum Dis 2006;65(Suppl II):556.

[2] Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of Tramadol in Treatment of Pain in Fibromyalgia. J Clin Rheumatol 2000 Oct;6:250-257. [PMID=19078481]

43 Detailed results for tramadol/acetaminophen

43.1 Available trials

Only one trial which randomized 313 patients was identified: it compared tramadol/acetaminophen with placebo.
This trial included 313 patients and was published in 2003.
This trial was double blind in design.
It was reported in English language.
Anxit data was reported in 1 trials; 1 trials reported data on sommeil; 1 trials reported data on fatigue; 1 trials reported data on douleur; 1 trials reported data on dpression; 1 trials reported data on points douloureux (nombre); and 1 trials reported data on FIQ.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of tramadol/acetaminophen.

Table 43.1: *Treatment description - tramadol - tramadol/acetaminophen*

Trial	Studied treatment	Control treatment
Tramadol/acetaminophen versus placebo		
Bennett (2003) [?, ?]	association tramadol 37.5 mg acetaminophen 325 mg	placebo

Table 43.2: *Descriptions of participants - tramadol - tramadol/acetaminophen*

Trial	Patients
Tramadol/acetaminophen versus placebo	
Bennett (2003) [?, ?]	Critres ACR, VAS douleur >=40mm (/100)

Table 43.3: *Main patients characteristics - tramadol - tramadol/acetaminophen*

Trial	Characteristics
Tramadol/acetaminophen versus placebo	
Bennett, 2003 [?, ?]	age (mean), years: 50y femmes (%): 94% critres d'inclusion: ACR nombre de points douloureux: 16 douleur: 72 (/100)

Table 43.4: *Design and methodological quality of trials - tramadol - tramadol/acetaminophen*

Trial	Design	Duration	Centre	Primary endpoint
Tramadol/acetaminophen versus placebo				
Bennett, 2003 [?, ?] n=313	Parallel groups double blind	91 jours	27 centres	

43.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Tramadol/acetaminophen versus placebo

The single study eligible for this comparison provided data on **FIQ**. The analysis detected a statistically significant difference in favor of tramadol/acetaminophen in FIQ, with a ES of -0.37 (95% CI -0.60 to -0.15, p=0.0000).
The single study eligible for this comparison provided data on **douleur**. The analysis detected a statistically significant difference in favor of tramadol/acetaminophen in douleur, with a ES of -0.39 (95% CI -0.62 to -0.17, p=0.0000).
The single study eligible for this comparison provided data on **points douloureux (nombre)**. No statistically significant difference between the groups was found in points douloureux (nombre), with a ES of -0.22 (95% CI -0.44 to 0.01, p=0.0562).
The single study eligible for this comparison provided data on **fatigue**. No statistically significant difference between the groups was found in fatigue, with a ES of -0.12 (95% CI -0.35 to 0.10, p=0.2705).
The single study eligible for this comparison provided data on **sommeil**. No statistically significant difference between the groups was found in sommeil, with a ES of 0.00 (95% CI -0.22 to 0.22, p=1.0000).
The single study eligible for this comparison provided data on **dpression**. No statistically significant difference between the groups was found in dpression, with a ES of -0.13 (95% CI -0.35 to 0.09, p=0.2477).
The single study eligible for this comparison provided data on **anxit**. The analysis detected a statistically significant difference in favor of tramadol/acetaminophen in anxit, with a ES of -0.27 (95% CI -0.49 to -0.04, p=0.0191).

Table 43.5: *Results details - tramadol - tramadol/acetaminophen*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
tramadol/acetaminophen versus placebo						
FIQ	ES=-0.37	[-0.60;-0.15]	0.0000	1.0000 (I^2=1.00)	1	313
douleur	ES=-0.39	[-0.62;-0.17]	0.0000	1.0000 (I^2=0.00)	1	313
points douloureux (nombre)	ES=-0.22	[-0.44;0.01]	0.0562	1.0000 (I^2=1.00)	1	313
fatigue	ES=-0.12	[-0.35;0.10]	0.2705	1.0000 (I^2=0.00)	1	313
sommeil	ES=0.00	[-0.22;0.22]	1.0000	1.0000 (I^2=0.00)	1	313
dpression	ES=-0.13	[-0.35;0.09]	0.2477	1.0000 (I^2=0.00)	1	313
anxit	ES=-0.27	[-0.49;-0.04]	0.0191	1.0000 (I^2=0.00)	1	313

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 43.1: *Forest's plot for FIQ*

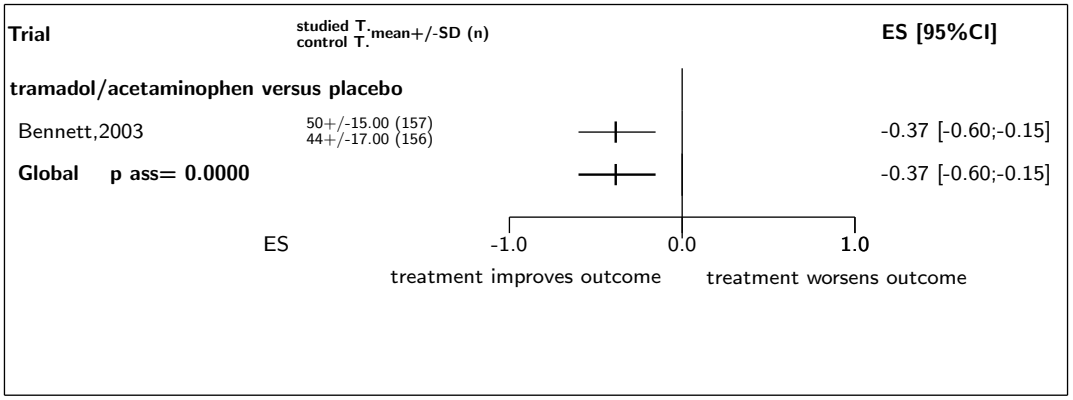


Figure 43.2: *Forest's plot for Douleur*

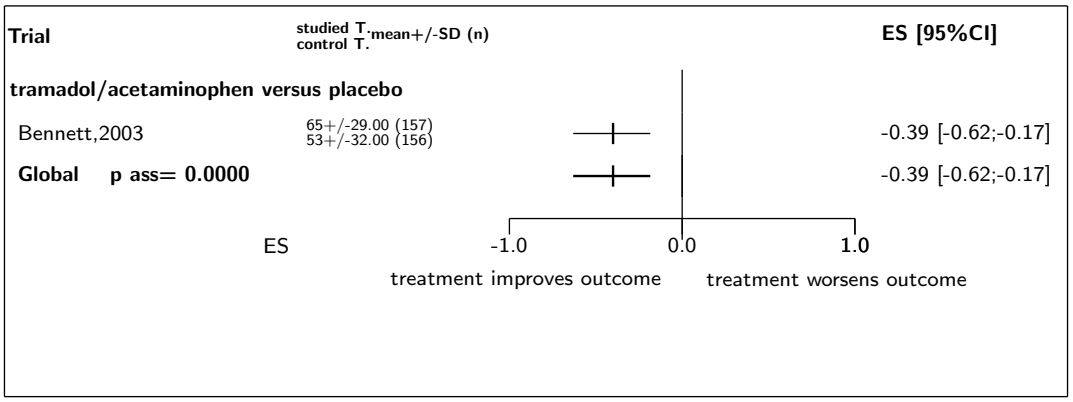


Figure 43.3: *Forest's plot for Points douloureux (nombre)*

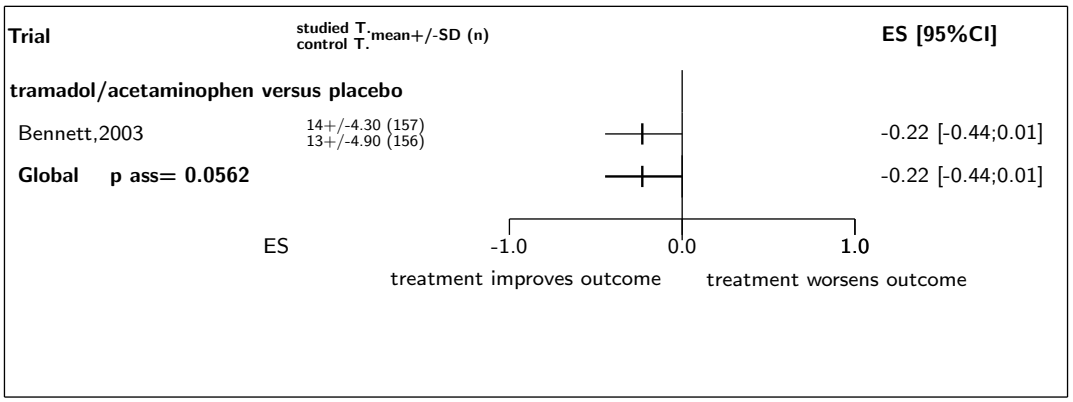


Figure 43.4: *Forest's plot for Fatigue*

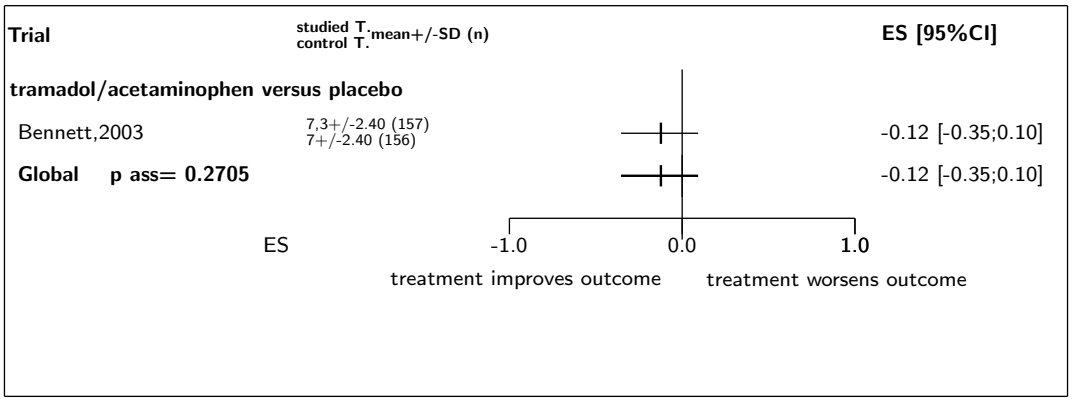


Figure 43.5: *Forest's plot for Sommeil*

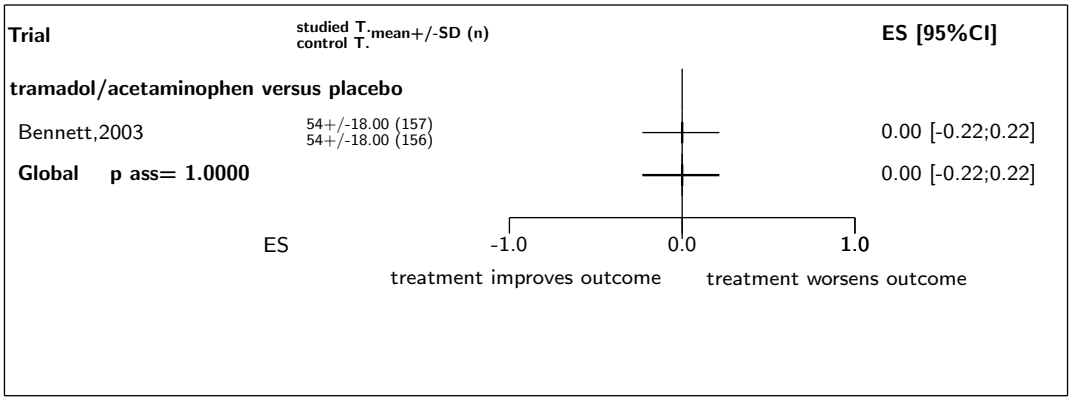


Figure 43.6: *Forest's plot for Dpression*

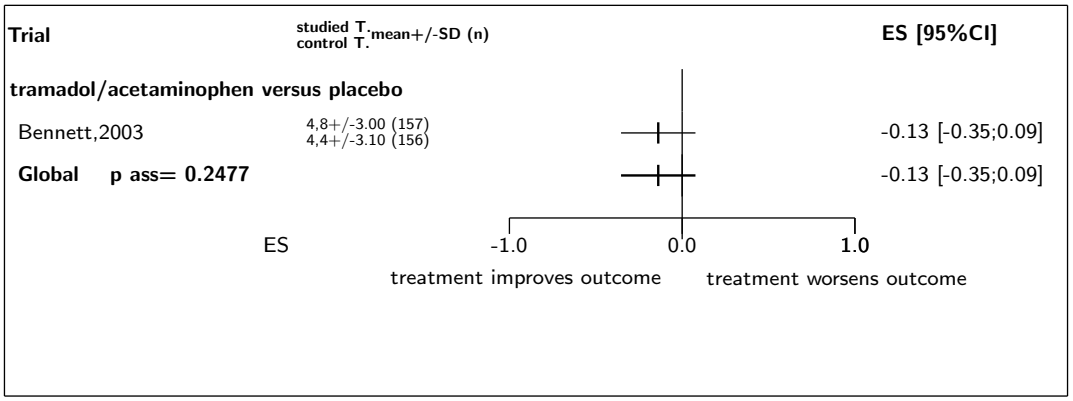
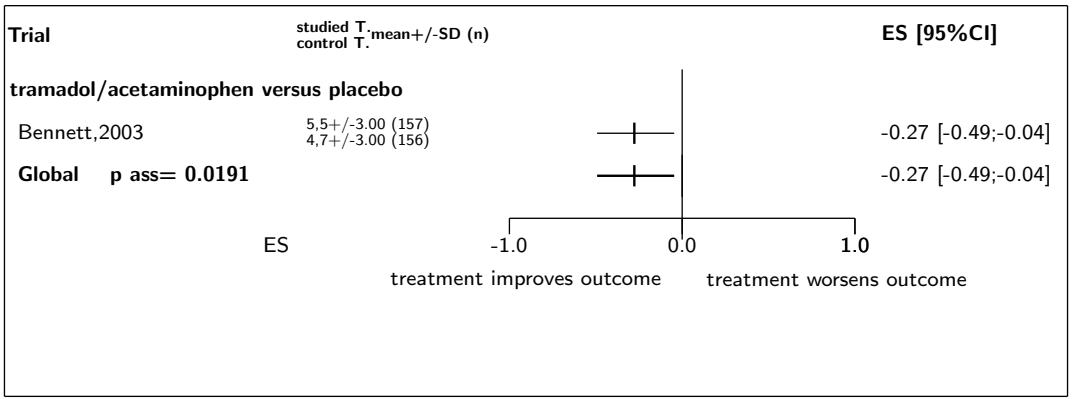


Figure 43.7: *Forest's plot for Anxit*



References

[1] Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114:537-45. [PMID=12753877]

[2] Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Rheum 2005;53:519-27. [PMID=16082646]

44 Global meta-analysis: all tramadol

44.1 Global meta-analysis: all tramadol versus placebo

Table 44.1: *All tramadolversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
FIQ	ES=-0.33	-0.54;-0.13	0.0000	0.4068 (0.00)	2	382
douleur	ES=-0.41	-0.61;-0.21	0.0000	0.7196 (0.00)	2	382
points douloureux (nombre)	ES=-0.22	-0.44;0.01	0.0562	1.0000 (1.00)	1	313
fatigue	ES=-0.12	-0.35;0.10	0.2705	1.0000 (0.00)	1	313
sommeil	ES=0.00	-0.22;0.22	1.0000	1.0000 (0.00)	1	313
dpression	ES=-0.13	-0.35;0.09	0.2477	1.0000 (0.00)	1	313
anxit	ES=-0.27	-0.49;-0.04	0.0191	1.0000 (0.00)	1	313

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
amlioration globale (patient)	RR=2.02	1.27;3.21	0.0030	1.0000 (0.00)	1	69

legend B

45 Ongoing studies of tramadol

No ongoing trial was identified.

46 Excluded studies for tramadol

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 46.1: *Excluded studies of tramadol*

Study	Exclusion reason
NCT00766675 (0)	essai non control
Biasi (1998) [**?**]	traitement IV non assimilable un traitement chroniqueevaluation 2 heures

Part X

Venlafaxine

47 Overview of venlafaxine

47.1 Included trials

Only one trial which randomized 90 patients was identified. In all, 1 randomized comparison concerned venlafaxine.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for venlafaxine.

This trial included 90 patients and was published in 2007.
This trial was double blind in design.
It was reported in English language.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

47.2 Summary of meta-analysis results

The meta-analysis of the available trials about venlafaxine provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

47.2.1 Venlafaxine

Data were insufficient to compare **venlafaxine** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 47.1: *Main study characteristics - venlafaxine*

Trial	Patients	Treatments	Trial design and method
Venlafaxine			
Venlafaxine versus placebo			
Zijlstra, 2007 [**?**, **?**] n = 45 vs. 45	ACR, age >18 ans	venlafaxine 75 mg/j **versus** placebo	double blind parallel groups Primary endpoint: EVA douleur + McGill pain Questionnaire

Table 47.2: *Summary of all results for venlafaxine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
venlafaxine versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

48 Details

48.1 Available trials

Only one trial which randomized 90 patients was identified: it compared venlafaxine with placebo.
This trial included 90 patients and was published in 2007.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of venlafaxine.

Table 48.1: *Treatment description - venlafaxine - venlafaxine*

Trial	Studied treatment	Control treatment
Venlafaxine versus placebo		
Zijlstra (2007) [?, ?]	venlafaxine 75 mg/j	placebo

Table 48.2: *Descriptions of participants - venlafaxine - venlafaxine*

Trial	Patients
Venlafaxine versus placebo	
Zijlstra (2007) [?, ?]	ACR, age >18 ans

Table 48.3: *Main patients characteristics - venlafaxine - venlafaxine*

Trial	Characteristics
Venlafaxine versus placebo	
Zijlstra, 2007 [?, ?]	age (mean), years: 46 ans

Table 48.4: *Design and methodological quality of trials - venlafaxine - venlafaxine*

Trial	Design	Duration	Centre	Primary endpoint
Venlafaxine versus placebo				
Zijlstra, 2007 [?, ?] n=90	Parallel groups double blind	6 semaines		EVA douleur + McGill pain Questionnaire

48.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Venlafaxine versus placebo

No data were presented in the 1 trial identified

Table 48.5: *Results details - venlafaxine - venlafaxine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
venlafaxine versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Zijlstra TR, Taal E, van de Laar MA, Rasker JJ. Validation of a Dutch translation of the fibromyalgia impact questionnaire. Rheumatology (Oxford) 2007 Jan;46:131-4. [PMID=16757485]

[2] Zijlstra TR, Barendregt PJ, van De Laar MAF. Venlafaxine infibromyalgia: results of a randomized, placebo-controlled, doubleblindtrial. Arthritis Rheum 2002;46:S105.

49 Global meta-analysis: all venlafaxine

49.1 Global meta-analysis: all venlafaxine versus placebo

Table 49.1: *All venlafaxineversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

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50 Ongoing studies of venlafaxine

No ongoing trial was identified.

51 Excluded studies for venlafaxine

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 51.1: *Excluded studies of venlafaxine*

Study	**Exclusion reason**
Borman (2004) [**?**]	essai non en double aveugle
Sayar (2003) [**?**]	essai non control