

Supplementary material

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Chapter 1

Details about analyses

- Duration subgroup studies separate studies lasting less than or equal to 12 weeks, and those greater than 12 weeks.
- Many head to head analyses were not possible given the disconnected nature of the networks; where data was available head to head analyses were undertaken.
- Funnel plots are shaded to show 90, 95, and 99 significance regions.

Chapter 2

Primary outcomes

2.1 Substantial pain relief

Substantial pain relief was reported in 43 studies (5 crossover, 38 parallel design) including 14,880 participants and comparing 18 interventions for adults with chronic pain. The length of trials ranged from 4 to 28 weeks, with the majority lasting 12 weeks. 7 studies did not include a placebo trial, comparing antidepressants with pregabalin (3 studies), gabapentin (1 study), morphine (1 study), and one study comparing amitriptyline with duloxetine without a placebo.

Summary of findings 2.1 shows the evidence network of post-intervention comparisons of treatments for chronic pain in adults. Of the 43 studies included, 36 had a placebo-controlled trial.

Interventions (18): placebo (36 studies); duloxetine (26); milnacipran (4); pregabalin (4); venlafaxine (3); desvenlafaxine (2); esreboxetine (2); mianserin (2); nortriptyline (2); amitriptyline (1); carbamazepine (1); clomipramine (1); gabapentin (1); imipramine (1); mirtazapine (1); morphine (1); nortriptyline + morphine (1); pregabalin + imipramine (1); trazodone + gabapentin (1).

2.1.1 Meta-analyses

Duloxetine

The NMA-estimated odds-ratio (OR) was 2.02 (95% CI 1.72 to 2.37) for duloxetine, consistent with direct results. Majority of participants were fibromyalgia and neuropathic pain patients, in which subgroups the results were consistent. Duloxetine did not show these results at low doses, but was consistent across standard to high doses. Funnel plot asymmetry (Figure 2.1) suggests publication bias may be present.

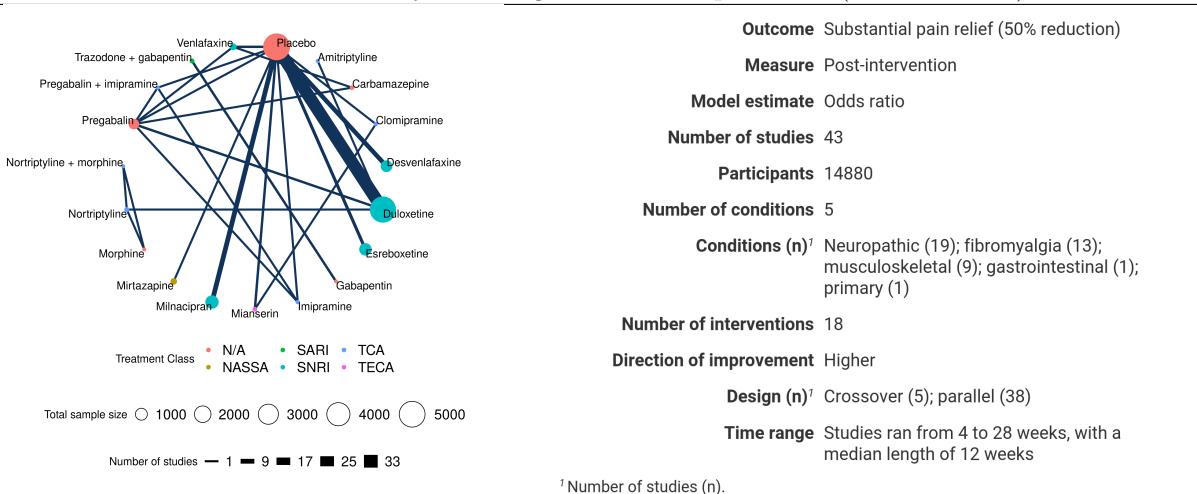
Milnacipran: The NMA estimate (OR) was 1.67 (95% CI 1.11 to 2.52) for milnacipran; these studies are primarily in fibromyalgia patients.

The evidence for substantial pain relief is not consistent across interventions, and is focussed on SNRI-class antidepressant interventions. Thus, the results for other interventions are based on small evidence bases (low number of participants and or few studies).

The network meta-anlaysis results show significant substantial pain relief in chronic pain patients for SNRI antidepressants compared with placebo, with odds-ratios (OR) of between and 1 and 2.5 for duloxetine and milnacipran .

Appendix 2 provides meta-analyses, where the direct evidence is consistent with the results of the network meta-analysis. There was little inconsistency between results for fibromyalgia and neuropathic subgroups. In terms of dose, there was only sufficient data for duloxetine, which only showed efficacy for standard and high doses, whereas meta-analysis suggests duloxetine is ineffective at low doses.

Table 2.1: Summary of findings: Substantial pain relief (50% reduction).



Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Duloxetine	26	8169 (3293, 4876)	2.01 (1.72 to 2.37)	7 (4 to 11)	0.42
Milnacipran	4	1862 (724, 1138)	1.67 (1.11 to 2.52)	9 (4 to 14)	0.75
Pregabalin	4	747 (69, 678)	2.18 (1.4 to 3.49)	7 (3 to 12)	0.25
Venlafaxine	3	371 (139, 232)	1.51 (0.88 to 2.64)	10 (5 to 15)	0.33
Desvenlafaxine	2	1064 (215, 849)	1.25 (0.76 to 2.04)	12 (7 to 17)	0.5
Esreboxetine	2	1374 (408, 966)	1.81 (1.06 to 3.08)	9 (3 to 14)	0.5
Mianserin	2	177 (88, 89)	2.77 (1.27 to 6.17)	5 (1 to 12)	0
Nortriptyline	2	108 (0, 108)	0.46 (0.16 to 1.24)	17 (13 to 19)	0
Amitriptyline	1	58 (0, 58)	1.74 (0.67 to 4.61)	9 (2 to 17)	1
Carbamazepine	1	85 (0, 85)	0.85 (0.36 to 2.04)	14 (8 to 19)	1
Clomipramine	1	128 (66, 62)	2.21 (0.88 to 5.54)	7 (2 to 15)	0
Gabapentin	1	48 (0, 48)	0.78 (0 to 766751.32)	11 (1 to 19)	0
Imipramine	1	138 (69, 69)	4.29 (1.54 to 12.37)	4 (1 to 10)	0
Mirtazapine	1	422 (211, 211)	1.3 (0.6 to 2.88)	11 (4 to 17)	0
Morphine	1	51 (0, 51)	0.26 (0.06 to 1.07)	18 (15 to 19)	0
Nortriptyline + morphine	1	51 (0, 51)	0.88 (0.21 to 3.67)	13 (3 to 18)	0
Pregabalin + imipramine	1	138 (69, 69)	6.49 (2.43 to 17.95)	2 (1 to 5)	0
Trazodone + gabapentin	1	93 (0, 93)	1.28 (0 to 1475010)	10 (1 to 19)	0
Placebo				14 (11 to 17)	

[†] Table is ordered by interventions with greatest number of studies.

[‡] Direction of improvement: higher.

[§] Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table use this work as a guide: Yépez-Nuñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. Journal of Clinical Epidemiology, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

Substantial pain relief (50% reduction): duloxetine vs placebo

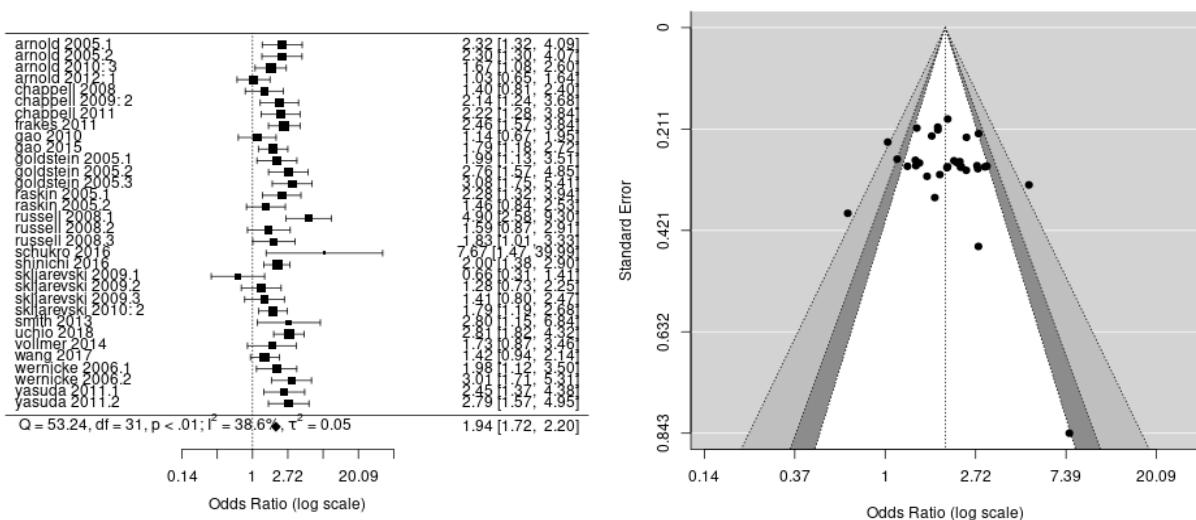


Figure 2.1: Substantial pain: duloxetine compared with placebo

2.1.2 Head to head comparisons and subgroup sensitivity analyses

Duloxetine

Duloxetine did not show inconsistency or imprecision, within the meta-analysis, and compared to the network meta-analysis estimates, however some funnel plot asymmetry suggests publication bias (Figure 2.1). Heterogeneity was not explained by condition, dose, duration of study, or risk of bias.

Milnacipran

Meta-analysis of milnacipran was consistent with network meta-analysis estimates. No inconsistency, imprecision, or publication bias detected, however, one third of studies included were high risk of bias. Heterogeneity was not explained by risk of bias or duration of study.

2.2 Pain intensity (change scores)

Pain intensity was reported in 46 studies (3 crossover, 43 parallel) evaluating 46 interventions in trials comprising 14,887 total participants. Studies ran from 5 to 52 weeks, with median length 12 weeks. In the trials reporting placebo, most compared interventions with placebo; with exceptions being two trials comparing duloxetine and pregabalin, and 5 other trials with unique comparators. See Summary of findings Table 2.2 for the geometry of this network.

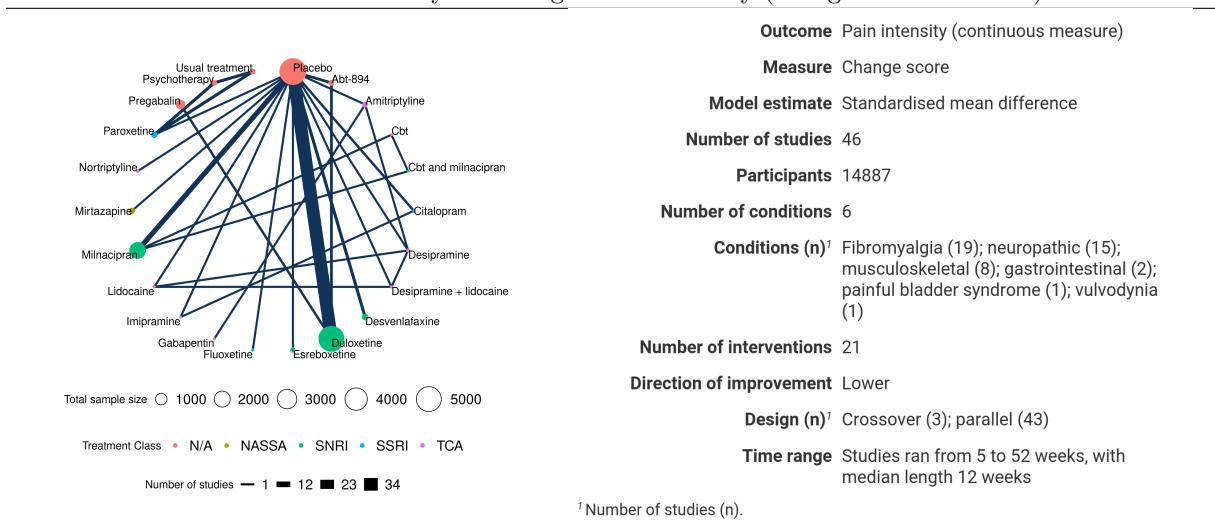
Interventions (number of studies): Placebo (39); duloxetine (27); milnacipran (6); amitriptyline (3); citalopram (2); desipramine (2); paroxetine (2); pregabalin (2); abt-894 (1); cbt (1); cbt and milnacipran (1); desipramine + lidocaine (1); desvenlafaxine (1); esreboxetine (1); fluoxetine (1); gabapentin (1); imipramine (1); lidocaine (1); mirtazapine (1); nortriptyline (1); psychotherapy (1); usual treatment (1).

2.2.1 Meta-analyses

Duloxetine

No significant imprecision or inconsistency was detected in duloxetine results. Publication bias was not detected, however there is serious risk of bias in these observations. Heterogeneity was not explained by

Table 2.2: Summary of findings: Pain intensity (change score measures).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³
Duloxetine	27	8469 (3368, 5101)	-0.3 (-0.49 to -0.12)	10 (6 to 15)	0.33
Milnacipran	6	3434 (1426, 2008)	-0.3 (-0.67 to 0.1)	10 (5 to 17)	0.67
Amitriptyline	3	287 (119, 168)	-0.17 (-1 to 0.65)	12 (4 to 20)	1
Citalopram	2	75 (37, 38)	-0.18 (-0.96 to 0.62)	12 (4 to 20)	1
Desipramine	2	88 (29, 59)	-0.05 (-0.94 to 0.86)	13 (4 to 21)	0.5
Paroxetine	2	273 (58, 215)	-0.19 (-1.15 to 0.76)	12 (3 to 20)	1
Pregabalin	2	550 (0, 550)	1.82 (1.11 to 2.52)	22 (21 to 22)	0
Abt-894	1	220 (50, 170)	0.12 (-0.54 to 0.81)	16 (7 to 21)	0
Cbt	1	15 (0, 15)	-0.69 (-1.89 to 0.5)	7 (2 to 20)	1
Cbt and milnacipran	1	17 (0, 17)	-0.95 (-2.19 to 0.3)	6 (2 to 18)	1
Desipramine + lidocaine	1	59 (29, 30)	-0.22 (-1.25 to 0.8)	11 (3 to 21)	0
Desvenlafaxine	1	296 (72, 224)	-0.42 (-1.19 to 0.35)	9 (3 to 19)	0
Esreboxetine	1	266 (133, 133)	-0.29 (-1.28 to 0.71)	11 (3 to 21)	0
Fluoxetine	1	51 (26, 25)	-0.9 (-2.01 to 0.14)	6 (2 to 17)	0
Gabapentin	1	19 (0, 19)	0.21 (-1.13 to 1.62)	15 (3 to 21)	1
Imipramine	1	34 (16, 18)	-1.02 (-2.07 to 0.03)	5 (2 to 15)	1
Lidocaine	1	56 (29, 27)	0.24 (-0.82 to 1.26)	16 (5 to 21)	0
Mirtazapine	1	422 (211, 211)	-4.37 (-5.38 to -3.41)	1 (1 to 1)	0
Nortriptyline	1	78 (40, 38)	0.45 (-0.6 to 1.51)	18 (6 to 21)	0
Psychotherapy	1	146 (0, 146)	-0.1 (-1.29 to 1.08)	13 (3 to 21)	1
Usual treatment	1	156 (0, 156)	-0.03 (-1.22 to 1.17)	13 (3 to 21)	1
Placebo				15 (10 to 19)	

¹ Table is ordered by interventions with greatest number of studies.

² Direction of improvement: lower.

³ Proportion of studies with at least one with high risk of bias (ROB) criterion.

condition, dose, or duration of studies. No significant inconsistency or imprecision was detected; see, for example, Figure 2.2.

Milnacipran

No serious inconsistency or imprecision was detected. Risk of bias is serious but publication bias was not detected. Heterogeneity was not explained by condition, dose, risk of bias, or duration of studies.

2.3 Pain intensity (post intervention)

Pain intensity was reported as a post-intervention measure in 80 studies (18 crossover, 62 parallel) evaluating 70 interventions in trials comprising a total of 8016 participants. Studies ran from 2 to 36 weeks, with median length 8 weeks. In post-intervention measures (Summary of findings Table 2.3), amitriptyline was compared to benzotropine mesylate in three studies, and amitriptyline against pregablin in two. There were 27 other unique comparators.

Interventions (number of studies): Placebo (47); amitriptyline (23); duloxetine (13); milnacipran (8); fluoxetine (6); pregabalin (6); benzotropine mesylate (5); gabapentin (4); maprotiline (4); nortriptyline (4); paroxetine (4); cbt (3); escitalopram (3); acupuncture (2); citalopram (2); desipramine (2); melatonin (2); morphine (2); saffron/crocin (2); sertraline (2); venlafaxine (2); active placebo (1); aerobic exercise (1); amitriptyline + fluoxetine (1); amitriptyline + fluphenazine (1); amitriptyline + psychotherapy (1); amitriptyline + riboflavin (vitamin b2) (1); amitriptyline + splint (1); amitriptyline + support (1); benzotropine mesylate + cbt (1); bupropion (1); carbamazepine (1); clomipramine (1); cst (1); cst + sertraline (1); cyclobenzaprine (1); desipramine + cbt (1); diphenhydramine (1); disease management (1); dothiepin (1); education (1); epidural injection (1); epidural injection + amitriptyline (1); esreboxetine (1); fluoxetine + melatonin (1); fluphenazine (1); gabapentin + nortriptyline (1); glycopyrrolate (1); lamotrigine (1); melatonin + amitriptyline (1); mianserin (1); mirtazapine (1); moclobemide (1); morphine + nortriptyline (1); neurofeedback (1); nortriptyline + cbt (1); nortriptyline + disease management (1); nortriptyline + morphine (1); physical therapy (1); pirlindole (1); pregabalin + duloxetine (1); psychotherapy (1); reboxetine (1); riboflavin (vitamin b2) (1); support (1); tens (1); trazodone (1); trazodone + gabapentin (1); trimipramine (1); waitlist (1); zimeldine (1).

Subgroup analysis by dose was not possible with these data.

2.3.1 Meta-analyses

Duloxetine

No significant imprecision or inconsistency was detected in duloxetine results. Publication bias was not detected, however there is serious risk of bias in these observations. Heterogeneity of observations for duloxetine was not explained by condition, dose, risk of bias, or duration of study (for example,).

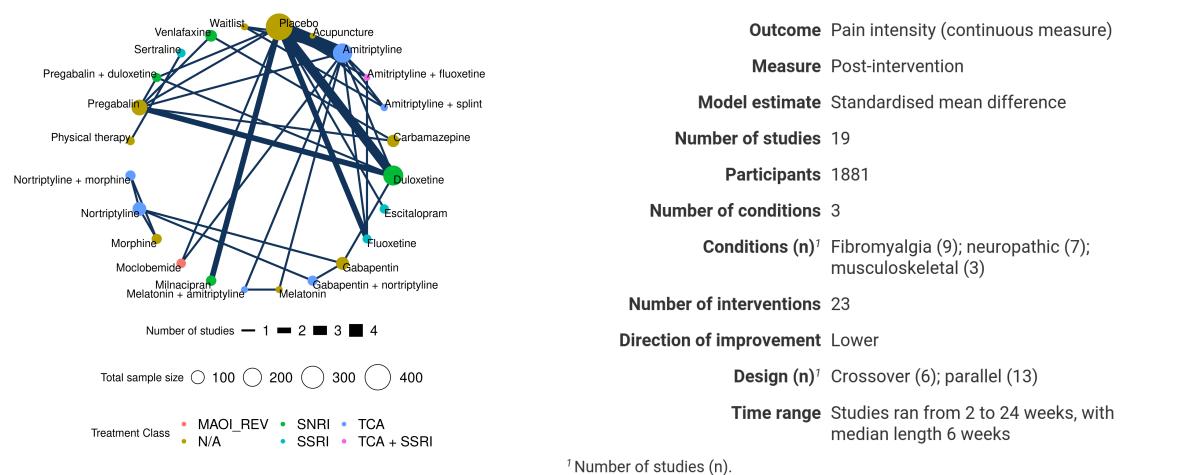
Milnacipran

No serious inconsistency or imprecision was detected. Risk of bias is serious but publication bias was not detected. Heterogeneity of observations for milnacipran was not explained by condition, dose, or duration of study .

Amitriptyline

No imprecision, inconsistency, or publication bias was detected, however these observations have serious risk of bias. Heterogeneity of observations for amitriptyline was not explained by condition, risk of bias, or duration of study.

Table 2.3: Summary of findings: Pain intensity (post-intervention measures).



Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Amitriptyline	7	354 (143, 211)	-0.47 (-0.76 to -0.19)	6 (3 to 11)	0.43
Duloxetine	5	401 (175, 226)	-0.1 (-0.39 to 0.22)	11 (7 to 17)	0.4
Pregabalin	3	174 (39, 135)	-0.38 (-0.8 to 0.07)	7 (3 to 14)	0.67
Fluoxetine	2	65 (28, 37)	-0.16 (-0.71 to 0.4)	11 (4 to 20)	1
Gabapentin	2	87 (0, 87)	0.33 (-0.35 to 1.03)	18 (10 to 23)	0
Milnacipran	2	107 (54, 53)	0.04 (-0.45 to 0.55)	14 (6 to 21)	0.5
Nortriptyline	2	101 (0, 101)	0.38 (-0.51 to 1.26)	18 (8 to 23)	0
Acupuncture	1	13 (0, 13)	-0.54 (-1.42 to 0.3)	6 (2 to 18)	1
Amitriptyline + fluoxetine	1	37 (19, 18)	-1.11 (-1.87 to -0.38)	3 (1 to 8)	1
Amitriptyline + splint	1	23 (0, 23)	-0.25 (-1.04 to 0.49)	10 (3 to 20)	1
Carbamazepine	1	78 (0, 78)	0.22 (-0.43 to 0.91)	16 (8 to 22)	1
Escitalopram	1	82 (41, 41)	-0.4 (-1.01 to 0.2)	8 (2 to 17)	1
Gabapentin + nortriptyline	1	50 (0, 50)	-0.24 (-1.11 to 0.68)	9 (2 to 19)	0
Melatonin	1	21 (0, 21)	0.16 (-0.66 to 0.95)	15 (5 to 23)	0
Melatonin + amitriptyline	1	21 (0, 21)	0.08 (-0.76 to 0.86)	14 (4 to 22)	0
Moclobemide	1	86 (43, 43)	0.31 (-0.24 to 0.85)	17 (9 to 23)	0
Morphine	1	51 (0, 51)	0.34 (-0.7 to 1.43)	17 (5 to 23)	0
Nortriptyline + morphine	1	51 (0, 51)	0.27 (-0.81 to 1.29)	16 (4 to 23)	0
Physical therapy	1	34 (0, 34)	7.84 (-6.57 to 22.28)	21 (2 to 24)	1
Pregabalin + duloxetine	1	78 (39, 39)	-0.68 (-1.23 to -0.1)	4 (2 to 11)	1
Sertraline	1	36 (0, 36)	-7.76 (-22.32 to 6.99)	4 (1 to 23)	1
Venlafaxine	1	69 (0, 69)	0.47 (-0.22 to 1.18)	19 (11 to 23)	1
Waitlist	1	21 (0, 21)	0.91 (0.05 to 1.76)	22 (14 to 24)	1
Placebo				13 (9 to 18)	

[†] Table is ordered by interventions with greatest number of studies.

[‡] Direction of improvement: lower.

[§] Proportion of studies with at least one with high risk of bias (ROB) criterion.

2.4 Mood (Change score results)

37 parallel-design studies reported mood as change-score measures evaluating 18 interventions over a population of 12,697 participants. Studies ran from 6 to 28 weeks, with median length 12 weeks. Three studies did not include placebo trials, using cognitive behavioural therapy, pregabalin, and psychotherapy as comparators with antidepressants. Summary of findings Table 2.4 shows the network meta-analysis estimates for mood outcomes measured as change scores. These studies ran from 6 to 28 weeks, with median length 12 weeks.

Interventions (number of studies): Placebo (33); duloxetine (26); milnacipran (4); citalopram (2); pregabalin (2); abt-894 (1); cbt (1); cbt and milnacipran (1); desipramine (1); desipramine + lidocaine (1); esreboxetine (1); fluoxetine (1); imipramine (1); lidocaine (1); mirtazapine (1); nortriptyline (1); paroxetine (1); psychotherapy (1); usual treatment (1).

Conditions: fibromyalgia; musculoskeletal; neuropathic; gastrointestinal; vulvodynia.

Summary of findings (Table 2.4) shows 26 studies evaluated duloxetine, 4 studies evaluated milnacipran, and all other interventions were evaluated in 1 or 2 studies.

2.4.1 Meta-analyses

Duloxetine

Heterogeneity in mood measured as change scores was not explained by condition, dose, duration of study, or risk of bias.

Milnacipran

Heterogeneity was not explained by dose.

Amitriptyline

2.5 Mood (Post intervention results)

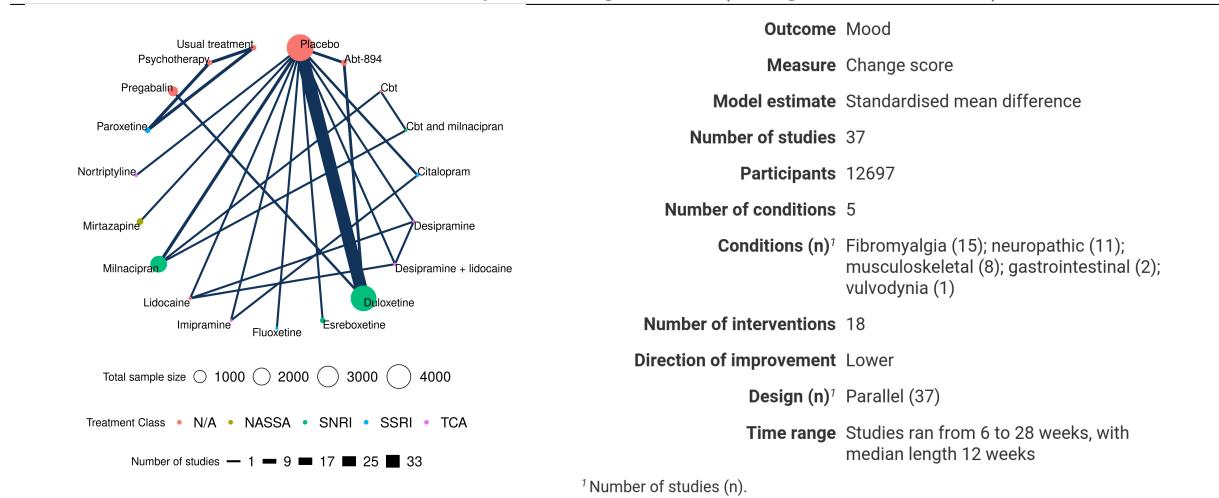
47 studies (9 crossover, 38 parallel) reported mood as post-intervention measures. These studies evaluated 50 interventions over a population of 3804; i.e., this is a network (Summary of findings Table 2.5) of several small trial. For post-intervention measures, several other comparators were considered in the literature, notably amitriptyline (7 studies), citalopram (2 studies), fluoxetine (2 studies), and acupuncture (2 studies). Most comparators were either combined or unique, with trials included in only one study. Studies ran from 2 to 34 weeks, with median length 8 weeks.

Interventions (number of studies): Placebo (27); amitriptyline (10); duloxetine (8); benzotropine mesylate (4); fluoxetine (4); pregabalin (4); venlafaxine (4); escitalopram (3); milnacipran (3); nortriptyline (3); paroxetine (3); acupuncture (2); cbt (2); citalopram (2); morphine (2); saffron/crocin (2); aerobic exercise (1); amitriptyline + fluoxetine (1); amitriptyline + fluphenazine (1); amitriptyline + riboflavin (vitamin b2) (1); amitriptyline + splint (1); carbamazepine (1); clomipramine (1); cst (1); cst + sertraline (1); cyclobenzaprine (1); disease management (1); dothiepin (1); fluoxetine + melatonin (1); fluphenazine (1); gabapentin (1); gabapentin + nortriptyline (1); glycopyrrolate (1); maprotiline (1); melatonin (1); mirtazapine (1); moclobemide (1); morphine + nortriptyline (1); neurofeedback (1); nortriptyline + cbt (1); nortriptyline + disease management (1); nortriptyline + morphine (1); pirlindole (1); pregabalin + duloxetine (1); reboxetine (1); riboflavin (vitamin b2) (1); sertraline (1); tens (1); trazodone (1); trimipramine (1); waitlist (1).

Conditions: musculoskeletal; primary; neuropathic; fibromyalgia; atypical facial pain; non-cardiac chest pain; burning mouth syndrome; phantom/residual limb pain; unspecified.

In Summary of Findings Table 2.5, there are 10 studies that evaluate amitriptyline and 8 that evaluate duloxetine. Of the 50 interventions evaluated, most are included in 3 studies or fewer.

Table 2.4: Summary of findings: Mood (change-score measures).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³
Duloxetine	25	7472 (3029, 4443)	-0.15 (-0.26 to -0.03)	9 (5 to 14)	0.32
Milnacipran	4	3109 (1356, 1753)	-0.12 (-0.41 to 0.18)	10 (5 to 15)	0.75
Citalopram	2	75 (37, 38)	-0.14 (-0.74 to 0.45)	10 (3 to 17)	1
Pregabalin	2	548 (0, 548)	0.78 (0.36 to 1.2)	17 (14 to 19)	0
Abt-894	1	215 (49, 166)	-0.13 (-0.54 to 0.3)	10 (4 to 17)	0
Cbt	1	15 (0, 15)	-0.19 (-1.14 to 0.71)	9 (2 to 17)	1
Cbt and milnacipran	1	17 (0, 17)	-0.06 (-0.98 to 0.84)	11 (2 to 18)	1
Desipramine	1	56 (29, 27)	-0.21 (-0.93 to 0.53)	9 (2 to 17)	0
Desipramine + lidocaine	1	61 (29, 32)	0.04 (-0.67 to 0.78)	12 (3 to 18)	0
Esreboxetine	1	252 (126, 126)	-0.26 (-0.85 to 0.32)	8 (2 to 16)	0
Fluoxetine	1	51 (26, 25)	-0.73 (-1.54 to 0.06)	5 (1 to 13)	0
Imipramine	1	34 (16, 18)	-1.07 (-1.81 to -0.32)	3 (1 to 7)	1
Lidocaine	1	59 (29, 30)	0.19 (-0.54 to 0.92)	13 (5 to 18)	0
Mirtazapine	1	406 (202, 204)	-0.49 (-1.03 to 0.07)	6 (2 to 14)	0
Nortriptyline	1	78 (40, 38)	0.64 (-0.09 to 1.36)	16 (10 to 19)	0
Paroxetine	1	131 (0, 131)	-0.14 (-11.56 to 11.38)	10 (1 to 19)	1
Psychotherapy	1	117 (0, 117)	-0.19 (-11.56 to 11.33)	10 (1 to 19)	1
Usual treatment	1	124 (0, 124)	-0.04 (-11.4 to 11.52)	11 (1 to 19)	1
Placebo				12 (8 to 16)	

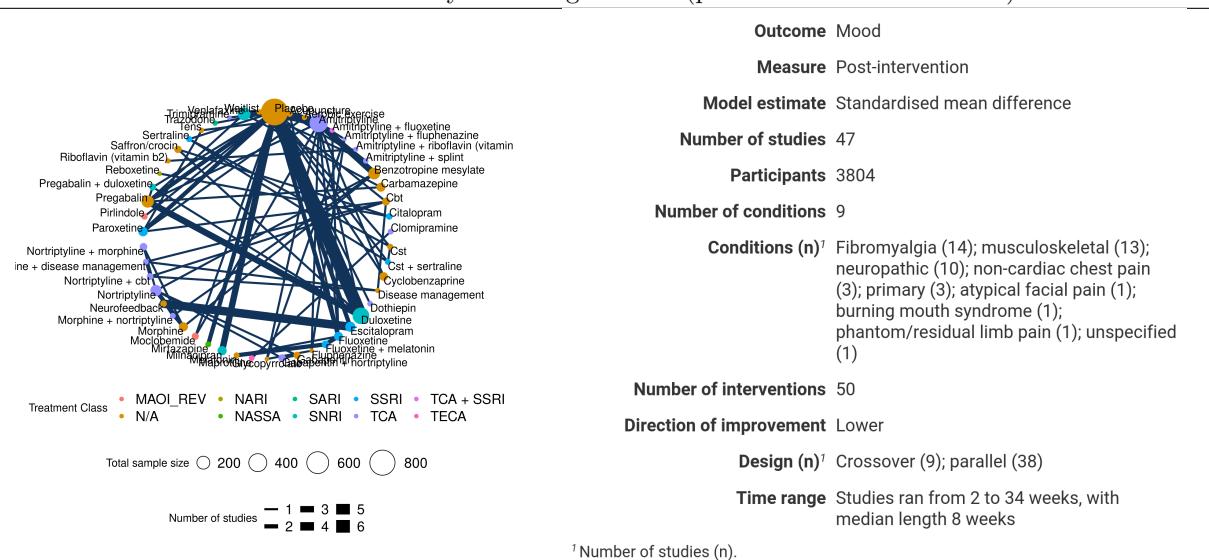
¹ Table is ordered by interventions with greatest number of studies.

² Direction of improvement: lower.

³ Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table follows the recommendations of Yepes-Nuñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology*, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

Table 2.5: Summary of findings: Mood (post-intervention measures).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³	
Amitriptyline	10	537 (159, 378)	-0.37 (-0.96 to 0.2)	24 (13 to 36)	0.4	
Duloxetine	8	580 (269, 311)	-0.53 (-1.03 to -0.01)	20 (9 to 34)	0.62	
Benzotropine mesylate	4	143 (0, 143)	0.02 (-0.98 to 0.98)	33 (14 to 46)	0.5	
Fluoxetine	4	104 (28, 76)	-0.34 (-1.21 to 0.54)	25 (9 to 42)	0.75	
Pregabalin	4	218 (61, 157)	-0.42 (-1.1 to 0.26)	23 (9 to 39)	0.75	
Venlafaxine	4	271 (98, 173)	-0.09 (-0.76 to 0.6)	30 (13 to 44)	0.75	
Escitalopram	3	169 (67, 102)	-1.5 (-2.54 to -0.47)	8 (2 to 23)	0.67	
Milnacipran	3	150 (69, 81)	-0.44 (-1.26 to 0.39)	23 (7 to 42)	1	
Nortriptyline	3	129 (0, 129)	-0.18 (-1.79 to 1.41)	28 (6 to 47)	0.33	
Paroxetine	3	158 (71, 87)	-0.31 (-1.23 to 0.62)	26 (8 to 44)	0.67	
Acupuncture	2	28 (0, 28)	-0.38 (-1.57 to 0.81)	24 (6 to 45)	1	
Cbt	2	79 (23, 56)	-0.39 (-1.63 to 0.84)	24 (6 to 45)	1	
Citalopram	2	36 (0, 36)	-0.37 (-2.39 to 1.76)	25 (3 to 49)	0.5	
Morphine	2	79 (0, 79)	0.08 (-1.57 to 1.66)	33 (8 to 49)	0.5	
Saffron/crocin	2	49 (0, 49)	-0.46 (-1.93 to 1)	23 (4 to 46)	0	
Aerobic exercise	1	20 (0, 20)	-0.55 (-2.21 to 1.13)	22 (3 to 47)	1	
Amitriptyline + fluoxetine	1	37 (19, 18)	-0.46 (-1.66 to 0.76)	23 (5 to 45)	1	
Amitriptyline + fluphenazine	1	12 (0, 12)	-0.76 (-2.37 to 0.85)	18 (2 to 44)	0	
Amitriptyline + riboflavin (vitamin b2)	1	19 (0, 19)	-0.02 (-13.95 to 14.02)	27 (1 to 51)	1	
Amitriptyline + splint	1	23 (0, 23)	-0.54 (-1.91 to 0.89)	22 (4 to 45)	1	
Carbamazepine	1	78 (0, 78)	1.11 (-0.13 to 2.31)	45 (30 to 51)	1	
Clomipramine	1	27 (0, 27)	-0.07 (-13.8 to 13.59)	27 (1 to 51)	1	
Cst	1	57 (28, 29)	0.38 (-1.01 to 1.74)	37 (11 to 50)	1	
Cst + sertraline	1	56 (28, 28)	-0.01 (-1.37 to 1.33)	31 (7 to 48)	1	
Cyclobenzaprine	1	106 (36, 70)	14	-0.35 (-1.5 to 0.8)	25 (6 to 45)	1
Disease management	1	19 (0, 19)	-0.87 (-2.78 to 0.98)	17 (2 to 46)	1	
Dothiepin	1	48 (23, 25)	-0.12 (-1.52 to 1.24)	29 (6 to 48)	1	

2.5.1 Meta-analyses

Duloxetine

Heterogeneity was not explained by dose. Possibly some heterogeneity is explained by duration of study (Figure 2.3).

2.6 Mood

Mood was reported in 84 studies with 37 parallel-design studies reporting change score (CS) measures and 47 studies reporting post intervention (PI) measures (9 crossover, 38 parallel design). These trials include 16501 participants (CS 12,697, PI 3804) and comparing interventions (CS 18, PI 50) for adults with chronic pain. The direct evidence networks for the two measurement groups are shown in Summary of findings Tables 2.4 and 2.5.

2.7 Adverse events

Adverse events were reported in 90 studies (15 crossover, 75 parallel design) including 21,718 participants and comparing 46 interventions for adults with chronic pain. The length of trials ranged from 2 to 34 weeks, with a median length of 10 weeks. Summary of findings (Table 2.6) shows a disconnected network. In addition to placebo, three studies compared duloxetine to pregabalin, 2 compared amitriptyline to benzotropine mesylate, and 2 further studies compared amitriptyline to gabapentin. There were 16 comparators unique to single trials.

Interventions (number of studies): Placebo (67); duloxetine (29); amitriptyline (18); milnacipran (15); venlafaxine (6); gabapentin (5); pregabalin (5); benzotropine mesylate (4); imipramine (4); carbamazepine (3); nortriptyline (3); paroxetine (3); cbt (2); desipramine (2); desvenlafaxine (2); esreboxetine (2); mirtazapine (2); abt-894 (1); acetaminophen (1); active placebo (1); benzotropine mesylate + cbt (1); cbt and milnacipran (1); citalopram (1); clonidine (1); cst (1); cst + sertraline (1); cyclobenzaprine (1); desipramine + cbt (1); disease management (1); dothiepin (1); escitalopram (1); fluvoxamine (1); lamotrigine (1); lorazepam (1); maprotiline (1); melatonin (1); melatonin + amitriptyline (1); moclobemide (1); morphine (1); morphine + nortriptyline (1); nortriptyline + cbt (1); nortriptyline + disease management (1); pirlindole (1); pregabalin + imipramine (1); reboxetine (1); sertraline (1); trazodone + gabapentin (1).

2.7.1 Meta-analyses

Duloxetine

The direct evidence for duloxetine compared with placebo was consistent with the network meta-analysis estimates, however publication bias (Figure 2.4) is strongly suspected, also implied by the comparison of duloxetine and pregabalin (Figure 2.5). Heterogeneity in duloxetine observations were not explained by condition, dose, or duration of studies.

Milnacipran

Studies evaluating milnacipran compared with placebo showed some inconsistency and publication bias (Figure 2.6).

Heterogeneity observed in adverse events for milnacipran compared to placebo showed some difference (Figure 2.7) between fibromyalgia and musculoskeletal patients. Heterogeneity of milnacipran observations was not explained by duration of studies.

Some heterogeneity is also explained by dose, where there is inconsistency and significant imprecision between groups (Figure 2.8).

Post-intervention mood: duloxetine vs placebo

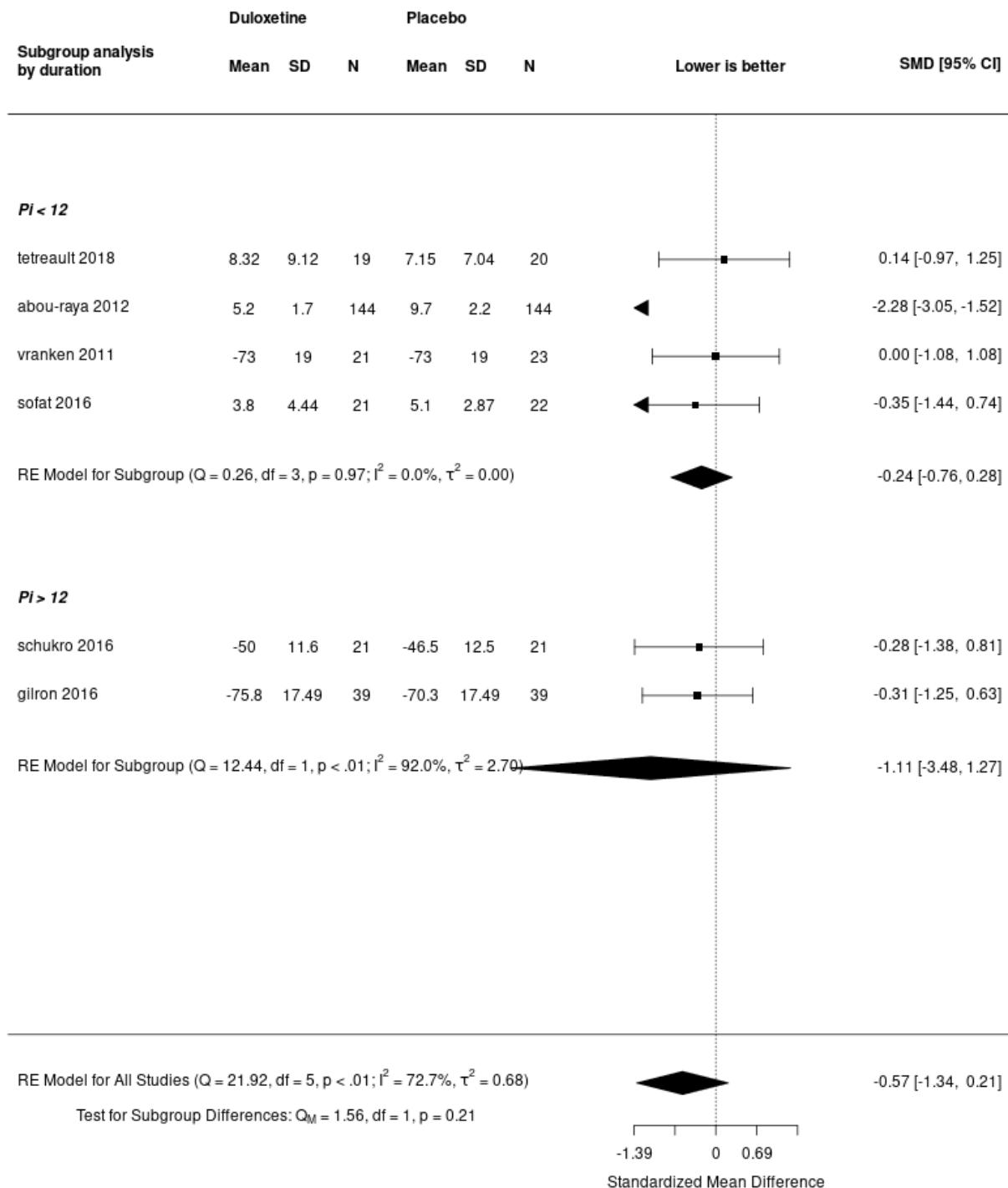
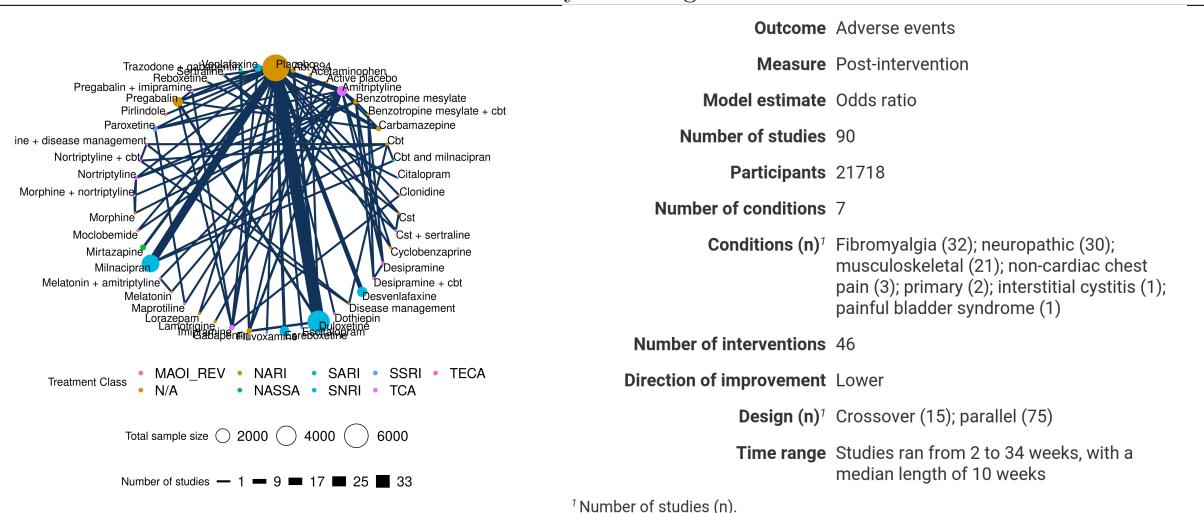


Figure 2.3: Subgroup analysis by duration of study.

Table 2.6: Summary of findings: Adverse events.



Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]	
Duloxetine	29	8503 (3503, 5000)	1.82 (1.45 to 2.23)	24 (16 to 32)	0.45	
Amitriptyline	18	1332 (463, 869)	2.67 (1.72 to 3.98)	32 (23 to 38)	0.5	
Milnacipran	15	4956 (1937, 3019)	1.79 (1.27 to 2.58)	24 (14 to 33)	0.87	
Venlafaxine	6	580 (163, 417)	2.03 (1.24 to 3.42)	26 (15 to 37)	0.5	
Gabapentin	5	201 (0, 201)	1.97 (0.86 to 4.43)	26 (11 to 38)	0.6	
Pregabalin	5	868 (69, 799)	1.73 (1.06 to 2.82)	23 (13 to 34)	0.4	
Benzotropine mesylate	4	175 (0, 175)	1.64 (0.62 to 4.1)	22 (8 to 37)	0.75	
Imipramine	4	383 (188, 195)	2.32 (1.3 to 4.53)	29 (17 to 39)	0.25	
Carbamazepine	3	180 (15, 165)	0.45 (0.21 to 1.02)	7 (3 to 15)	0.33	
Nortriptyline	3	118 (29, 89)	3.31 (0.89 to 13.11)	32 (13 to 43)	0.33	
Paroxetine	3	244 (58, 186)	1.47 (0.68 to 3.51)	20 (9 to 36)	0.33	
Cbt	2	57 (0, 57)	0.37 (0.05 to 2.35)	8 (3 to 27)	1	
Desipramine	2	92 (0, 92)	2.95 (0.95 to 9.28)	32 (14 to 42)	1	
Desvenlafaxine	2	1104 (220, 884)	1.61 (0.83 to 3.09)	22 (10 to 35)	0.5	
Ereboxetine	2	1207 (410, 797)	2.49 (1.32 to 4.84)	30 (16 to 40)	0.5	
Mirtazapine	2	470 (228, 242)	1.65 (0.61 to 4.58)	23 (8 to 39)	0	
Abt-894	1	223 (51, 172)	1.02 (0.44 to 2.27)	15 (6 to 28)	0	
Acetaminophen	1	50 (0, 50)	0 (0 to 0.23)	2 (1 to 5)	1	
Active placebo	1	36 (0, 36)	6.37 (1.21 to 40.63)	38 (17 to 46)	0	
Benzotropine mesylate + cbt	1	34 (0, 34)	2.05 (0.42 to 9.94)	26 (6 to 42)	1	
Cbt and milnacipran	1	20 (0, 20)	2 (0.36 to 10.99)	26 (7 to 43)	1	
Citalopram	1	15 (0, 15)	0.5 (0 to 25583250.09)	21 (1 to 47)	1	
Clonidine	1	40 (20, 20)	1.69 (0.41 to 7.22)	23 (6 to 41)	0	
Cst	1	57 (28, 29)	1.43 (0.29 to 7.34)	21 (4 to 41)	1	
Cst + sertraline	1	56 (28, 28)	1.52 (0.3 to 7.26)	22 (5 to 41)	1	
Cyclobenzaprine	1	126 (84, 42)	17	23.32 (2.8 to 499.12)	43 (32 to 47)	1
Desipramine + cbt	1	37 (0, 37)	1.54 (0.29 to 7.23)	22 (4 to 41)	1	
Disease management	1	24 (0, 24)	0.35 (0.03 to 3.66)	9 (2 to 35)	1	

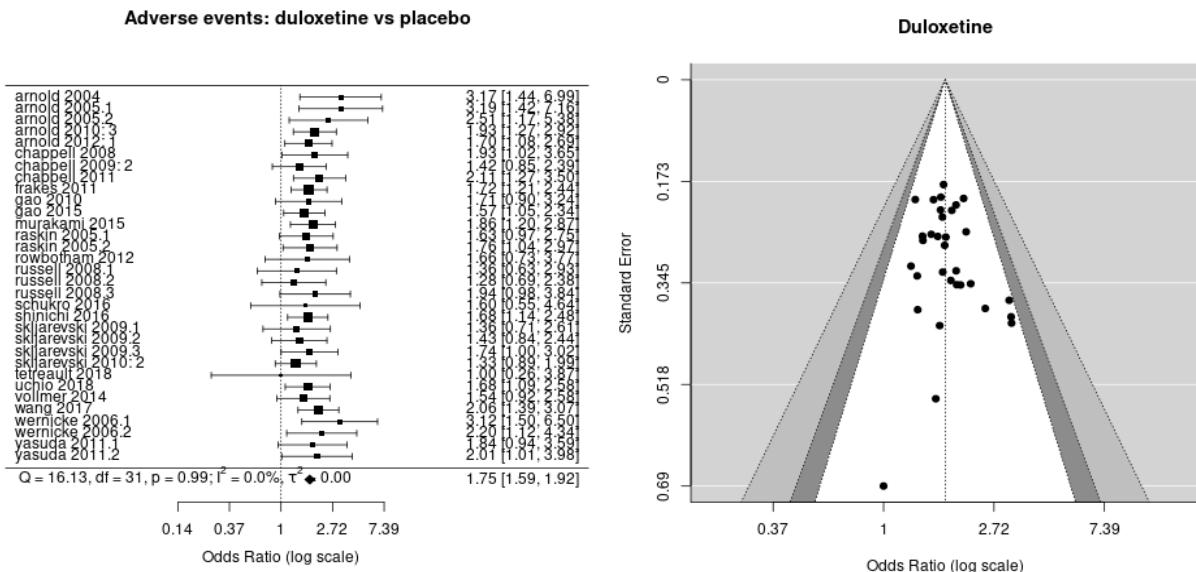


Figure 2.4: Outcome: adverse events. Measure: post-intervention. Intervention (duloxetine) compared with (placebo) Participants: 8791. Direction of improvement: lower. Meta-analysis results: $Q = 16.13$; $df = 31$; $p = 0.99$; $I^2 = 0$ per cent; $\tau^2 = 0$. Regression test for funnel plot asymmetry was significant: 0.42 (CI 0.08 to 0.76) with $p = 0.41$ and $z = 0.82$.

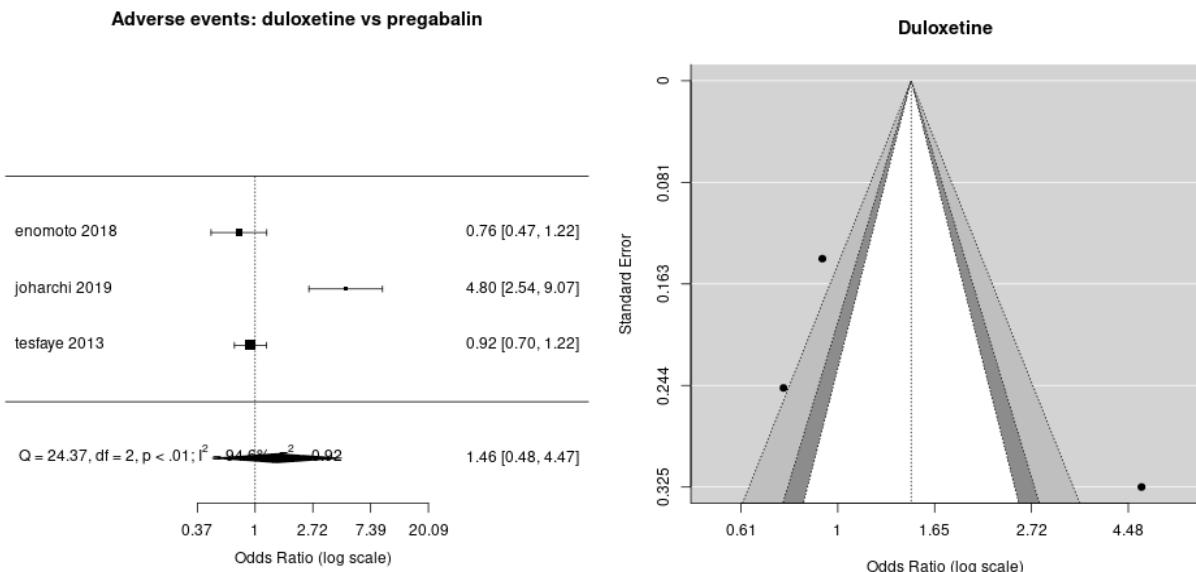


Figure 2.5: Outcome: adverse events. Measure: post-intervention. Intervention (duloxetine) compared with (pregabalin). duloxetine compared to pregabalin. Participants: 1287. Direction of improvement: lower. Meta-analysis results: $Q = 24.37$; $df = 2$; $p < .01$; $I^2 = 94.61$ per cent; $\tau^2 = 0.92$. Regression test for funnel plot asymmetry was not significant: -1.57 (CI -4.99 to 1.86) with $p = 0.24$ and $z = 1.17$.

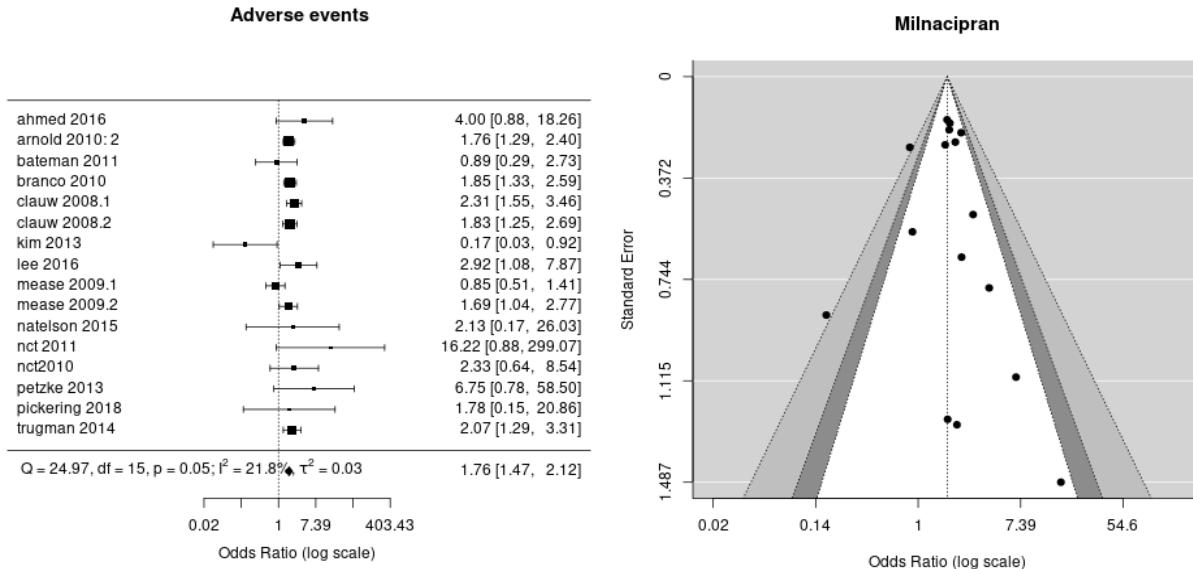


Figure 2.6: Outcome: adverse events. Measure: post-intervention. Intervention: milnacipran. Participants: 5455. Direction of improvement: lower. Meta-analysis results: $Q = 24.97$; $df = 15$; $p = 0.05$; $I^2 = 21.85$ per cent; $\tau^2 = 0.03$. Regression test for funnel plot asymmetry was significant: 0.51 (CI 0.2 to 0.83) with $p = 0.69$ and $z = 0.4$.

Amitriptyline

Amitriptyline results were inconsistent, with serious risk of bias, and there is some indication of publication bias (Figure 2.9).

Some heterogeneity is possibly explained by differences between conditions (Figure 2.10)

There was significant heterogeneity and imprecision between subgroups by duration of study for amitriptyline (Figure 2.11).

Post-intervention adverse events: milnacipran vs placebo

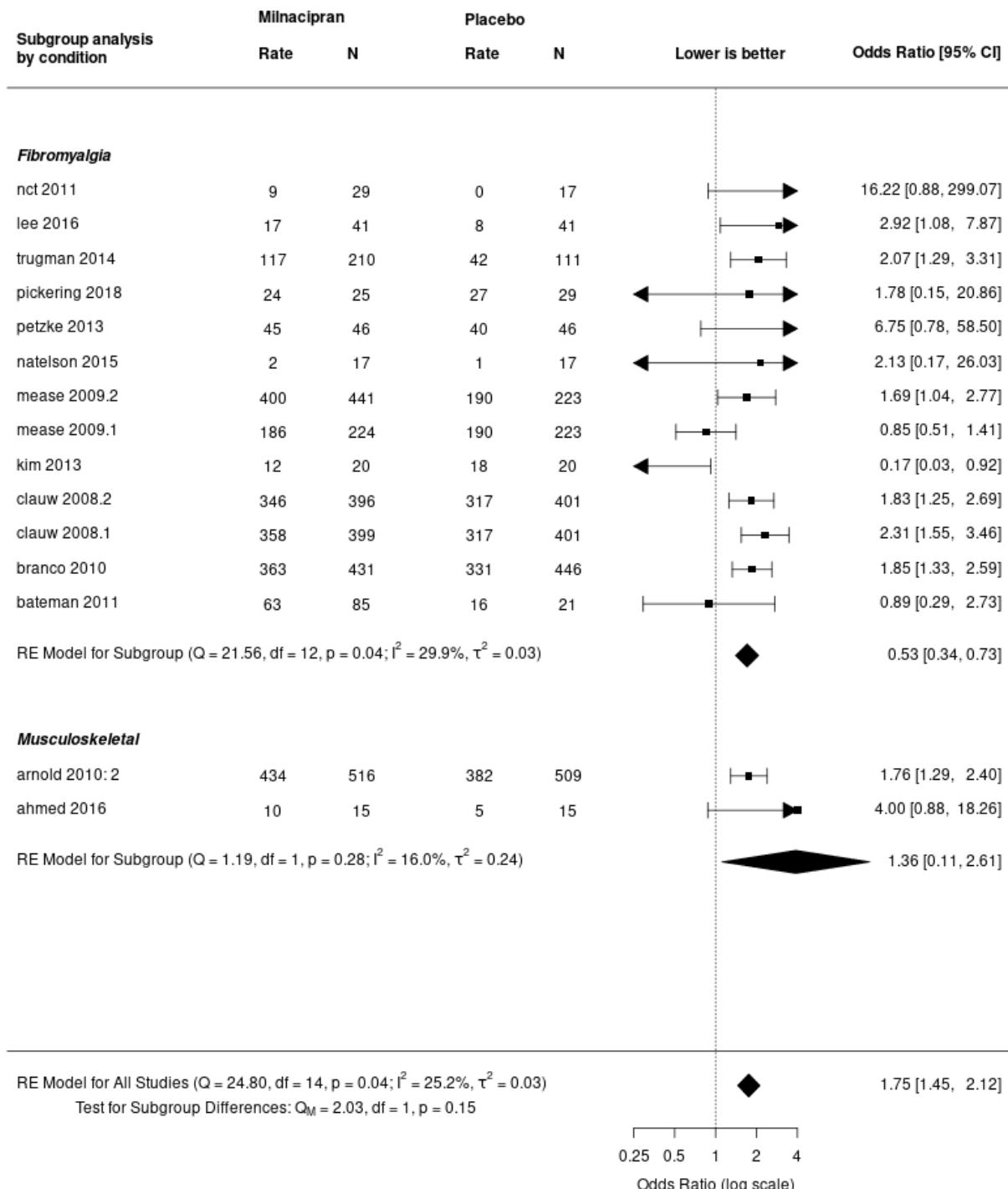


Figure 2.7: Subgroup analysis by condition. Outcome: adverse events. Measure: post-intervention. Intervention (milnacipran) compared with (placebo) Participants: 5455. Direction of improvement: lower. Meta-analysis results: $Q = 24.97$; $df = 15$; $p = 0.05$; $I^2 = 21.85$ per cent; $\tau^2 = 0.03$. Regression test for funnel plot asymmetry was significant: 0.51 (CI 0.2 to 0.83) with $p = 0.69$ and $z = 0.4$.

Post-intervention adverse events: milnacipran vs placebo

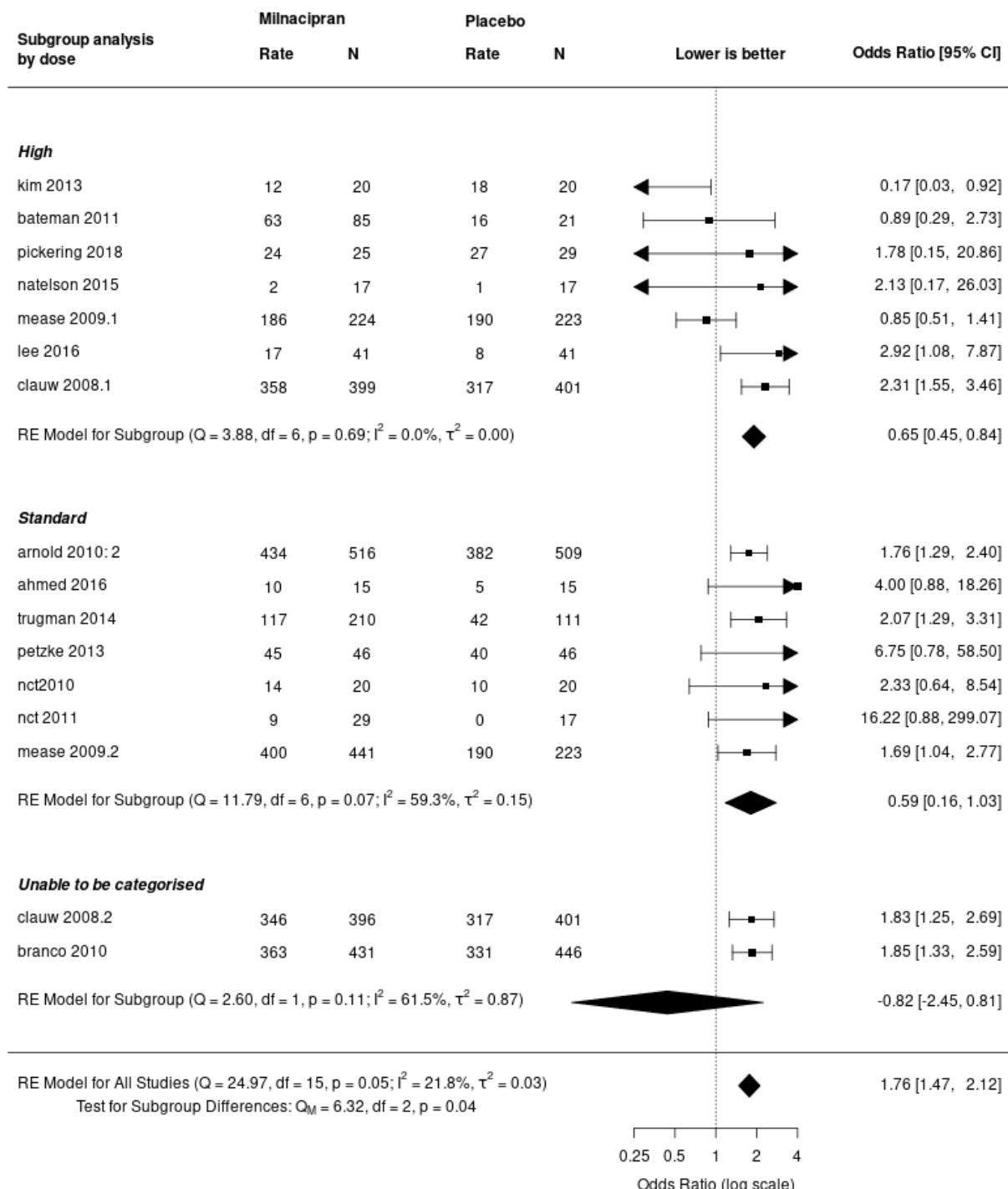


Figure 2.8: Subgroup analysis by dose. Outcome: adverse events. Measure: post-intervention. Intervention (milnacipran) compared with (placebo) Participants: 5455. Direction of improvement: lower. Meta-analysis results: $Q = 24.97$; $df = 15$; $p = 0.05$; $I^2 = 21.85$ per cent; $\tau^2 = 0.03$. Regression test for funnel plot asymmetry was significant: 0.51 (CI 0.2 to 0.83) with $p = 0.69$ and $z = 0.4$.

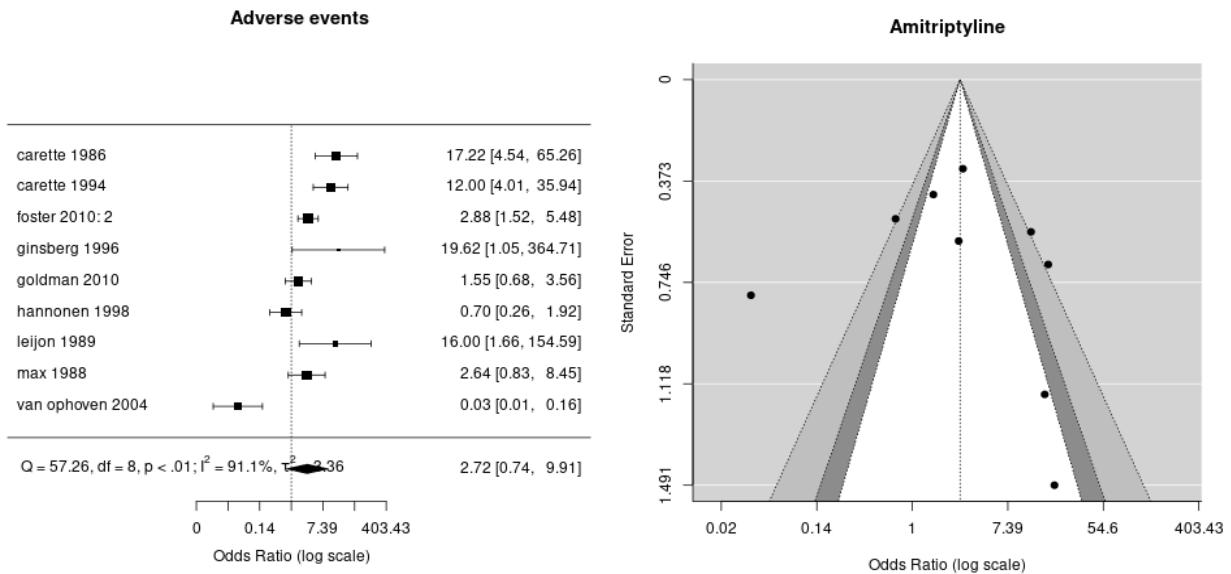


Figure 2.9: Outcome: adverse events. Measure: post-intervention. Intervention: amitriptyline. Participants: 915. Direction of improvement: lower. Meta-analysis results: $Q = 57.26$; $df = 8$; $p < .01$; $I^2 = 91.1$ per cent; $\tau^2 = 3.36$. Regression test for funnel plot asymmetry was not significant: -0.13 (CI -3.25 to 2.99) with $p = 0.43$ and $z = 0.79$.

Post-intervention adverse events: amitriptyline vs placebo

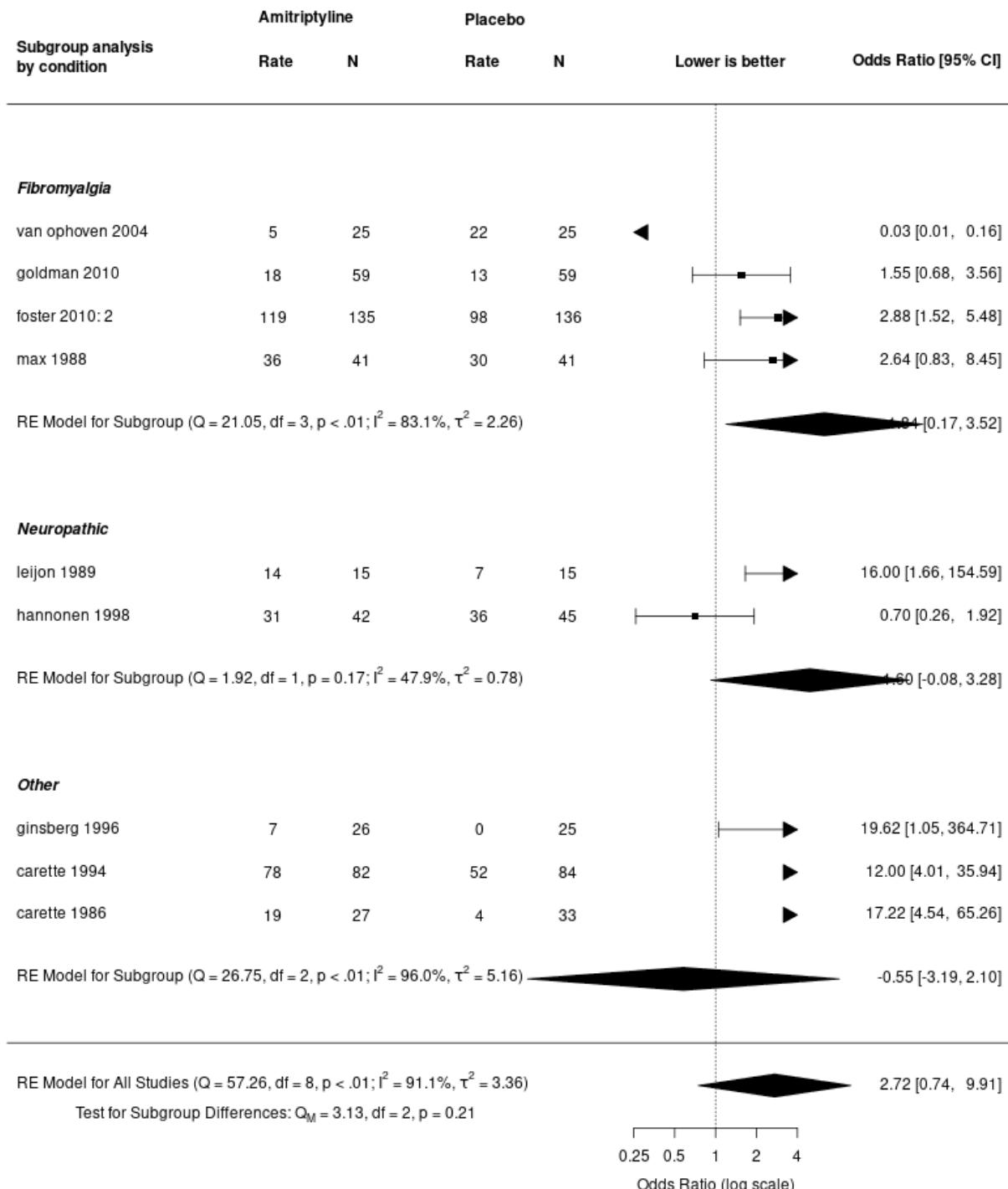


Figure 2.10: Subgroup analysis by condition. Outcome: adverse events. Measure: post-intervention. Intervention (amitriptyline) compared with (placebo) Participants: 915. Direction of improvement: lower. Meta-analysis results: $Q = 57.26$; $df = 8$; $p < .01$; $I^2 = 91.1$ per cent; $\tau^2 = 3.36$. Regression test for funnel plot asymmetry was not significant: -0.13 (CI -3.25 to 2.99) with $p = 0.43$ and $z = 0.79$.

Post-intervention adverse events: amitriptyline vs placebo

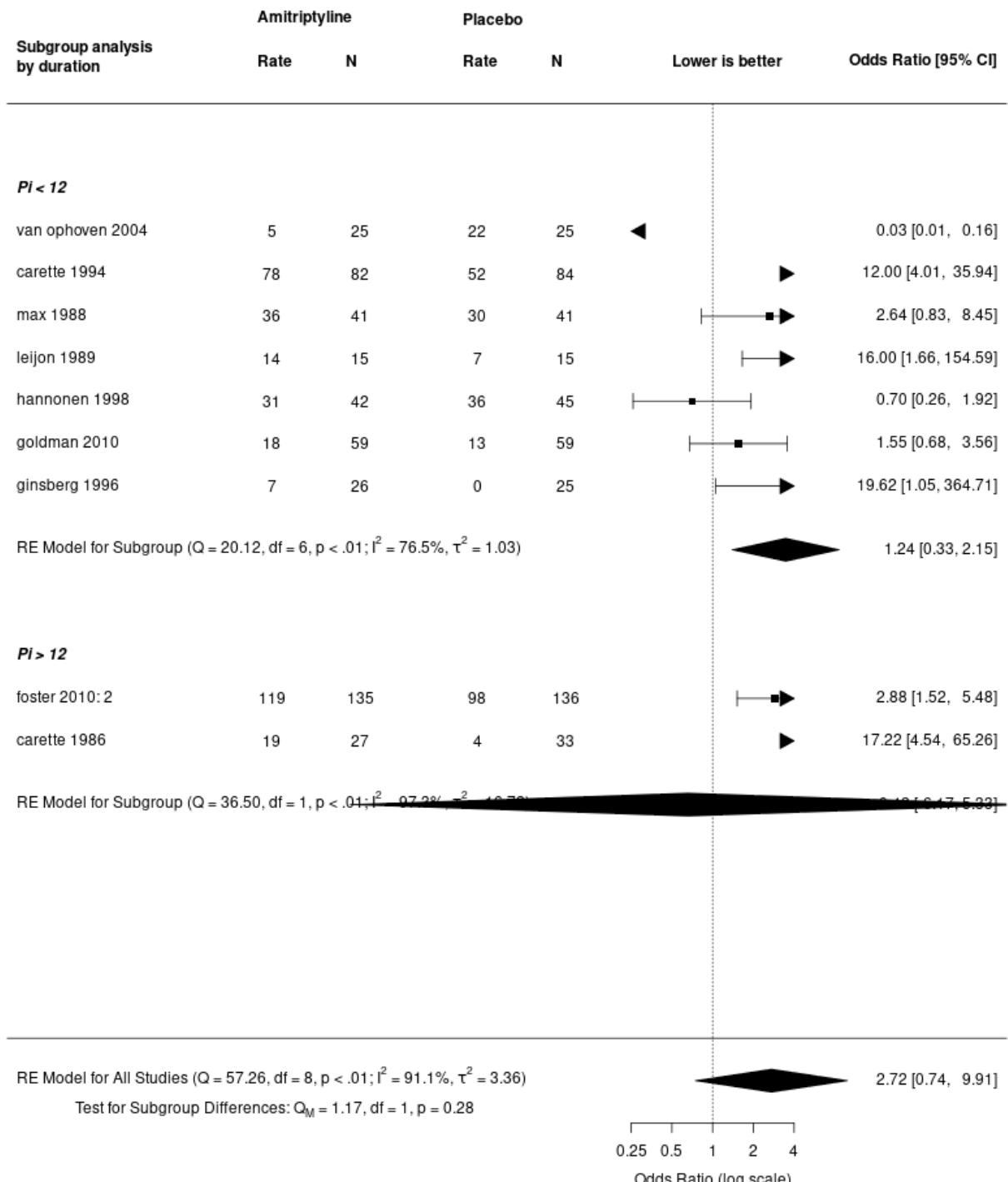


Figure 2.11: Subgroup analysis by duration. Outcome: adverse events. Measure: post-intervention. Intervention (amitriptyline) compared with (placebo) Participants: 915. Direction of improvement: lower. Meta-analysis results: $Q = 57.26$; $df = 8$; $p < .01$; $I^2 = 91.1$ per cent; $\tau^2 = 3.36$. Regression test for funnel plot asymmetry was not significant: -0.13 (CI -3.25 to 2.99) with $p = 0.43$ and $z = 0.79$.

Chapter 3

Secondary outcomes

3.1 Serious adverse events (SAE)

SAE were reported in 60 studies (8 crossover, 52 parallel) evaluating 30 interventions including 16,138 participants with one of seven pain conditions. The studies ranged from 2 to 34 weeks with most studies lasting 12 weeks. Summary of findings 3.1 shows the direct evidence network for SAE wherein there were many more participants in milnacipran and duloxetine trials than any other intervention. Aside from 2 studies comparing duloxetine to pregabalin, all other interventions evaluated by more than one study compared intervention to placebo. There are several single-study comparisons between other combinations.

Interventions (number of studies): Placebo (51); duloxetine (21); milnacipran (14); amitriptyline (6); paroxetine (4); mirtazapine (3); pregabalin (3); carbamazepine (2); citalopram (2); desvenlafaxine (2); nortriptyline (2); venlafaxine (2); benzotropine mesylate (1); benzotropine mesylate + cbt (1); bupropion (1); cbt (1); cst (1); cst + sertraline (1); desipramine (1); desipramine + cbt (1); disease management (1); esreboxetine (1); fluvoxamine (1); gabapentin (1); gabapentin + nortriptyline (1); imipramine (1); nabilone (1); nortriptyline + cbt (1); nortriptyline + disease management (1); reboxetine (1); sertraline (1).

3.1.1 Meta-analyses

There were only enough data to undertake subgroup analysis by condition for duloxetine.

Duloxetine

Duloxetine observations did not display inconsistency or imprecision, however there is serious risk of bias. Heterogeneity in duloxetine compared to placebo observations was not explained by condition, risk of bias, or duration of study.

Milnacipran

Heterogeneity of milnacipran compared to placebo was not explained by duration of study or risk of bias. Imprecision is present in these observations (Figure 3.1). There is no strong indication of risk of bias, however these observations have very serious risk of bias.

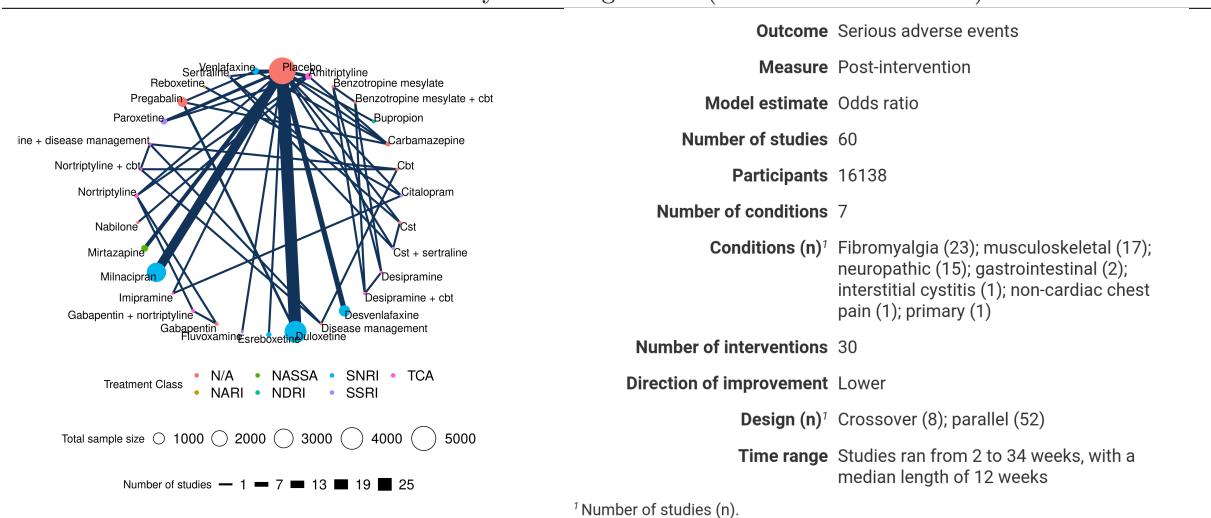
Amitriptyline

There is significant imprecision in these observations (Figure 3.2); serious risk of bias is suspected.

3.2 Dropout due to adverse events

Dropout due to adverse events was widely reported, in 110 studies (20 crossover, 90 parallel), evaluating 59 interventions over a population of 23,950. The studies ran from 2 to 34 weeks, with a median length

Table 3.1: Summary of findings: SAE (Serious adverse events).



Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]	
Duloxetine	21	6724 (2883, 3841)	0.94 (0.63 to 1.42)	14 (9 to 20)	0.38	
Milnacipran	14	4825 (1916, 2909)	0.97 (0.57 to 1.64)	15 (9 to 20)	0.79	
Amitriptyline	6	406 (139, 267)	166.08 (0.96 to 1296056.64)	24 (15 to 30)	0.33	
Paroxetine	4	334 (120, 214)	0.63 (0.1 to 3.49)	13 (7 to 21)	0.75	
Mirtazapine	3	510 (241, 269)	978.26 (0.33 to 925880843.95)	24 (10 to 31)	0	
Pregabalin	3	643 (0, 643)	1.47 (0.57 to 3.85)	17 (10 to 23)	0.33	
Carbamazepine	2	114 (15, 99)	76031.75 (8.33 to 77935045723.02)	28 (21 to 31)	0.5	
Citalopram	2	50 (16, 34)	0.42 (0 to 36670877.13)	15 (1 to 31)	1	
Desvenlafaxine	2	1110 (221, 889)	0.48 (0.22 to 1.05)	11 (6 to 17)	0.5	
Nortriptyline	2	134 (40, 94)	0.53 (0 to 94384924.51)	15 (1 to 31)	0.5	
Venlafaxine	2	331 (81, 250)	1.08 (0.39 to 3.06)	15 (9 to 22)	0.5	
Benzotropine mesylate	1	33 (0, 33)	0 (0 to 4361.99)	9 (1 to 26)	1	
Benzotropine mesylate + cbt	1	34 (0, 34)	0.01 (0 to 4496.93)	9 (1 to 26)	1	
Bupropion	1	108 (54, 54)	2.82 (0.19 to 77.43)	18 (8 to 25)	1	
Cbt	1	38 (0, 38)	0.87 (0 to 158686141)	15 (1 to 31)	1	
Cst	1	57 (28, 29)	0.72 (0 to 160952818.74)	15 (1 to 31)	1	
Cst + sertraline	1	56 (28, 28)	0.76 (0 to 364083690.46)	15 (1 to 31)	1	
Desipramine	1	38 (0, 38)	186 (0 to 18675572.1)	22 (6 to 31)	1	
Desipramine + cbt	1	37 (0, 37)	193.89 (0 to 21292188.66)	22 (6 to 31)	1	
Disease management	1	24 (0, 24)	0.98 (0 to 252499342.44)	15 (1 to 31)	1	
Eseboxetine	1	267 (133, 134)	2 (0.8 to 4.96)	18 (12 to 23)	0	
Fluvoxamine	1	60 (30, 30)	0.15 (0.01 to 1.59)	9 (4 to 18)	1	
Gabapentin	1	56 (0, 56)	0.66 (0 to 129733437.12)	15 (1 to 31)	0	
Gabapentin + nortriptyline	1	56 (0, 56)	0.67 (0 to 99048949.12)	15 (1 to 31)	0	
Imipramine	1	34 (16, 18)	0.61 (0 to 71923136.02)	15 (1 to 31)	1	
Nabilone	1	32 (0, 32)	26	0.59 (0 to 176943139.83)	15 (1 to 31)	1
Nortriptyline + cbt	1	41 (0, 41)	0.89 (0 to 114657033.22)	15 (1 to 31)	1	
Nortriptyline + disease management	1	37 (0, 37)	1.03 (0 to 180848887.45)	15 (1 to 31)	1	

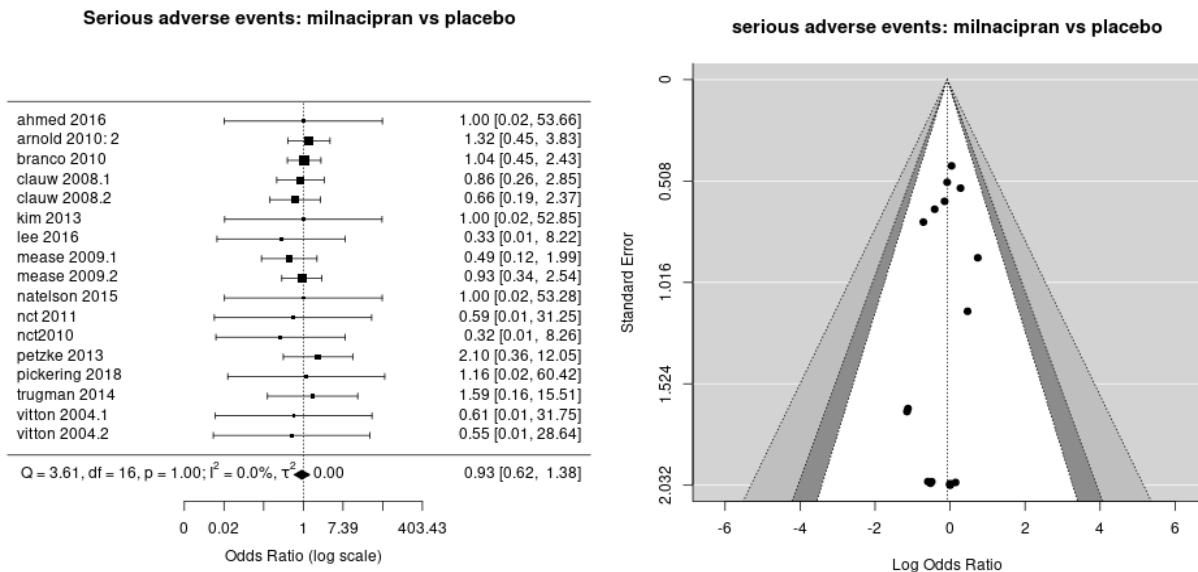


Figure 3.1: Outcome: serious adverse events. Measure: post-intervention. Intervention (amitriptyline) compared with (placebo) Participants: 278. Direction of improvement: lower. Meta-analysis results: $Q = 0$; $df = 3$; $p = 1.00$; $I^2 = 0$ per cent; $\tau^2 = 0$. Regression test for funnel plot asymmetry was not significant: 0 (CI -445.11 to 445.11) with $p = 1$ and $z = 0$.

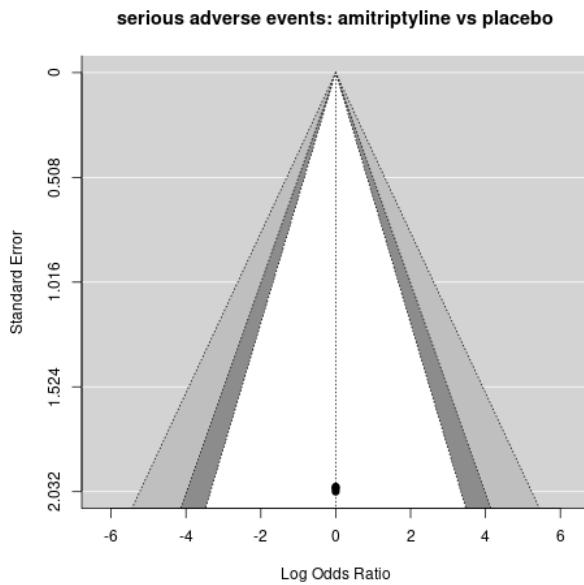


Figure 3.2: Outcome: serious adverse events. Measure: post-intervention. Intervention (amitriptyline) compared with (placebo) Participants: 278. Direction of improvement: lower. Meta-analysis results: $Q = 0$; $df = 3$; $p = 1.00$; $I^2 = 0$ per cent; $\tau^2 = 0$. Regression test for funnel plot asymmetry was not significant: 0 (CI -445.11 to 445.11) with $p = 1$ and $z = 0$.

of 10 weeks. The complexity of the network geometry (Summary of findings 3.2) is driven by the number of interventions and comparators. However, the majority of trials were in duloxetine, amitriptyline, and milnacipran. The population were primarily fibromyalgia, neuropathic, and musculoskeletal pain patients. Pregabalin was used as a comparator against duloxetine in three studies, and benztropine mesylate was compared again amitriptyline in two studies. The other comparators were unique to single trials.

Interventions (number of studies): Placebo (82); Duloxetine (32); Amitriptyline (25); Milnacipran (12); Pregabalin (8); Gabapentin (6); Venlafaxine (6); Nortriptyline (5); Paroxetine (5); Benzotropine mesylate (4); Fluoxetine (4); Carbamazepine (3); Desipramine (3); Imipramine (3); Mirtazapine (3); Cbt (2); Citalopram (2); Escitalopram (2); Esreboxetine (2); Maprotiline (2); Morphine (2); Sertraline (2); Trazodone (2); Acetaminophen (1); Amitriptyline + fluoxetine (1); Amitriptyline + fluphenazine (1); Amitriptyline + naproxen (1); Amitriptyline + riboflavin (vitamin b2) (1); Benzotropine mesylate + cbt (1); Bupropion (1); Clomipramine (1); Cst (1); Cst + sertraline (1); Cyclobenzaprine (1); Desipramine + cbt (1); Desipramine + lidocaine (1); Desvenlafaxine (1); Diphenhydramine (1); Doxepin (1); Education (1); Fluphenazine (1); Gabapentin + nortriptyline (1); Glycopyrrolate (1); Lidocaine (1); Lorazepam (1); Melatonin (1); Melatonin + amitriptyline (1); Moclobemide (1); Morphine + nortriptyline (1); Naproxen (1); Nortriptyline + morphine (1); Physical therapy (1); Pirlindole (1); Pregabalin + duloxetine (1); Pregabalin + imipramine (1); Reboxetine (1); Riboflavin (vitamin b2) (1); Trazodone + gabapentin (1); Trimipramine (1); Zimeldine (1).

3.2.1 Meta-analysis results

Duloxetine

When all trials are considered, i.e., across all doses, conditions, and other subgroups, meta-analytic results for duloxetine are consistent with the estimates of the network analysis. 0.4 of studies were ranked as high risk of bias. Some heterogeneity is explained by difference between pain condition groups (Figure 3.3), where neuropathic patients are more likely to drop out of the study due to adverse events than fibromyalgia patients.

There was not as much difference between different dose groups (Figure 3.4), but the higher the dosage, the more likely the participant was to drop out to adverse events. No heterogeneity was explained by risk of bias or duration of study.

Amitriptyline

As with duloxetine, above, amitriptyline trials were consistent within themselves, and with the network meta-anlaysis estimates. 0.5 of studies were raked as high risk of bias. Subgroup analysis by duration of study did not explain any heterogeneity observed.

Milnacipran

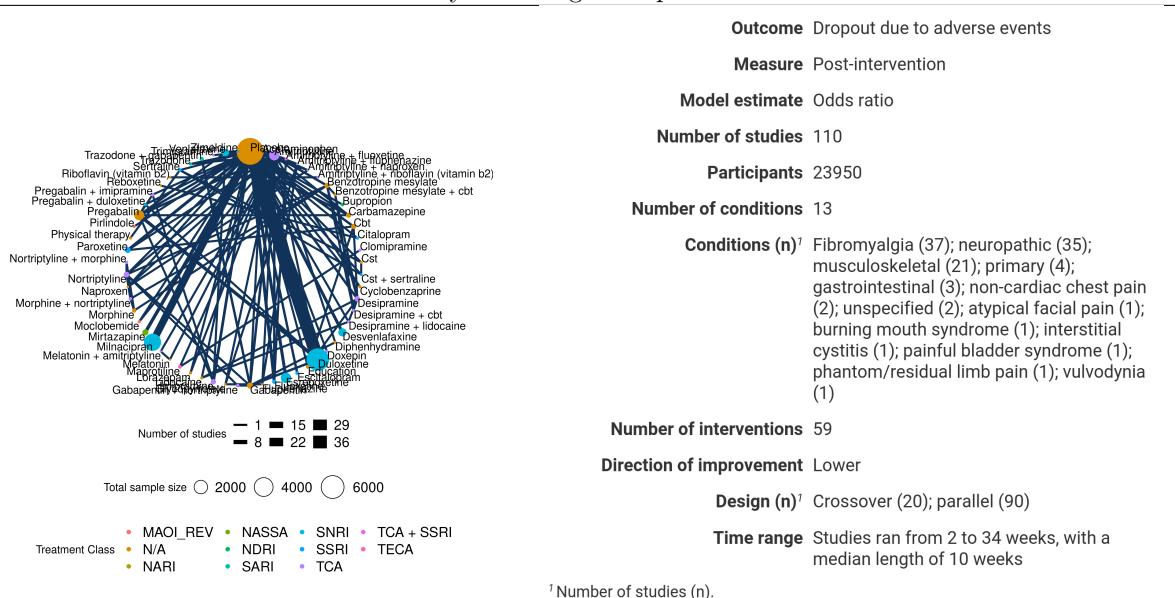
Meta-analysis results for milnacipran were consistent with network meta-analysis findings. 0.8 of studies were high risk of bias, and publication bias was also detected. Some heterogeneity explained by duration of study (Figure 3.5), with participants in trials lasting more than 12 weeks signficantly more likely to drop out due to adverse events.

3.3 Moderate pain relief (30 per cent reduction)

Moderate pain was reported in 41 studies (5 crossover, 36 parallel) evaluating 21 interventions over a total of 14,240 participants. The studies ran from 4 to 28 weeks, with a median length of 12 weeks. The network geometry shown in Summary of findings Table 3.3 is disconnected, with unique comparators within single trials. Comparators, other than placebo, were pregablin, amitriptyline, cognitive behavioural therapy, nortriptyline, and morphine. Pregablin was used as comparator in two studies, and the rest in single trials.

Interventions: Placebo (32); Duloxetine (25); Milnacipran (7); Pregabalin (4); Amitriptyline (2); Esreboxetine (2); Mirtazapine (2); Nortriptyline (2); Benzotropine mesylate (1); Benzotropine mesylate + cbt (1); Carbamazepine (1); Cbt (1); Cbt and milnacipran (1); Desipramine (1); Desipramine + cbt (1); Diphenhydramine (1); Gabapentin (1); Imipramine (1); Morphine (1); Nortriptyline + morphine (1); Pregabalin + imipramine (1); Venlafaxine (1).

Table 3.2: Summary of findings: Dropout due to adverse events.



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³	
Duloxetine	32	9133 (3694, 5439)	2.12 (1.72 to 2.65)	33 (26 to 41)	0.41	
Amitriptyline	25	1546 (562, 984)	1.86 (1.16 to 3)	31 (23 to 40)	0.48	
Milnacipran	12	5006 (1940, 3066)	2.25 (1.67 to 3.05)	35 (26 to 43)	0.83	
Pregabalin	8	1029 (114, 915)	1.56 (0.99 to 2.46)	28 (20 to 37)	0.38	
Gabapentin	6	269 (0, 269)	4.47 (1.44 to 14.39)	44 (27 to 54)	0.5	
Venlafaxine	6	597 (171, 426)	3.03 (1.48 to 6.52)	39 (26 to 50)	0.5	
Nortriptyline	5	274 (38, 236)	1.26 (0.34 to 4.65)	26 (14 to 44)	0.2	
Paroxetine	5	380 (143, 237)	1.78 (0.87 to 3.74)	30 (19 to 44)	0.8	
Benzotropine mesylate	4	181 (0, 181)	1.45 (0.52 to 4.23)	27 (15 to 43)	0.75	
Fluoxetine	4	187 (92, 95)	0.88 (0.1 to 6.9)	24 (11 to 49)	0.5	
Carbamazepine	3	180 (15, 165)	0.57 (0.14 to 2.11)	18 (11 to 34)	0.33	
Desipramine	3	320 (105, 215)	3.71 (1.29 to 11.21)	41 (25 to 52)	0.67	
Imipramine	3	351 (173, 178)	1.33 (0.46 to 3.81)	26 (15 to 43)	0.33	
Mirtazapine	3	510 (241, 269)	0.93 (0.33 to 2.55)	22 (13 to 37)	0	
Cbt	2	262 (95, 167)	0 (0 to 0.11)	6 (1 to 12)	1	
Citalopram	2	57 (19, 38)	606.07 (1.74 to 10959477.59)	55 (30 to 60)	0.5	
Escitalopram	2	133 (67, 66)	9.96 (1.07 to 210.54)	48 (22 to 58)	0.5	
Esrreboxetine	2	1381 (410, 971)	3.77 (1.95 to 7.42)	42 (30 to 51)	0.5	
Maprotiline	2	65 (0, 65)	0 (0 to 6.36)	11 (1 to 47)	1	
Morphine	2	107 (0, 107)	6.17 (1.17 to 35.63)	46 (25 to 56)	0.5	
Sertraline	2	94 (28, 66)	4.5 (0.8 to 34.29)	42 (20 to 56)	1	
Trazodone	2	60 (19, 41)	16.03 (3.44 to 117.36)	52 (41 to 58)	1	
Acetaminophen	1	50 (0, 50)	0.53 (0 to 84937608.38)	30 (1 to 60)	1	
Amitriptyline + fluoxetine	1	62 (31, 31)	29	7.22 (0.91 to 67.83)	46 (20 to 57)	1
Amitriptyline + fluphenazine	1	12 (0, 12)	0 (0 to 7.62)	10 (1 to 50)	0	
Amitriptyline + naproxen	1	38 (19, 19)	3.23 (0.08 to 128.26)	37 (11 to 58)	1	

Post-intervention dropout due to adverse events: duloxetine vs placebo

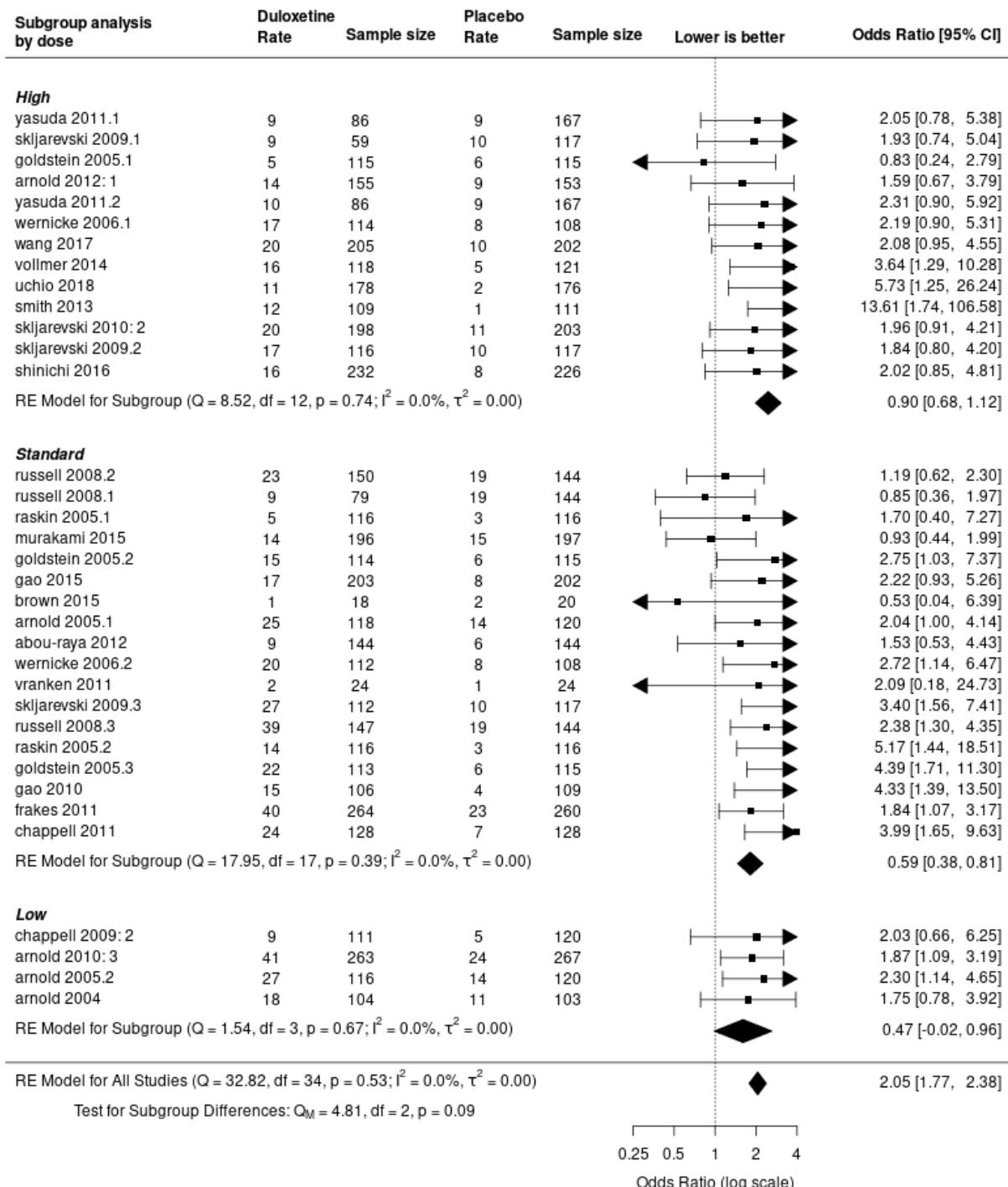


Figure 3.4: Subgroup analysis by dose. Outcome: dropout due to adverse events. Measure: post-intervention. Intervention (duloxetine) compared with (placebo) Participants: 9623. Direction of improvement: lower. Meta-analysis results: $Q = 32.95$; $df = 35$; $p = 0.57$; $I^2 = 0$ per cent; $\tau^2 = 0$. Regression test for funnel plot asymmetry was not significant: 0.39 (CI -0.08 to 0.87) with $p = 0.15$ and $z = 1.43$.

Post-intervention dropout due to adverse events: milnacipran vs placebo

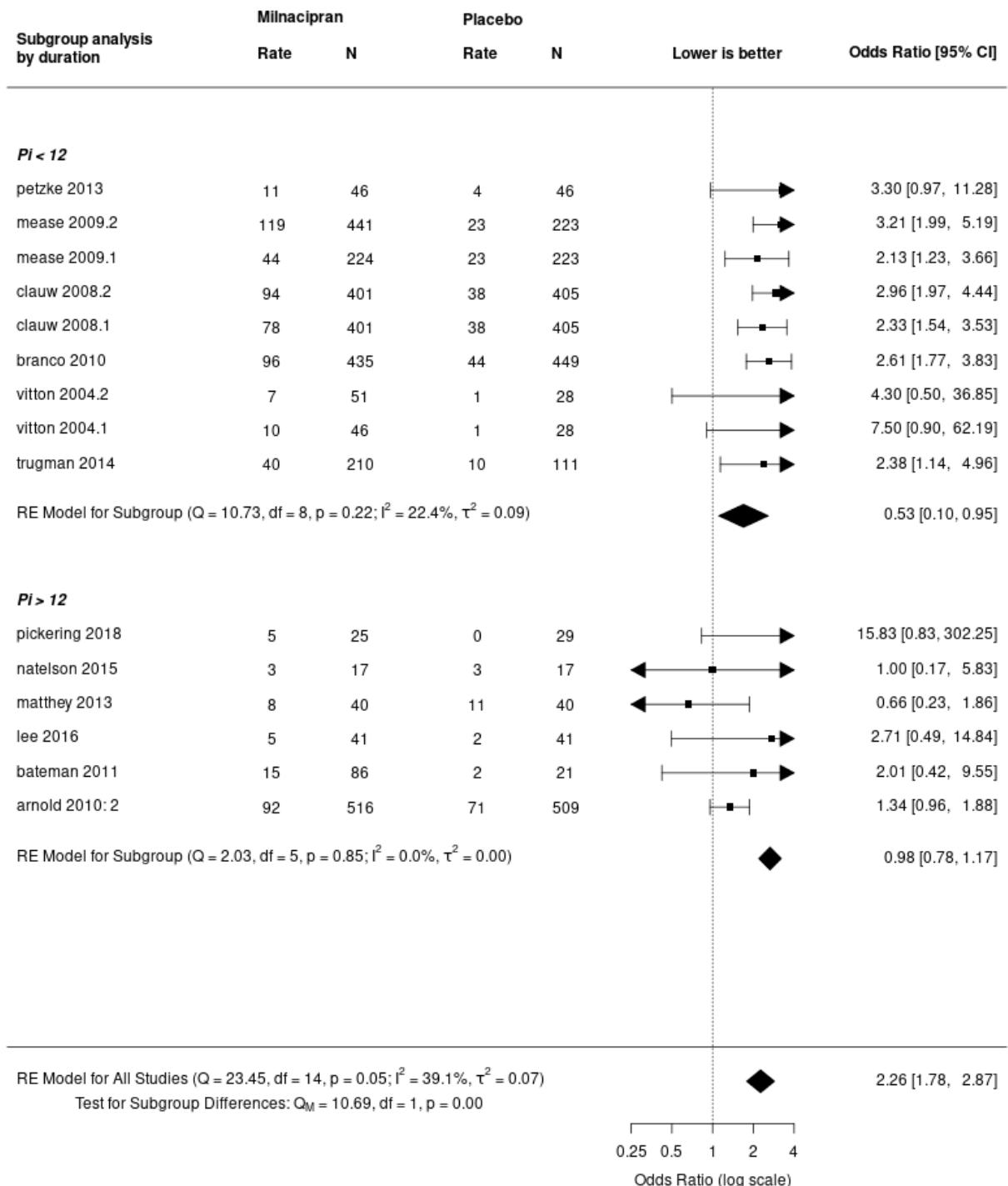
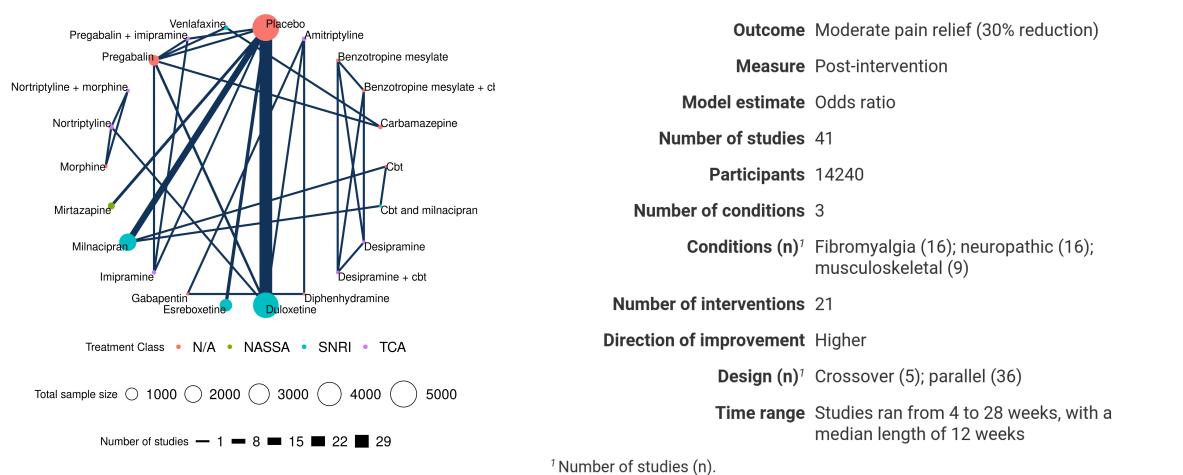


Figure 3.5: Subgroup analysis by duration.

Table 3.3: Summary of findings: Moderate pain relief (30% reduction).



Outcome Moderate pain relief (30% reduction)

Measure Post-intervention

Model estimate Odds ratio

Number of studies 41

Participants 14240

Number of conditions 3

Conditions (n)[†] Fibromyalgia (16); neuropathic (16); musculoskeletal (9)

Number of interventions 21

Direction of improvement Higher

Design (n)[†] Crossover (5); parallel (36)

Time range Studies ran from 4 to 28 weeks, with a median length of 12 weeks

[†] Number of studies (n).

Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Duloxetine	25	7708 (3176, 4532)	1.87 (1.61 to 2.17)	8 (4 to 13)	0.4
Milnacipran	7	3124 (1149, 1975)	1.68 (1.26 to 2.21)	10 (4 to 15)	0.86
Pregabalin	4	749 (69, 680)	1.28 (0.86 to 2.01)	12 (7 to 17)	0.25
Amitriptyline	2	80 (0, 80)	1.72 (0.68 to 4.24)	9 (3 to 16)	1
Eseboxetine	2	1374 (409, 965)	1.67 (1.08 to 2.57)	10 (4 to 16)	0.5
Mirtazapine	2	462 (224, 238)	1.91 (1.06 to 3.43)	8 (3 to 15)	0
Nortriptyline	2	108 (0, 108)	0.07 (0 to 0.46)	19 (15 to 22)	0
Benzotropine mesylate	1	33 (0, 33)	0.82 (0 to 13018.78)	12 (1 to 22)	1
Benzotropine mesylate + cbt	1	34 (0, 34)	0.68 (0 to 10456.35)	13 (1 to 22)	1
Carbamazepine	1	85 (0, 85)	5.7 (2.2 to 15.49)	3 (1 to 7)	1
Cbt	1	19 (0, 19)	0.65 (0.13 to 3.12)	15 (4 to 20)	1
Cbt and milnacipran	1	20 (0, 20)	1.75 (0.42 to 7.64)	9 (1 to 18)	1
Desipramine	1	37 (0, 37)	1.23 (0 to 18173.69)	10 (1 to 21)	1
Desipramine + cbt	1	37 (0, 37)	0.87 (0 to 13385.36)	12 (1 to 22)	1
Diphenhydramine	1	22 (0, 22)	0.63 (0.12 to 3.21)	15 (5 to 20)	1
Gabapentin	1	22 (0, 22)	0.63 (0.12 to 3.24)	15 (5 to 20)	1
Imipramine	1	138 (69, 69)	2.03 (0.86 to 4.77)	8 (3 to 16)	0
Morphine	1	51 (0, 51)	0.03 (0 to 0.3)	21 (17 to 22)	0
Nortriptyline + morphine	1	51 (0, 51)	0.08 (0 to 0.75)	19 (14 to 21)	0
Pregabalin + imipramine	1	138 (69, 69)	5.48 (2.51 to 12.58)	3 (1 to 7)	0
Venlafaxine	1	86 (0, 86)	2.03 (0.74 to 5.55)	8 (2 to 17)	1
Placebo				14 (10 to 18)	

[†] Table is ordered by interventions with greatest number of studies.

[‡] Direction of improvement: higher.

[§] Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table follows the recommendations of Yepes-Nuñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. Journal of Clinical Epidemiology, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

Summary of head to head comparisons

Head-to-head comparison by condition was only possible for duloxetine. There was no difference for all possible comparisons (duloxetine and milnacipran) by duration of study (less than 12 weeks or greater).

3.3.1 Meta-analyses

Duloxetine

Meta-analysis comparing duloxetine to placebo produces the same results as for substantial pain (see Figure 2.1); i.e., consistent, precise, in keeping with the network meta-analysis results, but some indication of publication bias (not significant). Subgroup analysis (Figure 3.6) by condition showed some difference between musculoskeletal patients and other pain conditions.

Heterogeneity of duloxetine (Figure 3.7) is partly explained by dose, where low dose does not show an effect. There was not a significant difference between high and low risk of bias studies comparing duloxetine with placebo. Similarly, no difference by duration of study.

Milnacipran

No publication bias, inconsistency, or imprecision detected for milnacipran. However, the proportion of studies with high risk of bias is 0.86. All milnacipran trials were in fibromyalgia patients. There was not a significant difference between dosages at high, standard, and dosages unable to be categorised. Similarly, no difference between long and short duration studies.

3.4 PGIC (Much or very much improved)

Patient global impression of change (PGIC) measured as *much or very much improved* was reported in 13 parallel-design studies evaluating 6 interventions, of which only one study did not include a placebo trial, including 7258 participants (4541 intervention, 2717 placebo). Studies ran from 6 to 27 weeks, with a median length of 14 weeks. The direct evidence network in Summary of findings 3.4 shows that aside from one study comparing paroxetine and amitriptyline, all other studies included a placebo trial and only one SNRI intervention.

Interventions (number of studies): Placebo (12); duloxetine (5); milnacipran (5); amitriptyline (1); desvenlafaxine (1); esreboxetine (1); paroxetine (1).

3.4.1 Meta-analyses

Subgroup analyses were not possible with these data.

Duloxetine

In Figure 3.8 we see duloxetine compared to placebo does not display imprecision or inconsistency, however, from visual inspection there is some indication of publication bias. These observations have serious risk of bias.

Milnacipran

Milnacipran observations display significant publication bias (Figure 3.9), and are of very serious risk of bias.

3.5 PGIC (Any improvement)

Patient global impression of change (PGIC) measured as *any improvement* was reported in 5 studies (2 crossover, 3 parallel) evaluating 5 interventions over trials including 550 participants (365 intervention, 185 placebo). Summary of findings 3.5 shows a disconnected network, wherein most comparisons are with

Post-intervention moderate pain relief (30% reduction): duloxetine vs placebo

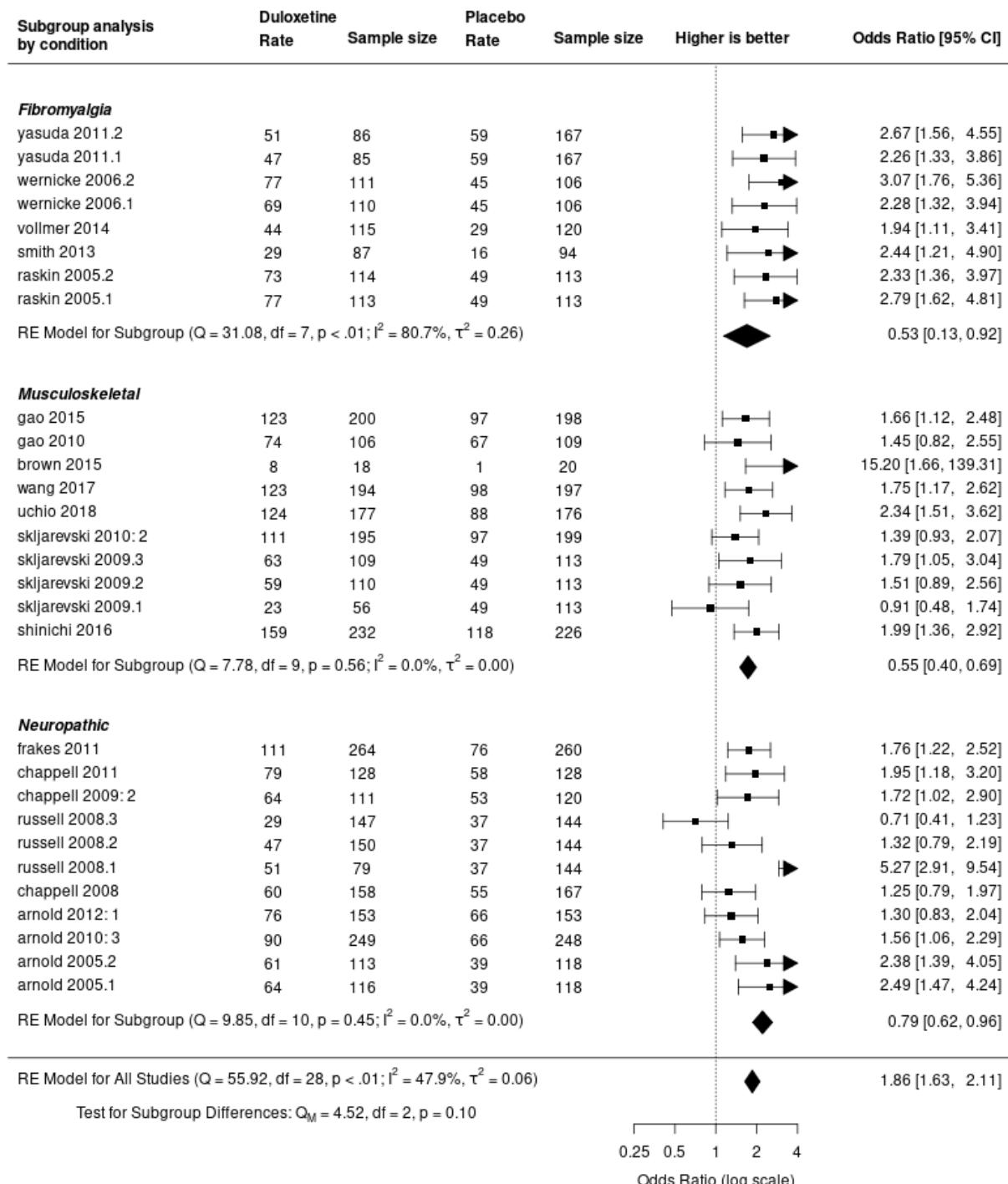


Figure 3.6: Subgroup analysis by condition. Outcome: moderate pain relief (30 per cent reduction). Measure: post-intervention. Intervention (duloxetine) compared with (placebo) Participants: 8080. Direction of improvement: higher. Meta-analysis results: $Q = 55.92$; $df = 28$; $p < .01$; $I^2 = 47.9$ per cent; $\tau^2 = 0.06$. Regression test for funnel plot asymmetry was not significant: 0.07 (CI -0.45 to 0.59) with $p = 0.03$ and $z = 2.14$.

Post-intervention moderate pain relief (30% reduction): duloxetine vs placebo

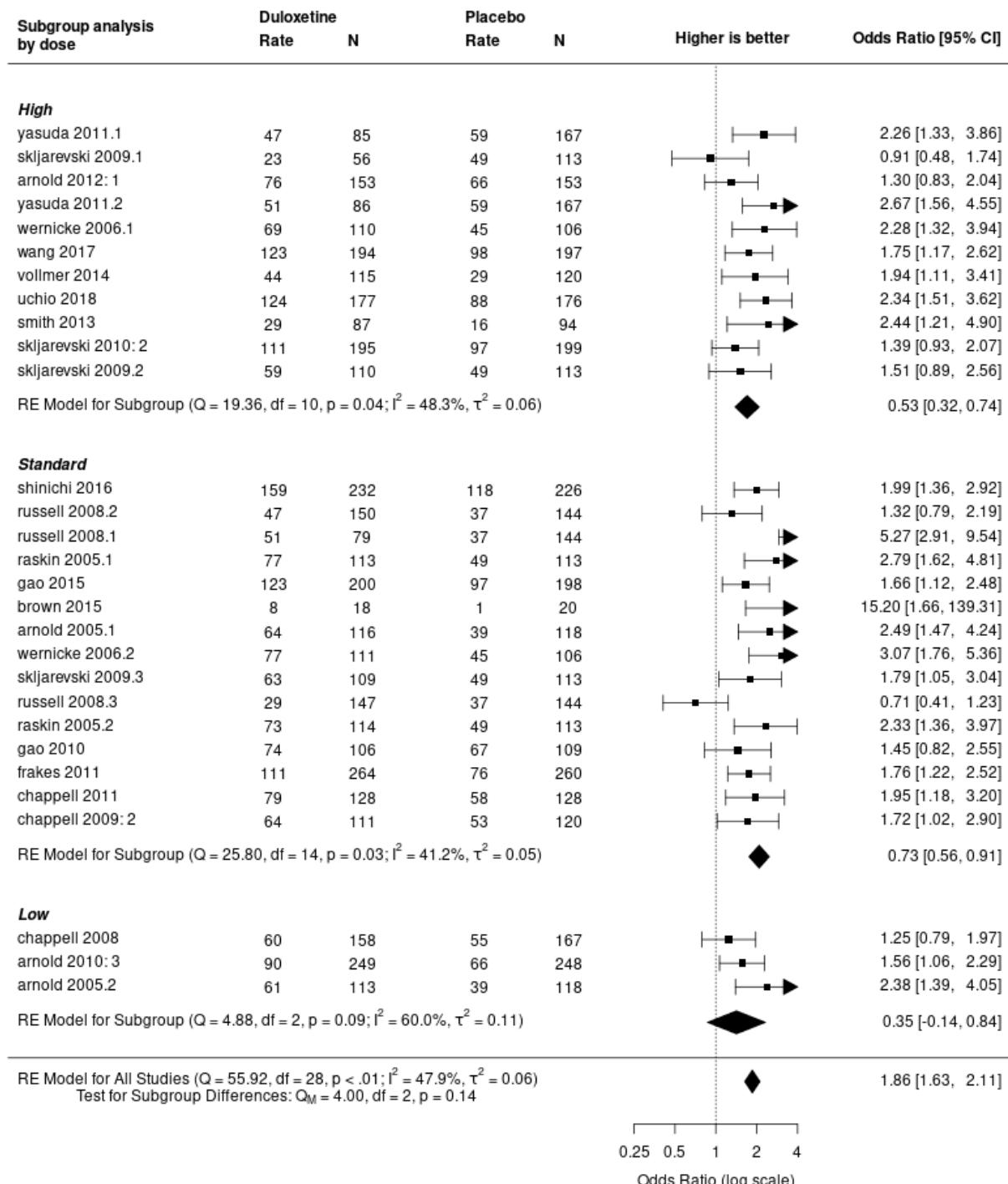
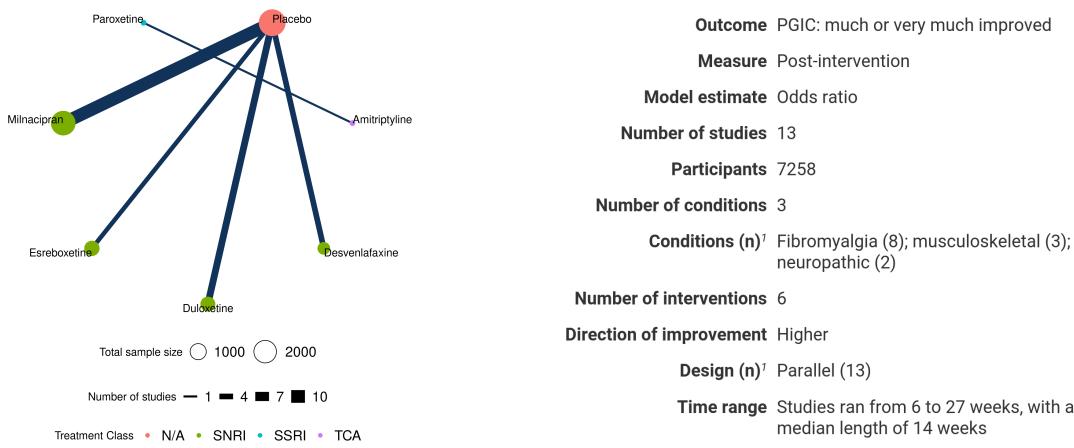


Figure 3.7: Subgroup analysis by dose. Outcome: moderate pain relief (30 per cent reduction). Measure: post-intervention. Intervention (duloxetine) compared with (placebo) Participants: 8080. Direction of improvement: higher. Meta-analysis results: $Q = 55.92$; $df = 28$; $p < .01$; $I^2 = 47.9\%$ per cent; $\tau^2 = 0.06$. Regression test for funnel plot asymmetry was not significant: 0.07 (CI -0.45 to 0.59) with $p = 0.03$ and $z = 2.14$.

Table 3.4: Summary of findings: PGIC (Much or very much improved).



Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Duloxetine	5	1541 (773, 768)	2.2 (1.7 to 2.84)	2 (1 to 5)	0.4
Milnacipran	5	3809 (1543, 2266)	1.95 (1.61 to 2.35)	3 (1 to 5)	0.8
Amitriptyline	1	81 (0, 81)	0.71 (0 to 979662.23)	5 (1 to 7)	0
Desvenlafaxine	1	659 (126, 533)	0.84 (0.54 to 1.29)	6 (4 to 7)	1
Esreboxetine	1	1086 (275, 811)	1.73 (1.18 to 2.54)	4 (1 to 5)	1
Paroxetine	1	82 (0, 82)	1.05 (0 to 1557320.89)	4 (1 to 7)	0
Placebo				5 (4 to 7)	

[†]Table is ordered by interventions with greatest number of studies.

[‡]Direction of improvement: higher.

[§]Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table use this work as a guide: Yépés-Núñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology*, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

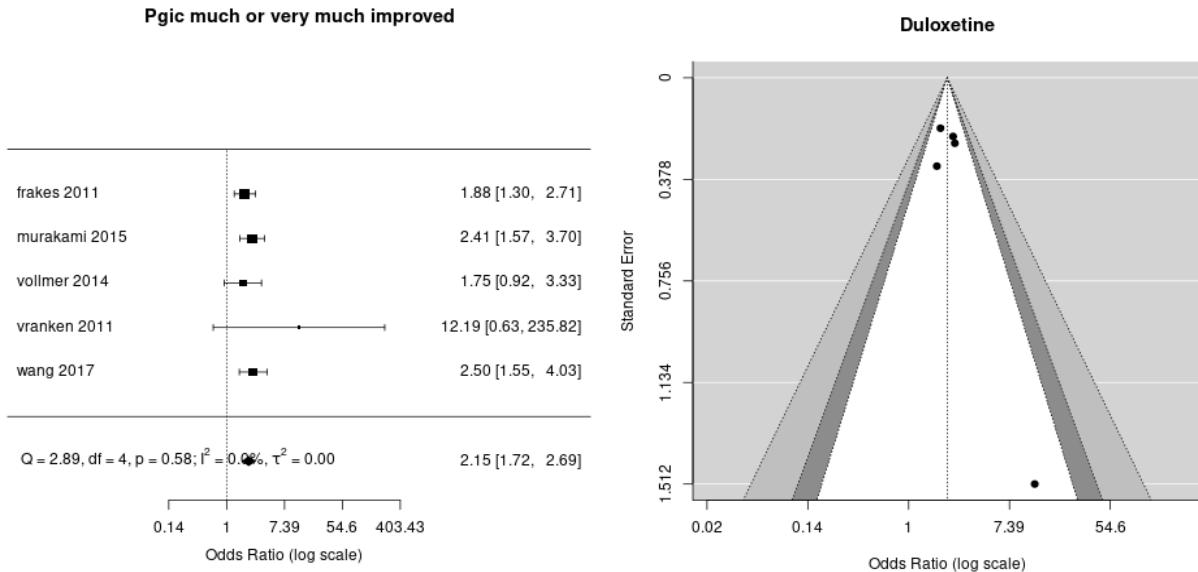


Figure 3.8: Outcome: PGIC much or very much improved. Measure: post-intervention. Intervention (duloxetine) compared with (placebo). Participants: 1541. Direction of improvement: higher. Meta-analysis results: $Q = 2.89$; $df = 4$; $p = 0.58$; $I^2 = 0$ per cent; $\tau^2 = 0$. Regression test for funnel plot asymmetry was not significant: 0.51 (CI -0.03 to 1.05) with $p = 0.31$ and $z = 1.02$.

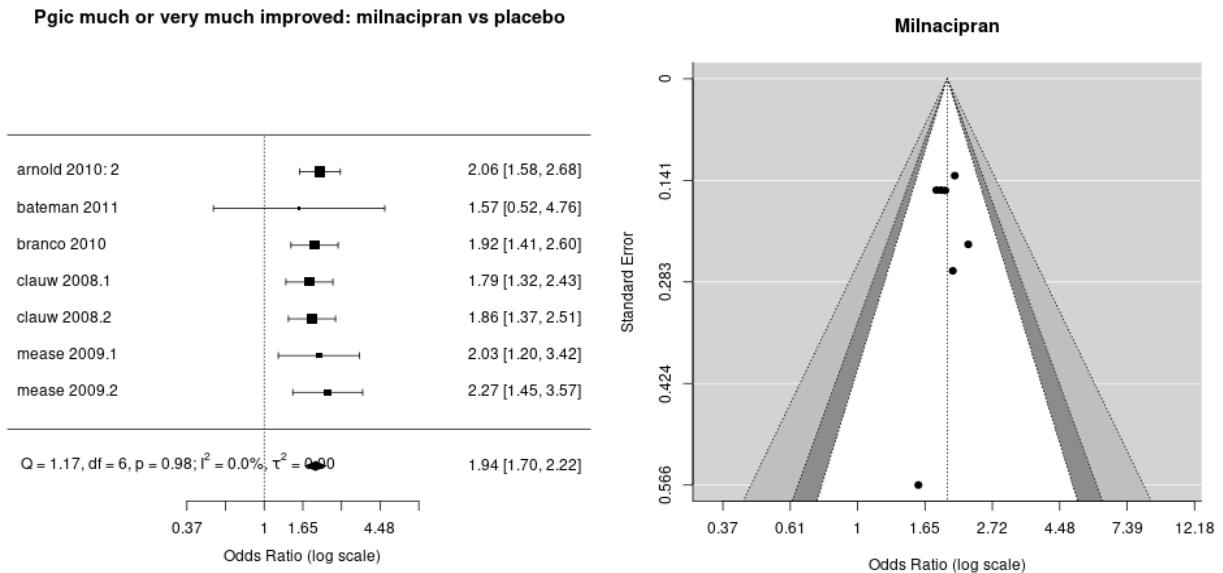
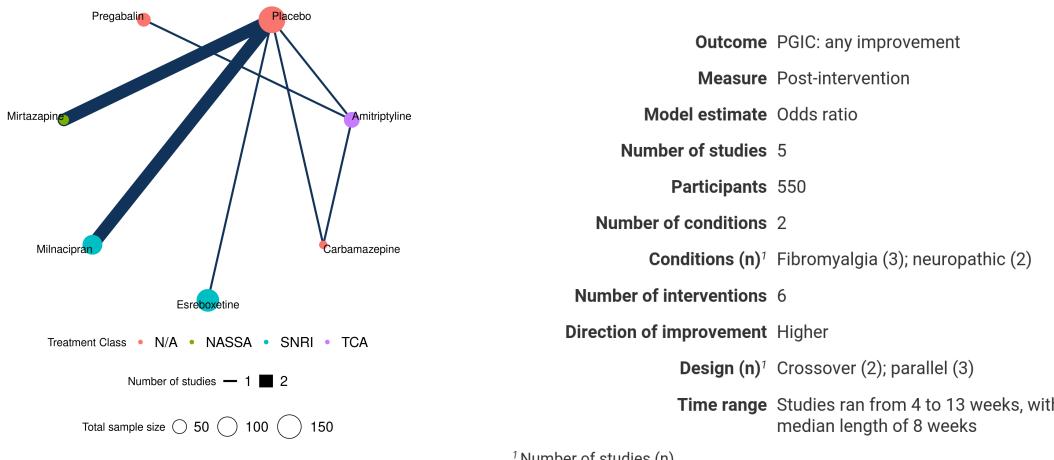


Figure 3.9: Outcome: PGIC much or very much improved. Measure: post-intervention. Intervention (milnacipran) compared with (placebo). Participants: 4255. Direction of improvement: higher. Meta-analysis results: $Q = 1.17$; $df = 6$; $p = 0.98$; $I^2 = 0$ per cent; $\tau^2 = 0$. Regression test for funnel plot asymmetry was significant: 0.68 (CI 0.28 to 1.07) with $p = 0.95$ and $z = -0.06$.

Table 3.5: Summary of findings: PGIC (Any improvement).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³
Amitriptyline	2	74 (15, 59)	37.55 (1.64 to 1133.1)	2 (1 to 5)	0
Carbamazepine	1	29 (15, 14)	9.96 (0.43 to 323.04)	4 (1 to 7)	0
Esreboxetine	1	261 (132, 129)	2.22 (0.23 to 28.43)	5 (2 to 7)	0
Milnacipran	1	125 (28, 97)	4.39 (0.46 to 34.29)	4 (1 to 7)	0
Mirtazapine	1	32 (10, 22)	2.76 (0.24 to 31.09)	5 (1 to 7)	0
Pregabalin	1	44 (0, 44)	43.33 (0.65 to 2334.48)	2 (1 to 6)	0
Placebo				7 (4 to 7)	

¹ Table is ordered by interventions with greatest number of studies.

² Direction of improvement: higher.

³ Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table uses this work as a guide: Yépez-Núñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology*, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

placebo, the exceptions being one study comparing pregabalin and amitriptyline, and another study comparing carbamazepine with amitriptyline. Studies ran from 4 to 13 weeks, with most studies lasting 8 weeks.

Interventions (number of studies): Placebo (4); amitriptyline (2); carbamazepine (1); esreboxetine (1); milnacipran (1); mirtazapine (1); pregabalin (1).

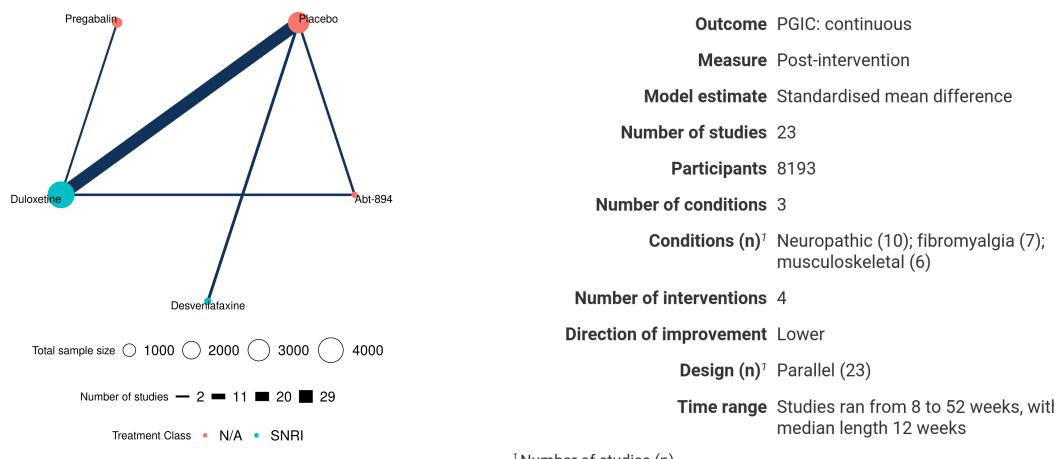
No two comparisons were the same in these trials, so no head-to-head analyses were possible from this dataset.

3.6 PGIC (Continuous measures)

Patient global impression of change (PGIC) was reported as a continuous measure in 5 studies (2 crossover, 3 parallel) evaluating 6 interventions in trials comprising 550 total participants. Studies ran from 4 to 13 weeks with a median length of 8 weeks. The network geometry in Summary of findings Table 3.6 shows that all studies bar one compared a single intervention with placebo, with two exceptions for amitriptyline and pregabalin, and a comparison between amitriptyline and carbamazepine.

Interventions (number of studies): Duloxetine (22); placebo (20); pregabalin (2); abt-894 (1); desven-

Table 3.6: Summary of findings: PGIC (post intervention).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³
Duloxetine	22	7155 (2687, 4468)	-0.33 (-0.39 to -0.28)	2 (1 to 3)	0.36
Pregabalin	2	552 (0, 552)	-0.11 (-0.29 to 0.05)	4 (3 to 5)	0
Abt-894	1	223 (51, 172)	-0.13 (-0.38 to 0.12)	4 (2 to 5)	0
Desvenlafaxine	1	314 (76, 238)	-0.5 (-0.78 to -0.21)	1 (1 to 3)	0
Placebo				5 (4 to 5)	

¹ Table is ordered by interventions with greatest number of studies.

² Direction of improvement: lower.

³ Proportion of studies with at least one with high risk of bias (ROB) criterion.

lafaxine (1).

It was only possible to run subgroup analyses for duloxetine.

3.6.1 Meta-analyses

Duloxetine

Heterogeneity for duloxetine compared with placebo was not explained by condition, dose, duration of study, or risk of bias, when duloxetine was considered under subgroup meta-analyses. Some funnel plot asymmetry was visually detected, but was not significant, suggesting there may be publication bias.

3.7 Withdrawal

Withdrawal was reported in 146 studies (22 crossover, 124 parallel) evaluating 82 interventions in trials comprising 27,288 total participants. Studies ran from 2 to 34 weeks, with most studies lasting 9 weeks. In the trials reporting placebo, most compared interventions with placebo. The geometry of the network (Summary of findings Table 3.7) shows the majority of trials to compare duloxetine, amitriptyline, and milnacipran against placebo. 3 studies compared amitriptyline and benozotropine mesylate, and another 3 studies compared duloxetine and pregabalin; there were 36 other comparators, in addition to placebo, unique to a single trial. The population were primarily fibromyalgia, neuropathic, and musculoskeletal pain patients.

Interventions (number of studies): Placebo (104); duloxetine (39); amitriptyline (32); milnacipran (17); pregabalin (9); nortriptyline (7); paroxetine (7); venlafaxine (7); fluoxetine (6); gabapentin (6); benzotropine mesylate (5); cbt (5); citalopram (4); desipramine (4); imipramine (4); carbamazepine (3); escitalopram (3); maprotiline (3); mirtazapine (3); trazodone (3); clomipramine (2); desvenlafaxine (2); dothiepin (2); es-reboxetine (2); mianserin (2); morphine (2); psychotherapy (2); saffron/crocin (2); sertraline (2); abt-894 (1); acetaminophen (1); active placebo (1); acupuncture (1); amitriptyline + fluoxetine (1); amitriptyline + fluphenazine (1); amitriptyline + naproxen (1); amitriptyline + psychotherapy (1); amitriptyline + riboflavin (vitamin b2) (1); amitriptyline + splint (1); amitriptyline + support (1); benzotropine mesylate + cbt (1); bupropion (1); cbt and amitriptyline (1); cbt and milnacipran (1); cst (1); cst + sertraline (1); cyclobenzaprine (1); desipramine + cbt (1); desipramine + lidocaine (1); diphenhydramine (1); disease management (1); doxepin (1); education (1); fluphenazine (1); gabapentin + nortriptyline (1); glycopyrrolate (1); lamotrigine (1); lidocaine (1); melatonin (1); melatonin + amitriptyline (1); moclobemide (1); morphine + nortriptyline (1); naproxen (1); neurofeedback (1); nortriptyline + cbt (1); nortriptyline + disease management (1); nortriptyline + morphine (1); panax ginseng (1); pft (1); pft + amitriptyline (1); physical therapy (1); physiotherapy + amitriptyline (1); pirlindole (1); pregabalin + duloxetine (1); pregabalin + imipramine (1); reboxetine (1); riboflavin (vitamin b2) (1); support (1); trazodone + gabapentin (1); trimipramine (1); usual treatment (1); waitlist (1); zimeldine (1).

3.7.1 Meta-analyses

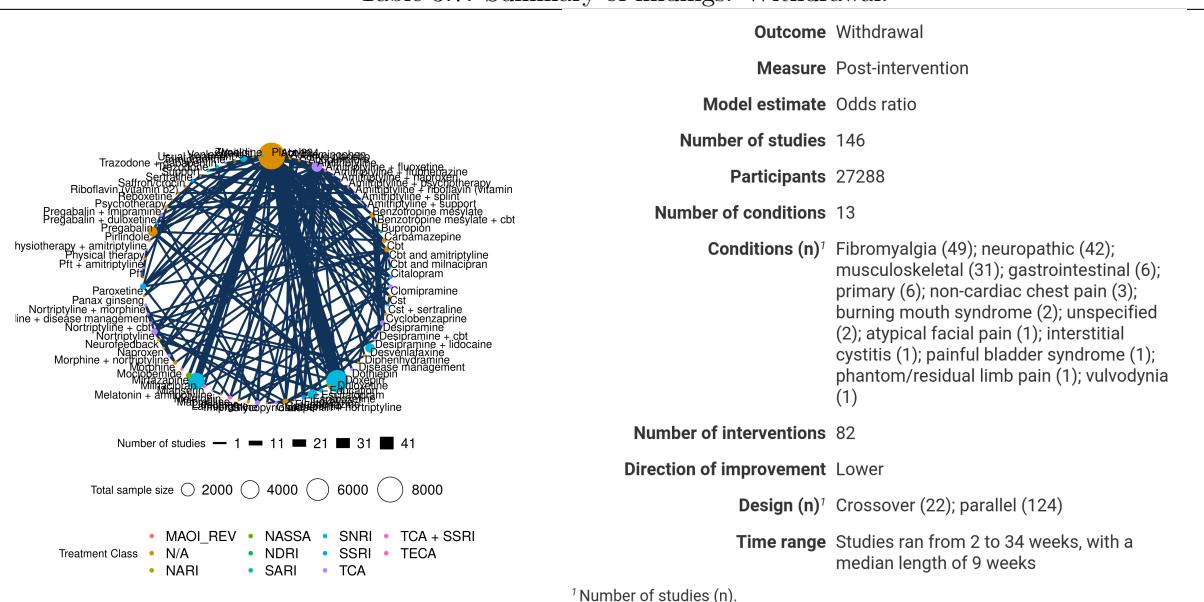
Duloxetine

Funnel-plot test for asymmetry was not significant, but visual inspection suggests there may be publication bias (Figure 3.10).

Some of the heterogeneity observed in duloxetine compared to placebo trials is explained by differences between pain condition groups (Figure 3.11), where neuropathic and musculoskeletal patients were more likely to withdraw from the trials than fibromyalgia patients.

Heterogeneity of duloxetine compared with placebo was not explained by risk of bias. However, some heterogeneity is explained by dose, whereby those given high dose more likely to experience withdrawal (Figure 3.12). Heterogeneity was not explained by duration of study.

Table 3.7: Summary of findings: Withdrawal.



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³	
Duloxetine	39	9758 (3957, 5801)	1.17 (1.04 to 1.33)	37 (27 to 47)	0.41	
Amitriptyline	32	1783 (616, 1167)	1.23 (0.92 to 1.67)	39 (26 to 52)	0.56	
Milnacipran	17	5195 (2019, 3176)	1.32 (1.1 to 1.57)	42 (30 to 54)	0.82	
Pregabalin	9	1055 (136, 919)	1.14 (0.82 to 1.59)	36 (22 to 52)	0.44	
Nortriptyline	7	419 (80, 339)	0.74 (0.41 to 1.32)	23 (11 to 41)	0.29	
Paroxetine	7	464 (143, 321)	1.58 (0.98 to 2.53)	49 (30 to 64)	0.71	
Venlafaxine	7	690 (215, 475)	1.38 (0.88 to 2.24)	44 (24 to 62)	0.57	
Fluoxetine	6	262 (122, 140)	1.19 (0.6 to 2.32)	38 (16 to 62)	0.33	
Gabapentin	6	269 (0, 269)	2.39 (1.18 to 4.88)	61 (37 to 75)	0.5	
Benzotropine mesylate	5	221 (0, 221)	1.27 (0.7 to 2.31)	40 (20 to 61)	0.6	
Cbt	5	343 (108, 235)	0.85 (0.48 to 1.49)	26 (14 to 47)	1	
Citalopram	4	111 (35, 76)	1.38 (0.43 to 4.16)	43 (13 to 73)	0.5	
Desipramine	4	335 (105, 230)	1.56 (0.92 to 2.72)	48 (27 to 65)	0.5	
Imipramine	4	368 (179, 189)	1.37 (0.75 to 2.46)	43 (21 to 64)	0.75	
Carbamazepine	3	180 (15, 165)	0.97 (0.44 to 2.17)	32 (12 to 60)	0.33	
Escitalopram	3	173 (67, 106)	2.04 (0.52 to 8.55)	53 (16 to 79)	0.67	
Maprotiline	3	98 (0, 98)	1.35 (0.58 to 3.15)	42 (17 to 68)	0.67	
Mirtazapine	3	510 (241, 269)	1.01 (0.54 to 1.85)	32 (15 to 56)	0	
Trazodone	3	102 (39, 63)	4.08 (1.69 to 10.26)	70 (50 to 81)	0.67	
Clomipramine	2	211 (87, 124)	2.73 (1.37 to 5.74)	64 (44 to 78)	0.5	
Desvenlafaxine	2	1105 (220, 885)	1.23 (0.85 to 1.79)	39 (23 to 56)	0.5	
Dothiepin	2	110 (55, 55)	0.99 (0.38 to 2.54)	33 (11 to 65)	1	
Esreboxetine	2	1389 (411, 978)	1.44 (1.01 to 2.06)	45 (28 to 61)	0.5	
Mianserin	2	218 (109, 109)	42	2.82 (1.32 to 6.25)	64 (42 to 78)	0
Morphine	2	107 (0, 107)		2.12 (0.83 to 5.36)	56 (25 to 76)	0.5
Psychotherapy	2	70 (0, 70)		1.21 (0.42 to 3.61)	39 (14 to 69)	1

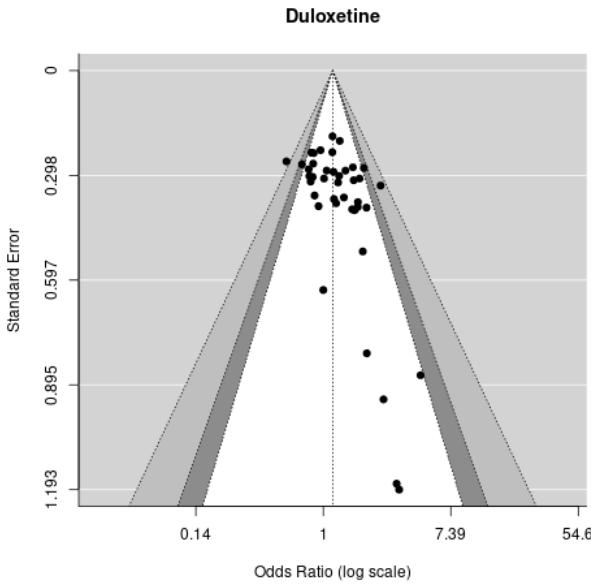


Figure 3.10: Subgroup analysis by condition. Outcome: withdrawal. Measure: post-intervention. Intervention (duloxetine) compared with (placebo) Participants: 10155. Direction of improvement: lower. Meta-analysis results: $Q = 48.91$; $df = 40$; $p = 0.16$; $I^2 = 20.71$ per cent; $\tau^2 = 0.03$. Regression test for funnel plot asymmetry was not significant: -0.29 (CI -0.61 to 0.02) with $p = 0$ and $z = 2.88$.

Milnacipran

Milnacipran observations have very serious risk of bias and some funnel-plot asymmetry (Figure 3.13) suggests possible publication bias.

Risk of bias explains some of the heterogeneity in milnacipran observations reporting withdrawal (Figure 3.14), where studies ranked with low risk of bias were significantly more likely to report higher withdrawal rates.

Length of study also explains some of the heterogeneity in withdrawal, with studies lasting more than 12 weeks more likely to report withdrawal (Figure 3.15).

Amitriptyline

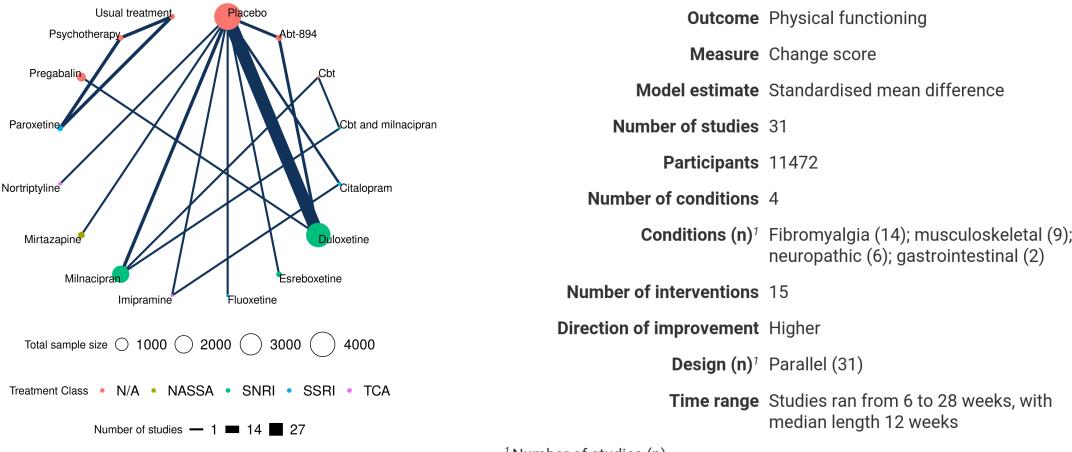
Amitriptyline showed serious inconsistency and imprecision (Figure 3.16), however little indication of publication bias. Heterogeneity was not explained by risk of bias or duration of study. These observations have very serious risk of bias.

3.8 Physical functioning (Change scores)

31 parallel-design studies reported phsycial funcitonning as change score measures, evaluating 15 interventions over a population of 11,472. Studies ran from 6 to 28 weeks, with median length 12 weeks. In addition to trials comparing placebo, there was one study that compared cognitive behavioural therapy and milnacipran, one study that compared duloxetine and pregabalin, and one that compared paroxetine against therapy. This creates the disconnected network shown in Summary of findings Table 3.8.

Interventions (number of studies): Placebo (28); duloxetine (20); milnacipran (4); citalopram (2); abt-894 (1); cbt (1); cbt and milnacipran (1); esreboxetine (1); fluoxetine (1); imipramine (1); mirtazapine (1); nortriptyline (1); paroxetine (1); pregabalin (1); psychotherapy (1); usual treatment (1).

Table 3.8: Summary of findings: Physical functioning (Change score).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³
Duloxetine	20	6512 (2768, 3744)	0.23 (0.17 to 0.29)	7 (3 to 10)	0.45
Milnacipran	4	3109 (1356, 1753)	0.15 (0.04 to 0.24)	8 (5 to 12)	0.75
Citalopram	2	75 (37, 38)	-0.21 (-0.68 to 0.28)	12 (6 to 16)	1
Abt-894	1	215 (49, 166)	0.03 (-0.22 to 0.29)	10 (5 to 14)	0
Cbt	1	15 (0, 15)	0.84 (0.12 to 1.55)	3 (1 to 8)	1
Cbt and milnacipran	1	17 (0, 17)	0.74 (0.04 to 1.45)	4 (1 to 10)	1
Esreboxetine	1	252 (126, 126)	0.38 (0.1 to 0.66)	5 (2 to 10)	0
Fluoxetine	1	51 (26, 25)	0.32 (-0.23 to 0.89)	6 (1 to 14)	0
Imipramine	1	34 (16, 18)	0.2 (-0.48 to 0.89)	8 (1 to 15)	1
Mirtazapine	1	406 (202, 204)	-0.62 (-0.84 to -0.38)	15 (12 to 16)	0
Nortriptyline	1	78 (40, 38)	-0.16 (-0.59 to 0.29)	12 (6 to 15)	0
Paroxetine	1	131 (0, 131)	0.11 (-11.08 to 10.93)	8 (1 to 15)	1
Pregabalin	1	401 (0, 401)	0.09 (-0.12 to 0.3)	9 (5 to 14)	0
Psychotherapy	1	117 (0, 117)	-0.02 (-11.19 to 10.83)	8 (1 to 15)	1
Usual treatment	1	124 (0, 124)	-0.49 (-11.67 to 10.32)	10 (3 to 16)	1
Placebo				11 (8 to 14)	

¹ Table is ordered by interventions with greatest number of studies.

² Direction of improvement: higher.

³ Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table follows the recommendations of Yepes-Nuñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology*, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

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## Error in include_graphics("img/withdrawal-milnacipran-placebo-forest.png"): Cannot
find the file(s): "img/withdrawal-milnacipran-placebo-forest.png"
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Figure 3.13: Outcome: withdrawal. Measure: post-intervention. Intervention (milnacipran) compared with (placebo) Participants: 5725. Direction of improvement: lower. Meta-analysis results: $Q = 22.34$; $df = 18$; $p = 0.22$; $I^2 = 21.29$ per cent; $\tau^2 = 0.02$. Regression test for funnel plot asymmetry was significant: 0.28 (CI 0.02 to 0.53) with $p = 0.79$ and $z = 0.27$.

3.8.1 Meta-analyses

Duloxetine

Results were not inconsistent or imprecise. Heterogeneity was not explained by condition or dose.

3.9 Physical functioning (Post intervention)

28 studies (5 crossover, 23 parallel) reported physical functioning as post-intervention measures, evaluating 32 interventions over a population of 3424 participants. Studies ran from 2 to 36 weeks, with median length 9 weeks. The network (Table 3.9) is very disconnected. There were three trials that compared amitriptyline to benzotropine mesylate, and 7 further comparators unique to single trials.

Interventions (number of studies): Placebo (18); amitriptyline (6); duloxetine (6); benzotropine mesylate (5); fluoxetine (3); pregabalin (3); milnacipran (2); nortriptyline (2); acupuncture (1); benzotropine mesylate + cbt (1); cst (1); cst + sertraline (1); cyclobenzaprine (1); desipramine (1); desipramine + cbt (1); dothiepin (1); epidural injection (1); epidural injection + amitriptyline (1); escitalopram (1); esreboxetine (1); fluoxetine + melatonin (1); gabapentin (1); gabapentin + nortriptyline (1); melatonin (1); mirtazapine (1); moclobemide (1); morphine (1); morphine + nortriptyline (1); paroxetine (1); pregabalin + duloxetine (1); sertraline (1); trazodone (1); venlafaxine (1).

3.10 Sleep quality (Change score)

Sleep was reported as a change-score measure in 17 parallel studies evaluating 4 interventions over a total of 6077 participants. Studies ran from 6 to 52 weeks, with median length 12 weeks. The geometry of the direct-evidence network (Summary of findings Table 3.10) shows all trials compared one intervention with placebo. The participants were mostly fibromyalgia nad neuropathic pain patients.

Interventions (number of studies): Placebo (16); duloxetine (13); milnacipran (2); citalopram (1); esreboxetine (1).

3.10.1 Meta-analyses

Duloxetine

No serious inconsistency, publication bias, or imprecision was detected. Heterogeneity of duloxetine compared with placebo not explained by condition, risk of bias, or duration of study.

Milnacipran

Meta-analysyis results are consistent for milnacipran compared to placebo, and with the network meta-analysis estimates. Some publication bias is suggested by funnel plot asymmetry, however not significant, and these results have high risk of bias. Heterogeneity of results not explained by duration of study.

Post-intervention withdrawal: milnacipran vs placebo

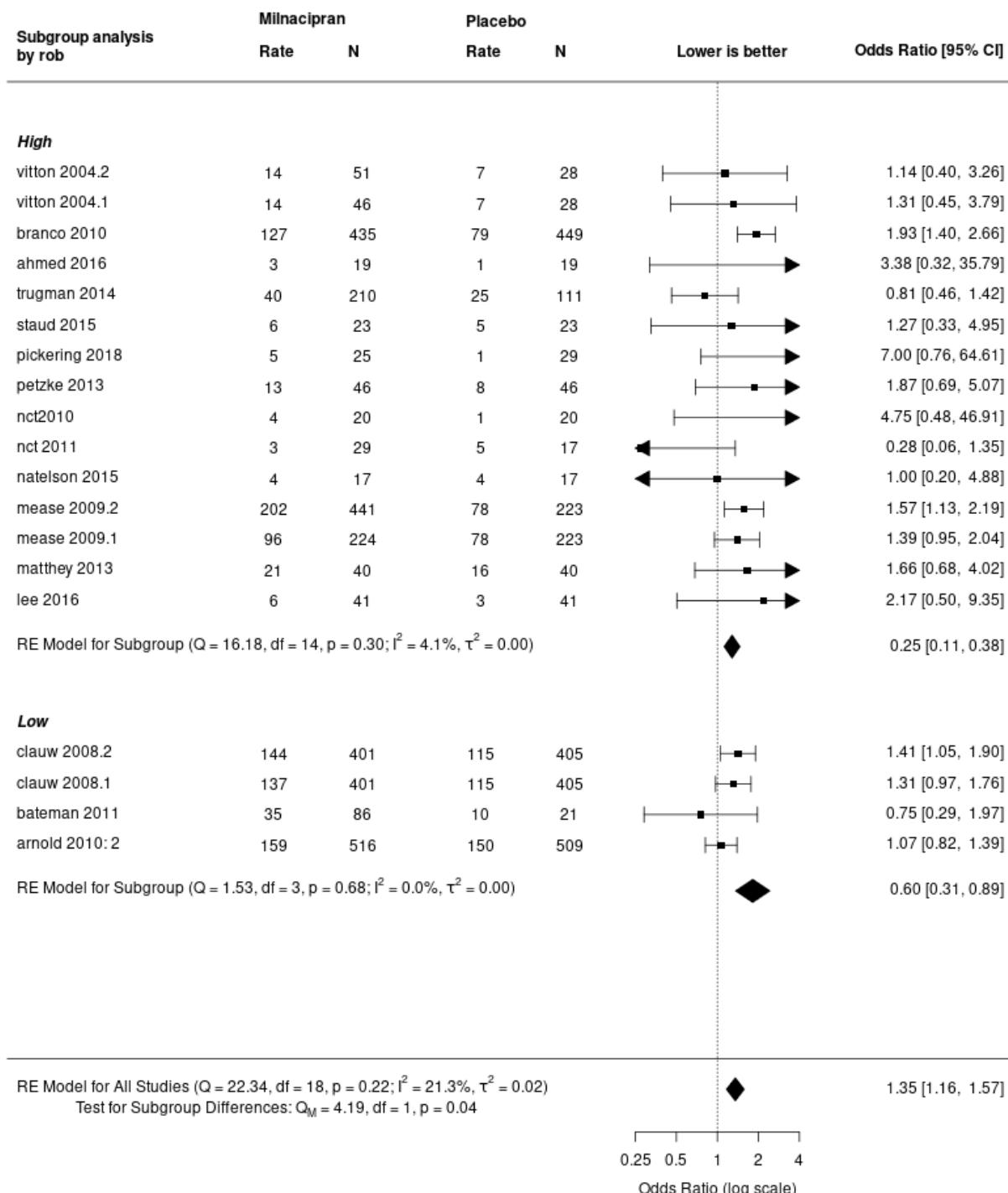


Figure 3.14: Subgroup analysis by rob. Outcome: withdrawal. Measure: post-intervention. Intervention (milnacipran) compared with (placebo) Participants: 5725. Direction of improvement: lower. Meta-analysis results: $Q = 22.34$; $df = 18$; $p = 0.22$; $I^2 = 21.29$ per cent; $\tau^2 = 0.02$. Regression test for funnel plot asymmetry was significant: 0.28 (CI 0.02 to 0.53) with $p = 0.79$ and $z = 0.27$.

Post-intervention withdrawal: milnacipran vs placebo

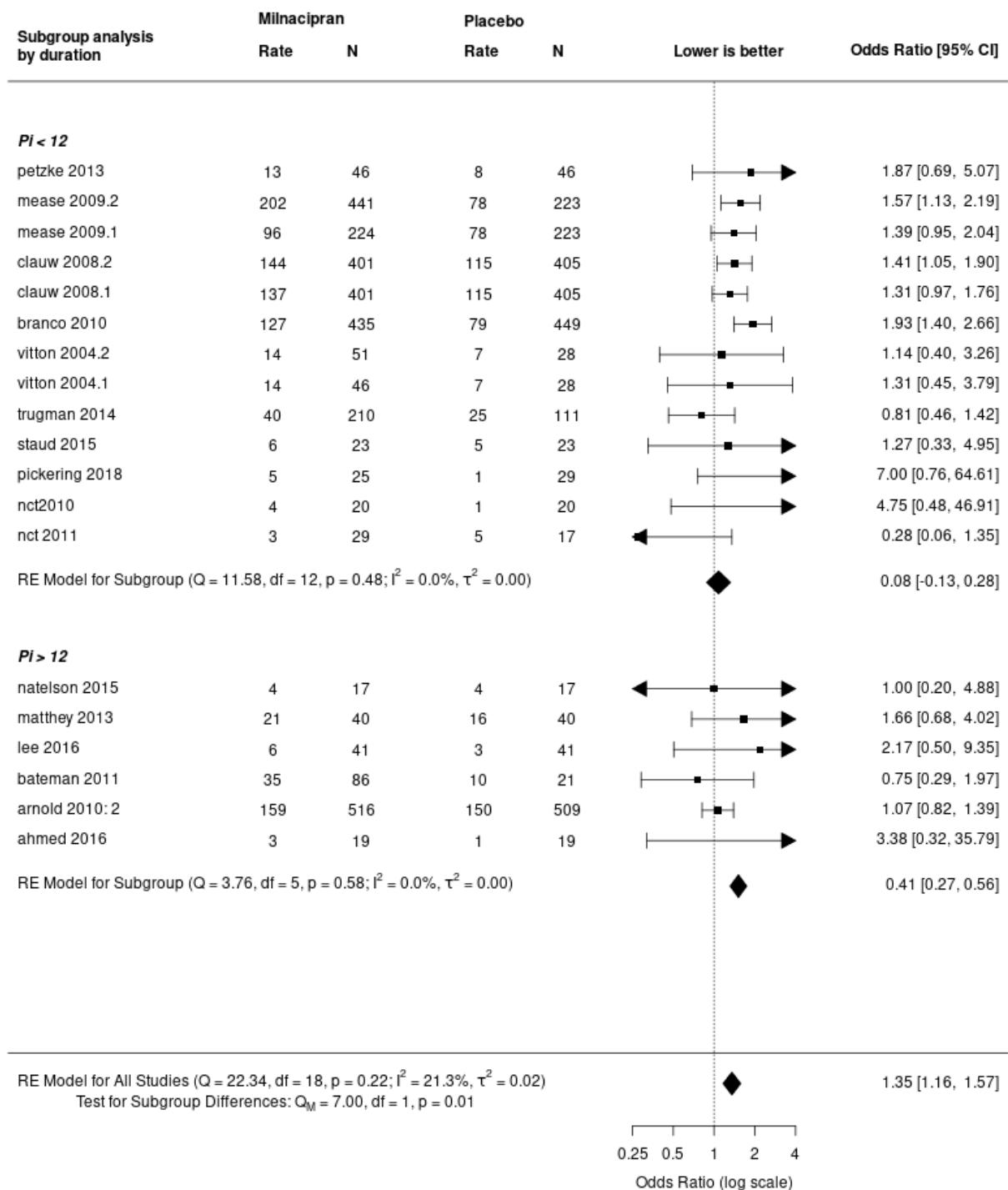
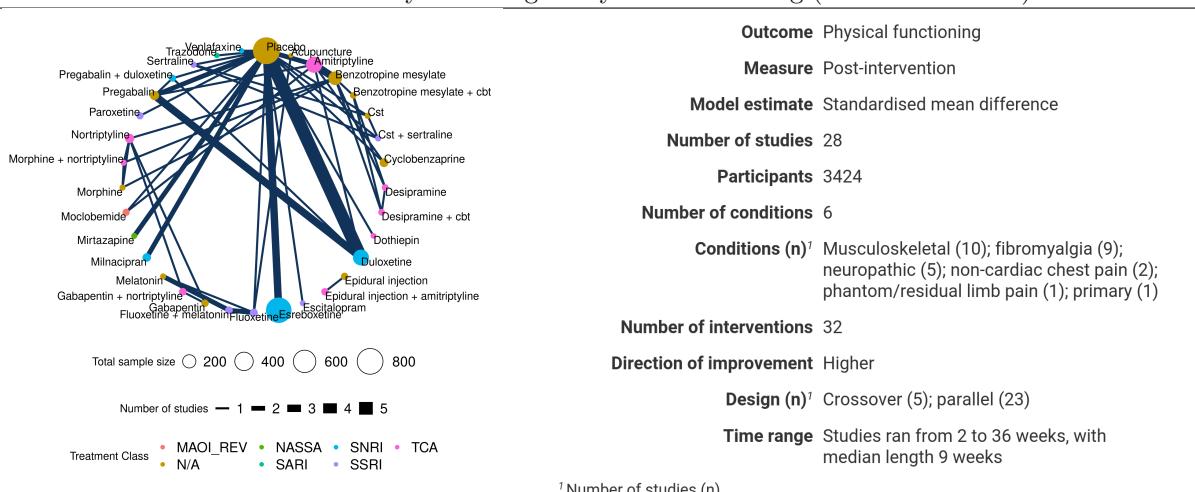


Figure 3.15: Subgroup analysis by duration.

Table 3.9: Summary of findings: Physical functioning (Post intervention).



[†] Number of studies (n).

Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Duloxetine	20	6512 (2768, 3744)	0.23 (0.17 to 0.29)	7 (3 to 10)	0.45
Milnacipran	4	3109 (1356, 1753)	0.15 (0.04 to 0.24)	8 (5 to 12)	0.75
Citalopram	2	75 (37, 38)	-0.21 (-0.68 to 0.28)	12 (6 to 16)	1
Abt-894	1	215 (49, 166)	0.03 (-0.22 to 0.29)	10 (5 to 14)	0
Cbt	1	15 (0, 15)	0.84 (0.12 to 1.55)	3 (1 to 8)	1
Cbt and milnacipran	1	17 (0, 17)	0.74 (0.04 to 1.45)	4 (1 to 10)	1
Eseboxetine	1	252 (126, 126)	0.38 (0.1 to 0.66)	5 (2 to 10)	0
Fluoxetine	1	51 (26, 25)	0.32 (-0.23 to 0.89)	6 (1 to 14)	0
Imipramine	1	34 (16, 18)	0.2 (-0.48 to 0.89)	8 (1 to 15)	1
Mirtazapine	1	406 (202, 204)	-0.62 (-0.84 to -0.38)	15 (12 to 16)	0
Nortriptyline	1	78 (40, 38)	-0.16 (-0.59 to 0.29)	12 (6 to 15)	0
Paroxetine	1	131 (0, 131)	0.11 (-11.08 to 10.93)	8 (1 to 15)	1
Pregabalin	1	401 (0, 401)	0.09 (-0.12 to 0.3)	9 (5 to 14)	0
Psychotherapy	1	117 (0, 117)	-0.02 (-11.19 to 10.83)	8 (1 to 15)	1
Usual treatment	1	124 (0, 124)	-0.49 (-11.67 to 10.32)	10 (3 to 16)	1
Placebo				11 (8 to 14)	

[†] Table is ordered by interventions with greatest number of studies.

[‡] Direction of improvement: higher.

[§] Proportion of studies with at least one with high risk of bias (ROB) criterion.

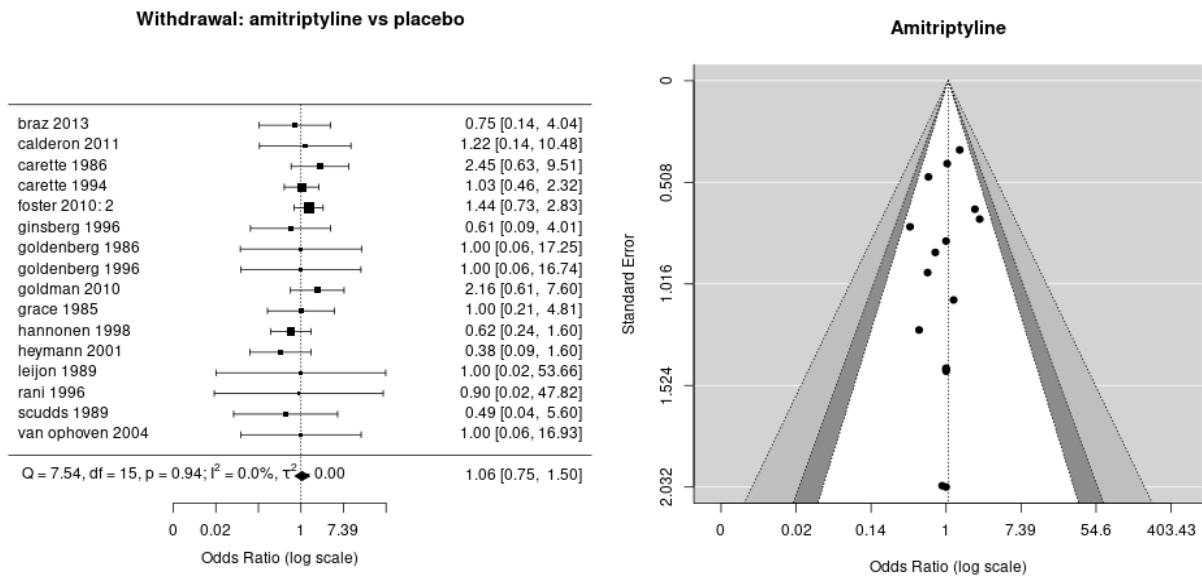
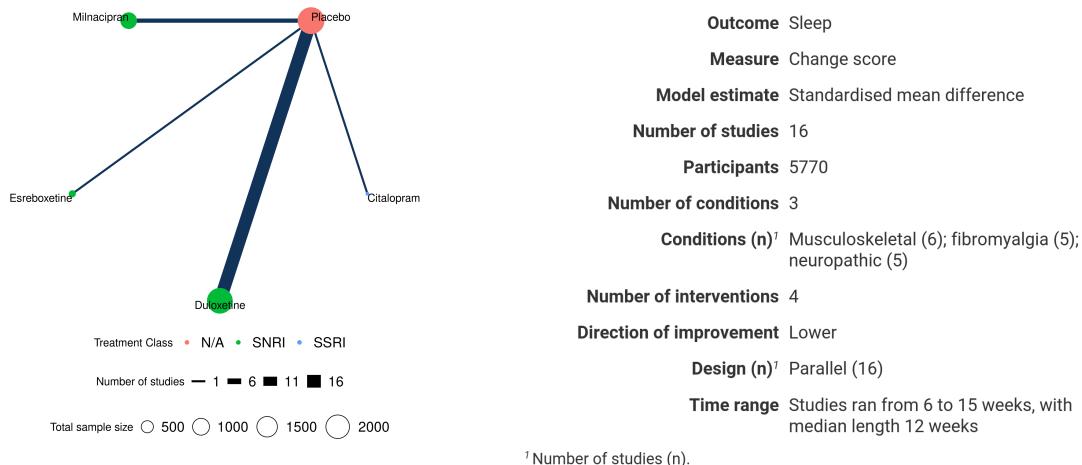


Figure 3.16: withdrawal-rob-amitriptyline-placebo-rma-captin.txt

Table 3.10: Summary of findings: Sleep quality (change score).



Intervention	Studies ¹	Participants (placebo, intervention) ¹	Relative effect (95% CI) ²	Rank (95% CI) ²	ROB ³
Duloxetine	12	4155 (1899, 2256)	-0.19 (-0.26 to -0.12)	2 (1 to 3)	0.17
Milnacipran	2	1320 (429, 891)	-0.07 (-0.23 to 0.08)	3 (2 to 5)	0.5
Citalopram	1	42 (21, 21)	-0.33 (-0.97 to 0.33)	2 (1 to 5)	1
Esreboxetine	1	253 (127, 126)	-0.09 (-0.36 to 0.19)	3 (1 to 5)	0
Placebo				4 (3 to 5)	

¹Table is ordered by interventions with greatest number of studies.

²Direction of improvement: lower.

³Proportion of studies with at least one with high risk of bias (ROB) criterion.

3.11 Sleep quality (post intervention)

Sleep was reported as post-intervention measure in 19 studies (6 crossover, 13 parallel) evaluating 23 interventions over a total of 1881 participants. Studies ran from 2 to 24 weeks, with median length 6 weeks. The geometry of the direct-evidence network (Summary of findings 3.11) is disconnected, with various comparators used, each of which unique to one trial, and almost half (9 studies) not including placebo trials.

Interventions: Placebo (11); amitriptyline (7); duloxetine (5); pregabalin (3); fluoxetine (2); gabapentin (2); milnacipran (2); nortriptyline (2); acupuncture (1); amitriptyline + fluoxetine (1); amitriptyline + splint (1); carbamazepine (1); escitalopram (1); gabapentin + nortriptyline (1); melatonin (1); melatonin + amitriptyline (1); moclobemide (1); morphine (1); nortriptyline + morphine (1); physical therapy (1); pregabalin + duloxetine (1); sertraline (1); venlafaxine (1); waitlist (1).

3.11.1 Meta-analyses

Subgroup analysis by dose was not possible.

Duloxetine

Meta-analysis results for duloxetine compared to placebo were consistent for both post-intervention and change-score measures within studies and with network meta-analysis estimates. Publication bias is suspected for post intervention results, and change score results have a proportion of 0.4 high risk of bias studies.

Amitriptyline

Meta-analysis of amitriptyline compared to placebo was consistent with findings of network meta-analysis estimates. The variation between studies accounts for most of the heterogeneity observed in the trials ($I^2 = 95\%$). Publication bias strongly suspected, as well as high risk of bias.

3.12 Quality of life

Quality of life was reported as post-intervention measures by 17 studies (3 crossover, 14 parallel) evaluating 21 interventions across a total of 2857 participants. The participants were primarily fibromyalgia patients. Studies ran from 6 to 24 weeks, with a median time range of 8 weeks. Most comparisons (see network in Summary of findings 3.12) were between esreboxetine and placebo, as well as duloxetine and placebo. The exceptions being two trials that did not include a placebo trial but instead cognitive behavioural therapy and pregabalin, respectively. The participants were largely fibromyalgia pain patients.

Interventions (number of studies): Placebo (10); Amitriptyline (6); Duloxetine (5); Fluoxetine (3); Acupuncture (2); Melatonin (2); Milnacipran (2); Pregabalin (2); Abt-894 (1); Amitriptyline + fluoxetine (1); Amitriptyline + splint (1); Benzotropine mesylate (1); Cbt (1); Desipramine (1); Education (1); Esreboxetine (1); Fluoxetine + melatonin (1); Melatonin + amitriptyline (1); Nortriptyline (1); Pregabalin + duloxetine (1); Saffron/crocin (1); Waitlist (1).

3.12.1 Meta-analyses

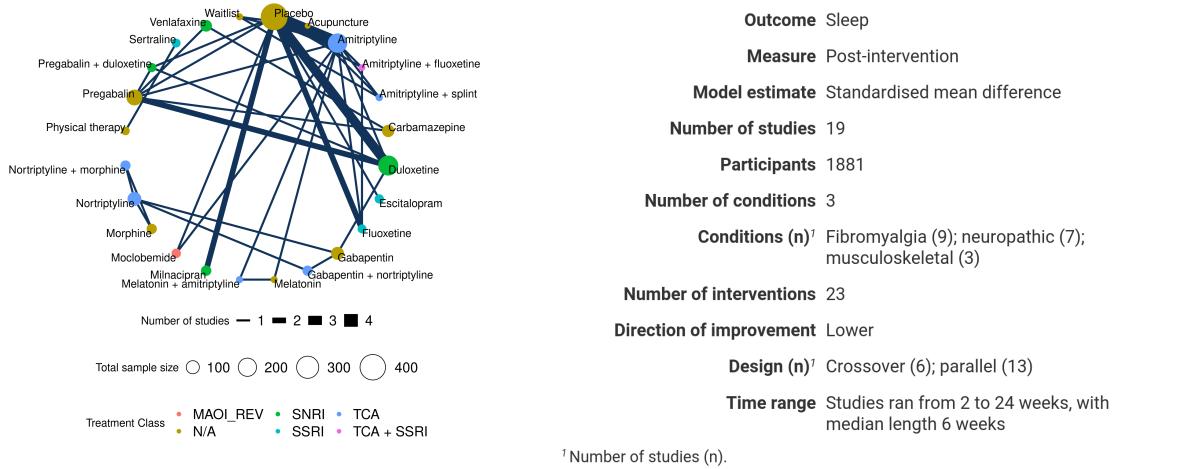
Most subgroup analyses were not possible. Meta-analyses were of two or three observations, and did not display, given the sparse nature of the plots, any particular outliers.

Duloxetine

There was significant difference between quality of life improvement for duloxetine compared to placebo between different pain condition groups (Figure 3.17).

There was not significant difference between low, standard, and high-dose groups, but there is still observable (Figure 3.18) variation between the groups.

Table 3.11: Summary of findings: Sleep quality (post intervention).



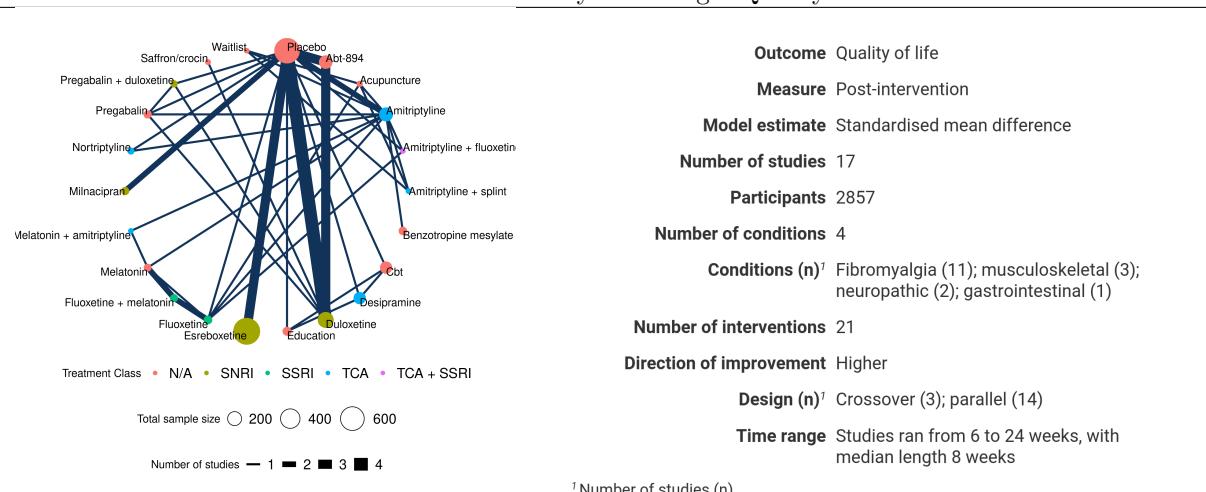
Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Amitriptyline	7	354 (143, 211)	-0.47 (-0.75 to -0.2)	6 (3 to 10)	0.43
Duloxetine	5	401 (175, 226)	-0.11 (-0.4 to 0.19)	11 (7 to 16)	0.4
Pregabalin	3	174 (39, 135)	-0.39 (-0.8 to 0.04)	7 (3 to 14)	0.67
Fluoxetine	2	65 (28, 37)	-0.16 (-0.7 to 0.37)	11 (4 to 19)	1
Gabapentin	2	87 (0, 87)	0.32 (-0.3 to 0.97)	18 (10 to 22)	0
Milnacipran	2	107 (54, 53)	0.04 (-0.41 to 0.5)	14 (6 to 21)	0.5
Nortriptyline	2	101 (0, 101)	0.36 (-0.48 to 1.16)	18 (8 to 23)	0
Acupuncture	1	13 (0, 13)	-0.55 (-1.37 to 0.28)	6 (2 to 17)	1
Amitriptyline + fluoxetine	1	37 (19, 18)	-1.11 (-1.84 to -0.37)	3 (1 to 7)	1
Amitriptyline + splint	1	23 (0, 23)	-0.26 (-1 to 0.5)	10 (3 to 20)	1
Carbamazepine	1	78 (0, 78)	0.21 (-0.41 to 0.88)	16 (7 to 22)	1
Escitalopram	1	82 (41, 41)	-0.39 (-0.95 to 0.16)	8 (2 to 16)	1
Gabapentin + nortriptyline	1	50 (0, 50)	-0.26 (-1.12 to 0.56)	9 (2 to 18)	0
Melatonin	1	21 (0, 21)	0.16 (-0.59 to 0.9)	15 (5 to 23)	0
Melatonin + amitriptyline	1	21 (0, 21)	0.09 (-0.72 to 0.88)	14 (4 to 23)	0
Moclobemide	1	86 (43, 43)	0.31 (-0.21 to 0.81)	18 (9 to 23)	0
Morphine	1	51 (0, 51)	0.32 (-0.68 to 1.3)	17 (5 to 23)	0
Nortriptyline + morphine	1	51 (0, 51)	0.24 (-0.74 to 1.22)	16 (4 to 23)	0
Physical therapy	1	34 (0, 34)	7.94 (-5.93 to 21.82)	21 (2 to 24)	1
Pregabalin + duloxetine	1	78 (39, 39)	-0.69 (-1.17 to -0.18)	4 (2 to 10)	1
Sertraline	1	36 (0, 36)	-7.67 (-21.59 to 5.98)	4 (1 to 23)	1
Venlafaxine	1	69 (0, 69)	0.46 (-0.17 to 1.13)	19 (11 to 23)	1
Waitlist	1	21 (0, 21)	0.92 (0.14 to 1.71)	22 (16 to 24)	1
Placebo				13 (9 to 18)	

[†] Table is ordered by interventions with greatest number of studies.

[‡] Direction of improvement: lower.

[§] Proportion of studies with at least one with high risk of bias (ROB) criterion.

Table 3.12: Summary of findings: Quality of life.



Intervention	Studies [†]	Participants (placebo, intervention) [†]	Relative effect (95% CI) [‡]	Rank (95% CI) [‡]	ROB [§]
Amitriptyline	6	233 (52, 181)	0.33 (-0.06 to 0.7)	10 (4 to 17)	0.83
Duloxetine	5	469 (227, 242)	0.29 (0.05 to 0.54)	11 (5 to 18)	0.6
Fluoxetine	3	80 (19, 61)	0.22 (-0.3 to 0.74)	13 (4 to 20)	0.67
Acupuncture	2	28 (0, 28)	0.27 (-0.37 to 0.92)	12 (3 to 21)	1
Melatonin	2	48 (0, 48)	0.07 (-0.52 to 0.68)	16 (6 to 21)	0
Milnacipran	2	107 (54, 53)	0.42 (-0.01 to 0.87)	9 (2 to 18)	0.5
Pregabalin	2	92 (39, 53)	0.54 (0.13 to 0.97)	6 (2 to 15)	1
Abt-894	1	220 (51, 169)	0 (-0.33 to 0.33)	17 (9 to 21)	0
Amitriptyline + fluoxetine	1	38 (19, 19)	0.92 (0.22 to 1.62)	3 (1 to 12)	1
Amitriptyline + splint	1	23 (0, 23)	0.64 (-0.07 to 1.36)	6 (1 to 18)	1
Benzotropine mesylate	1	57 (0, 57)	-1.55 (-2.18 to -0.9)	22 (22 to 22)	1
Cbt	1	201 (66, 135)	0.29 (-0.11 to 0.69)	11 (3 to 19)	1
Desipramine	1	201 (66, 135)	0.28 (-0.12 to 0.69)	11 (3 to 20)	1
Education	1	132 (66, 66)	0.1 (-0.34 to 0.53)	15 (6 to 21)	1
Esreboxetine	1	998 (262, 736)	0.3 (0.03 to 0.57)	11 (4 to 18)	1
Fluoxetine + melatonin	1	50 (0, 50)	0.47 (-0.16 to 1.11)	8 (1 to 19)	0
Melatonin + amitriptyline	1	21 (0, 21)	0.41 (-0.31 to 1.12)	9 (1 to 20)	0
Nortriptyline	1	69 (33, 36)	0.02 (-0.49 to 0.52)	17 (7 to 21)	1
Pregabalin + duloxetine	1	78 (39, 39)	0.88 (0.41 to 1.35)	3 (1 to 9)	1
Saffron/crocin	1	23 (0, 23)	0.22 (-0.44 to 0.91)	13 (2 to 21)	0
Waitlist	1	21 (0, 21)	0.21 (-0.51 to 0.95)	13 (2 to 21)	1
Placebo				18 (13 to 21)	

[†] Table is ordered by interventions with greatest number of studies.

[‡] Direction of improvement: higher.

[§] Proportion of studies with at least one with high risk of bias (ROB) criterion.

This table follows the recommendations of Yepes-Nuñez, J. J., Li, S.-A., Guyatt, G., Jack, S. M., Brozek, J. L., Beyene, J., Murad, M. H., Rochwerg, B., Mbuagbaw, L., Zhang, Y., Flórez, I. D., Siemieniuk, R. A., Sadeghirad, B., Mustafa, R., Santesso, N., & Schünemann, H. J. (2019). Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology*, 115, 1–13. <https://doi.org/10.1016/j.jclinepi.2019.04.018>

Change score quality of life: duloxetine vs placebo

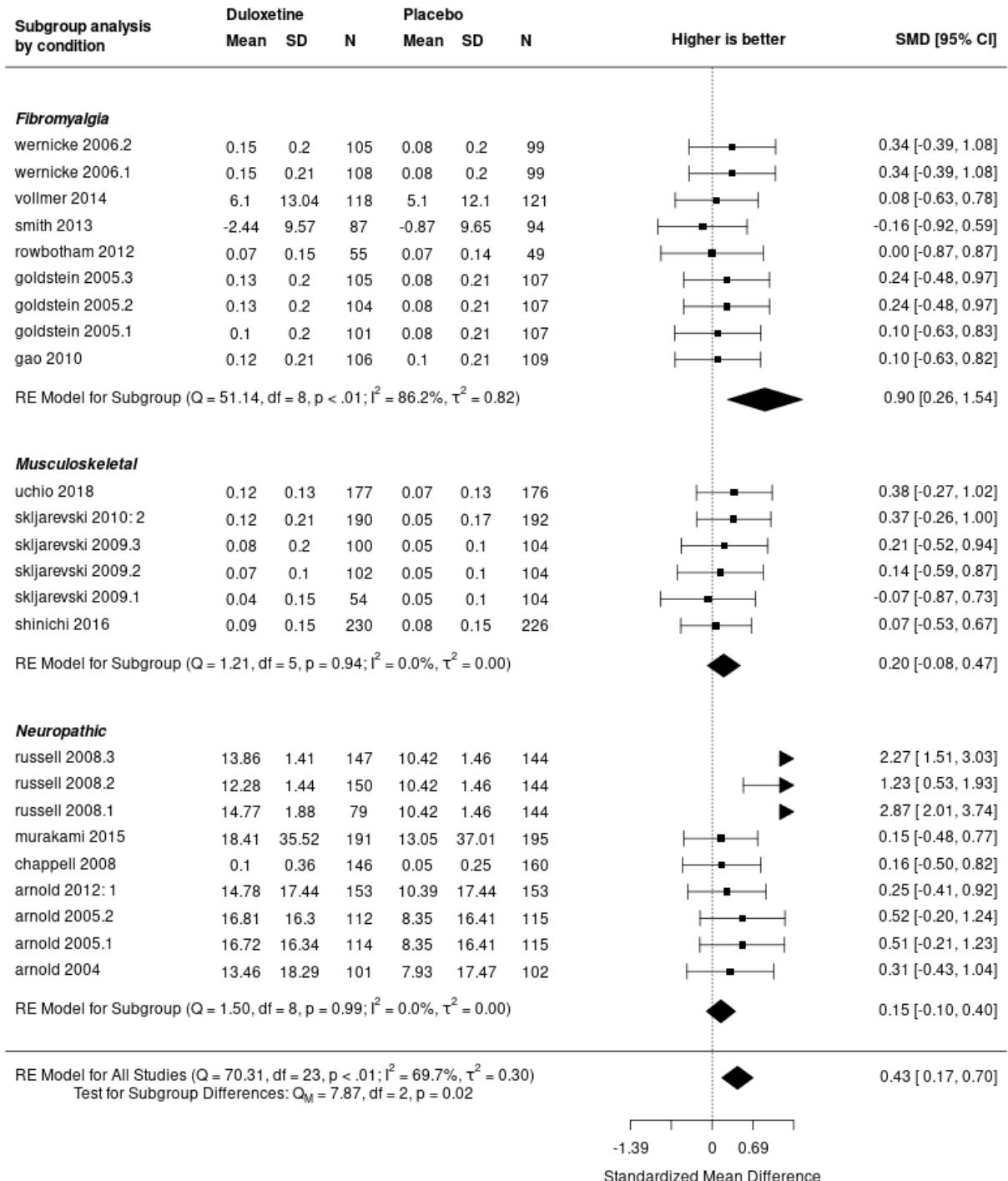


Figure 3.17: Subgroup analysis by condition. Outcome: quality of life. Measure: change score. Intervention (duloxetine) compared with (placebo). Participants: 0. Direction of improvement: higher. Meta-analysis results: $Q = 73.86$; $df = 25$; $p < .01$; $I^2 = 68.33$ per cent; $\tau^2 = 0.29$. Regression test for funnel plot asymmetry was not significant: -0.63 (CI -2.74 to 1.49) with $p = 0.34$ and $z = 0.95$.

Change score quality of life: duloxetine vs placebo

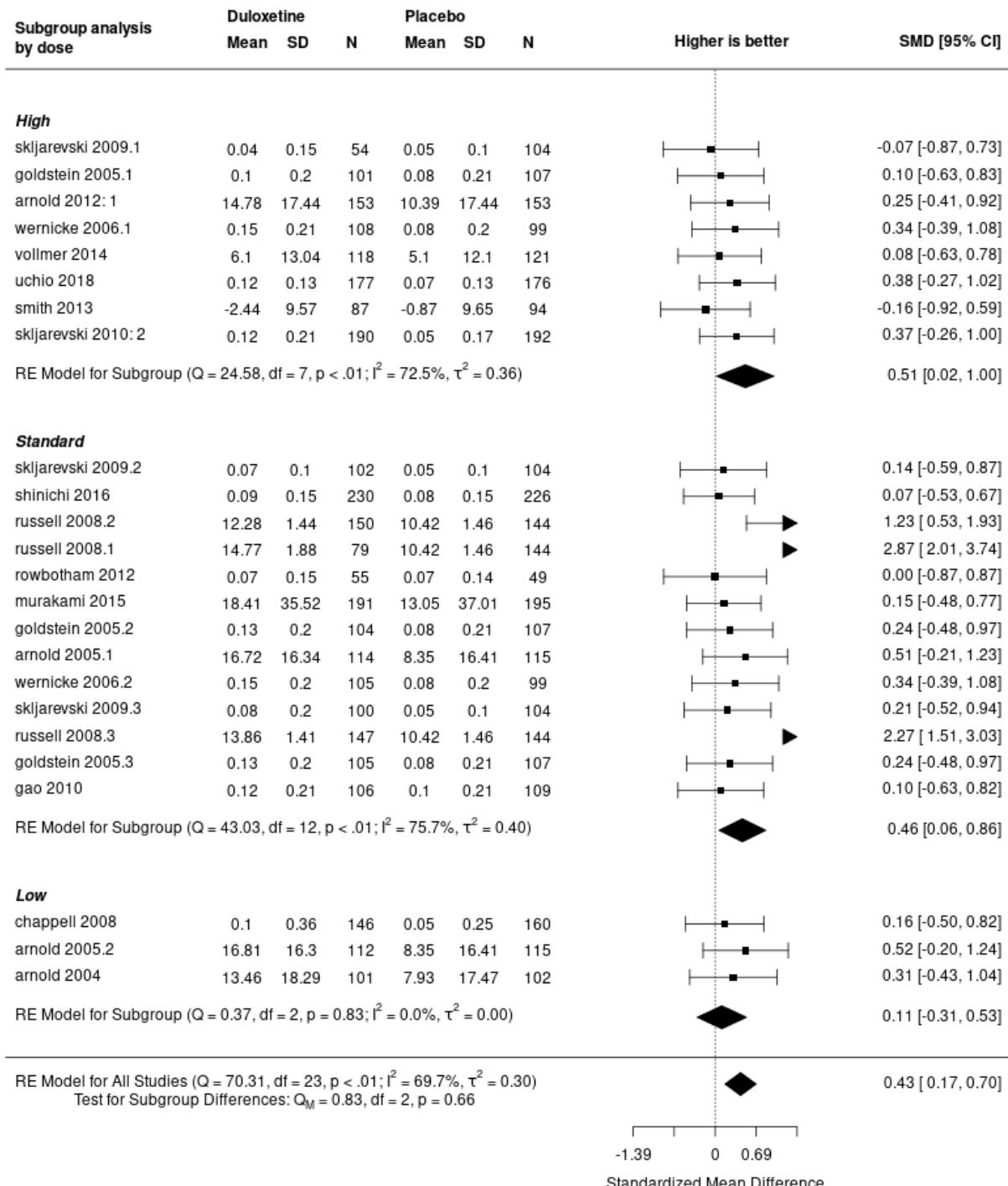


Figure 3.18: Subgroup anlaysis by dose. Outcome: quality of life. Measure: change score. Intervention (duloxetine) compared with (placebo) Participants: 0. Direction of improvement: higher. Meta-analysis results: $Q = 73.86$; $df = 25$; $p < .01$; $I^2 = 68.33$ per cent; $\tau^2 = 0.29$. Regression test for funnel plot asymmetry was not significant: -0.63 (CI -2.74 to 1.49) with $p = 0.34$ and $z = 0.95$.

Milnacipran

There is some heterogeneity in milnacipran compared to placebo measuring quality of life (Figure ??).

Change score quality of life: milnacipran vs placebo

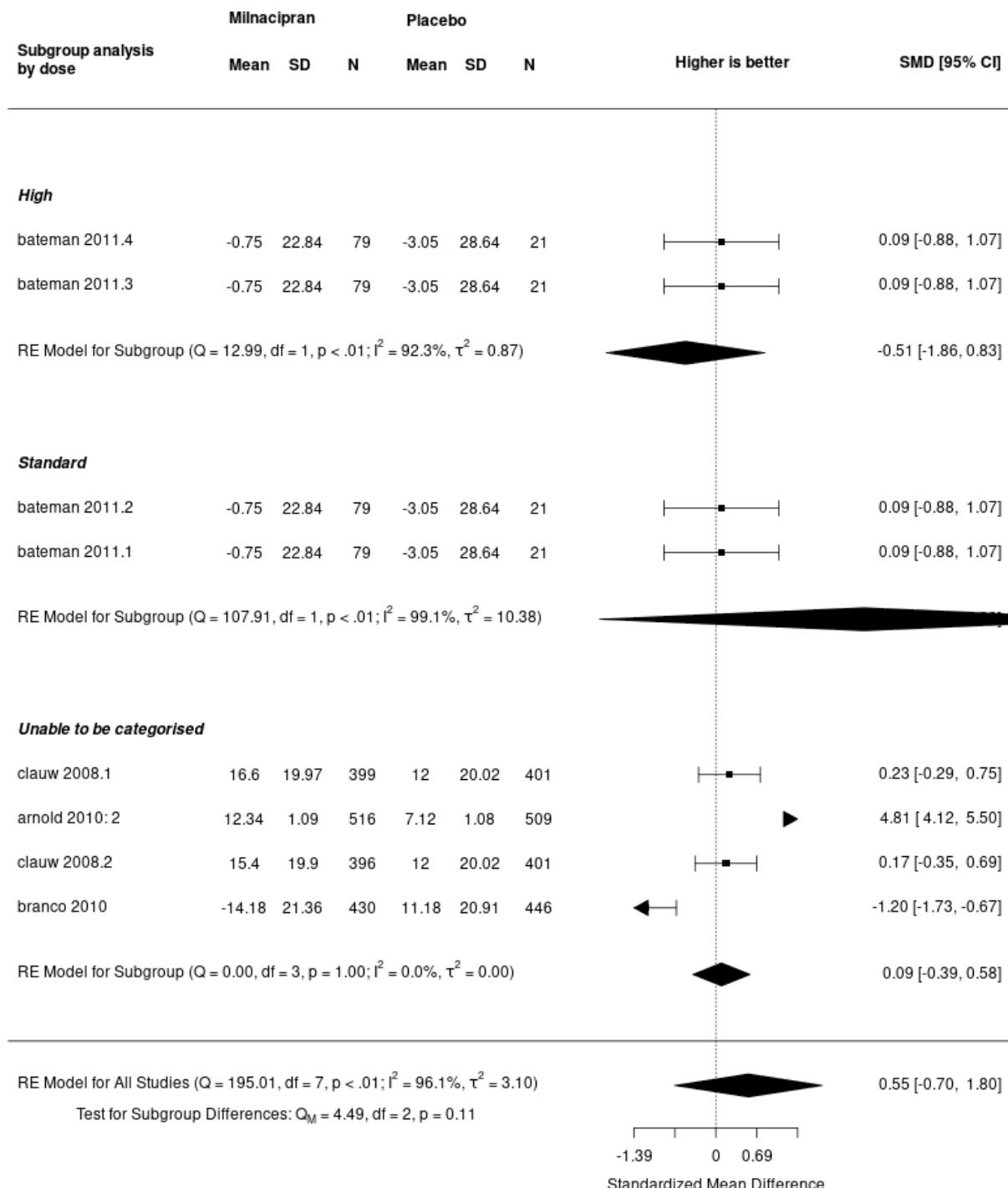


Figure 3.19: Subgroup analysis by dose. Outcome: quality of life. Measure: change score. Intervention (milnacipran) compared with (placebo) Participants: 0. Direction of improvement: higher. Meta-analysis results: $Q = 194.99$; $df = 7$; $p < .01$; $I^2 = 95.97$ per cent; $\tau^2 = 3.13$. Regression test for funnel plot asymmetry was not significant: 0.96 (CI -3.53 to 5.45) with $p = 0.85$ and $z = -0.19$.

fig.qolcs-dose-milna-plac

Chapter 4

Risk of bias summaries

Figure 4.1 shows the distribution of risk of bias for each of the criteria and Figure 4.2 shows each study's risk of bias criteria.

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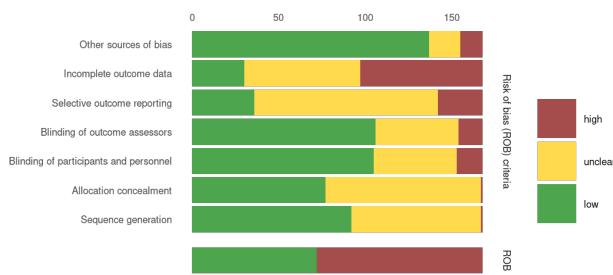


Figure 4.1: Risk of bias distributions for criteria.

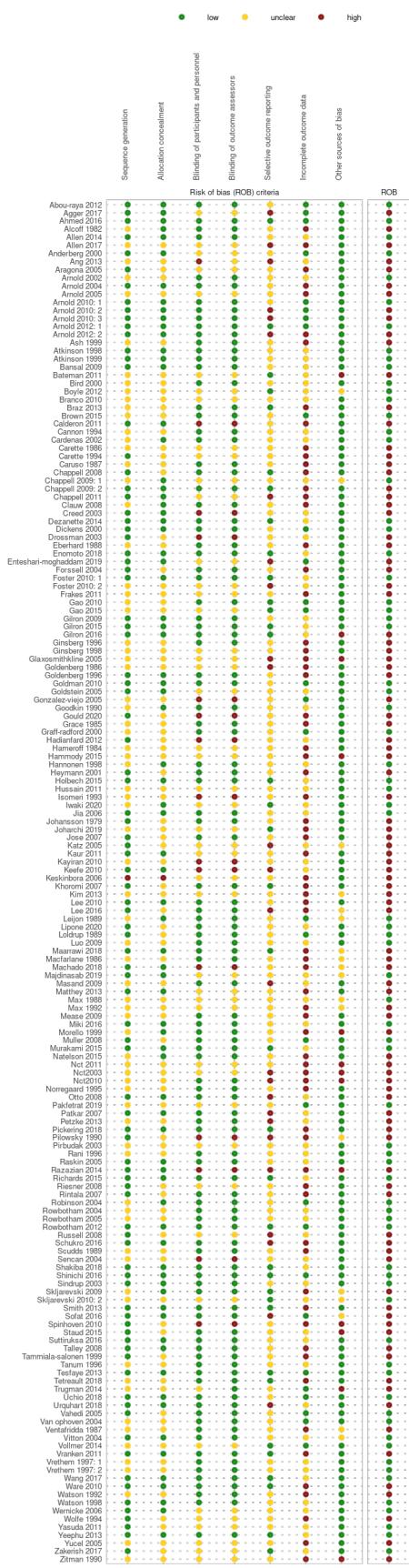


Figure 4.2: Risk of bias criteria for studies.