Appendix H GRADE profiles and results for 'peripheral neuropathic pain'

Outcome	Profile ID	Follow-up (days)	Number of RCTs	Interventions
Critical				
PGIC (at least moderate improvement)	1a (pg2)	28 +/- 7	1	pregabalin
	1b (pg3)	56 +/- 7	8	capsaicin patch, gabapentin, pregabalin, valproate
	1c (pg6)	84 +/- 14	8	capsaicin patch, lacosamide, lamotrigine, pregabalin
Sleep interference – normalised 10-point scale[1]	2a (pg9)	28 +/- 7	3	escitalopram, gabapentin, gabapentin+nortriptyline, nortriptyline
	2b (pg12)	56 +/- 7	2	gabapentin
	2c (pg13)	84 +/- 14	5	duloxetine, topiramate
Withdrawal due to adverse effects	3 (pg17)	All time points	75	23 (see page 17)
Specific adverse effects[2]	3a-t	All time points	See Appendix J	
Important				
30% pain relief	4a (pg29)	28 +/- 7	5	cannabis sativa extract, capsaicin cream, pregabalin, tramadol
	4b (pg33)	56 +/- 7	5	capsaicin patch, pregabalin
	4c (pg37)	84 +/- 14	16	cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate
50% pain relief	5a (pg41)	28 +/- 7	5	amitriptyline, cannabis sativa extract, pregabalin, tramadol
	5b (pg44)	56 +/- 7	8	capsaicin patch, gabapentin, lamotrigine, nortriptyline, pregabalin
	5c (pg47)	84 +/- 14	15	capsaicin patch, duloxetine, pregabalin, topiramate
Pain relief – normalised 10-point scale	6a (pg52)	28 +/- 7	22	18 (see page 52)
	6b (pg61)	56 +/- 7	17	11 (see page 61)
	6c (pg67)	84 +/- 14	13	9 (see page 67)

[1] this is the only synthesis possible for the outcome 'patient reported improvement in daily physical and emotional functioning including sleep'

[2] completed for 'all neuropathic pain' only.

(it was not possible to synthesise any results for the outcome 'use of rescue medication')

CRITICAL OUTCOMES (profiles 1 to 3)

Summary GRADE profile 1a: PGIC (at least moderate improvement) (28 +/-7 days) – pregabalin vs placebo

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Effect/outcome	Quality	Importance
PGIC – at least moderate improvement (28 +/-7 days)	1 RCT[a] n=252	serious[1]	not applicable[2]	not serious[3]	serious[4]	OR: 5.1997 (95% CI 2.94 to 9.19)	moderate	Critical

[1] it was unclear if groups were comparable at baseline in concomitant SSRI use; during the study, rescue analgesic usage permitted but not reported; inadequate length of follow-up (5 weeks)

[2] only 1 trial so no possibility of inconsistency between studies for a pairwise comparison

[3] all aspects of PICO conform to review protocol

[4] wide confidence intervals for effect estimate compared to placebo

[a] pregabalin vs placebo (n=252): Lesser et al. (2004); only SSRIs permitted

Abbreviations: CI, confidence interval; OR, odds ratio; PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

Figure 1 PGIC (at least moderate improvement) - 4 weeks - evidence diagram

Table 1 PGIC (at least moderate improvement) - 4 weeks - notes

- none

Summary GRADE profile 1b: Network meta-analysis for PGIC (at least moderate improvement) (56 +/-7 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
PGIC – at least moderate improvement (56 +/-7 days)	8 RCTs[a] n=2604	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Critical

[1] half of studies do not report the method of randomisation and half do not report about allocation concealment; concomitant drug use between arms within each study appears to be similar but concomitant drugs permitted varies across the studies in the network

[2] I^2 was 17% for gabapentin vs placebo which may indicate that any inconsistency might not be important; no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there are no head-to-head trials; most links in the network contain only one trial; wide confidence intervals for effect estimates compared to placebo for at least half of the interventions but particularly for valproate which is likely due to very small study sizes causing uncertainty of the ranking within the network

[a] Capsaicin Patch (n=1543): Irving et al. (2011); Irving et al. (2012); concomitant drugs permitted if stable

Gabapentin (n=778): Backonja et al. (1998), Rice & Maton (2001), Rowbotham et al. (1998), Simpson (2001); concomitant drugs not permitted in 1, but permitted in 3 (but anti-convulsants excluded in 1 and SSRIs excluded in another)

Pregabalin (n=238): Sabatowski et al. (2004); concomitant drugs permitted if stable

Valproate (n=45): Kochar et al. (2005); no concomitant drugs permitted

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

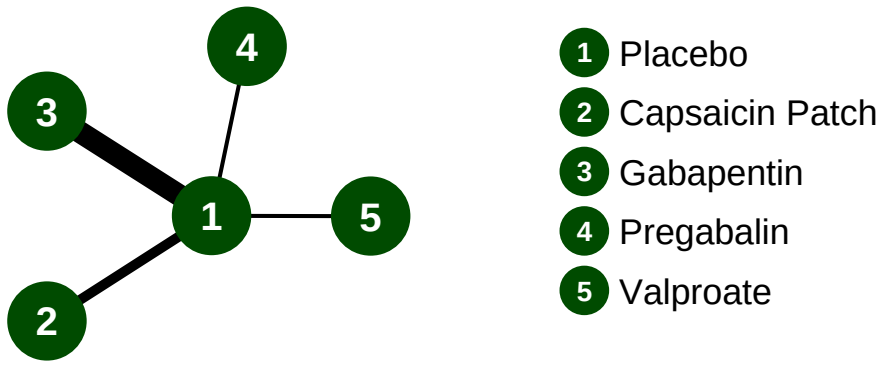

Figure 2 PGIC (at least moderate improvement) - 8 weeks - evidence network

Table 2 PGIC (at least moderate improvement) - 8 weeks - trials included in analysis

	Placebo	Capsaicin Patch	Gabapentin	Pregabalin
Capsaicin Patch	2 RCTs[2,3] total n=1543			
Gabapentin	4 RCTs[1,5,6,8] total n=778	-		
Pregabalin	1 RCT[7] total n=238	-	-	
Valproate	1 RCT[4] total n=45	-	-	-

(1) Backonja et al. (1998); (2) Irving et al. (2011); (3) Irving et al. (2012); (4) Kochar et al. (2005); (5) Rice & Maton (2001); (6) Rowbotham et al. (1998); (7) Sabatowski et al. (2004); (8) Simpson (2001)

Table 3 PGIC (at least moderate improvement) - 8 weeks - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Gabapentin	Pregabalin	Valproate
Placebo		1.69 (1.35, 2.12)	3.14 (2.16, 4.56)	3.34 (1.63, 6.83)	8.23 (1.89, 35.83)
Capsaicin Patch	1.68 (1.06, 2.65)		-	-	-
Gabapentin	3.18 (2.10, 4.87)	1.89 (1.02, 3.53)		-	-
Pregabalin	3.43 (1.52, 8.33)	2.04 (0.80, 5.52)	1.08 (0.43, 2.86)		-
Valproate	9.60 (2.12, 60.14)	5.73 (1.18, 37.71)	3.03 (0.62, 19.76)	2.79 (0.49, 20.92)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

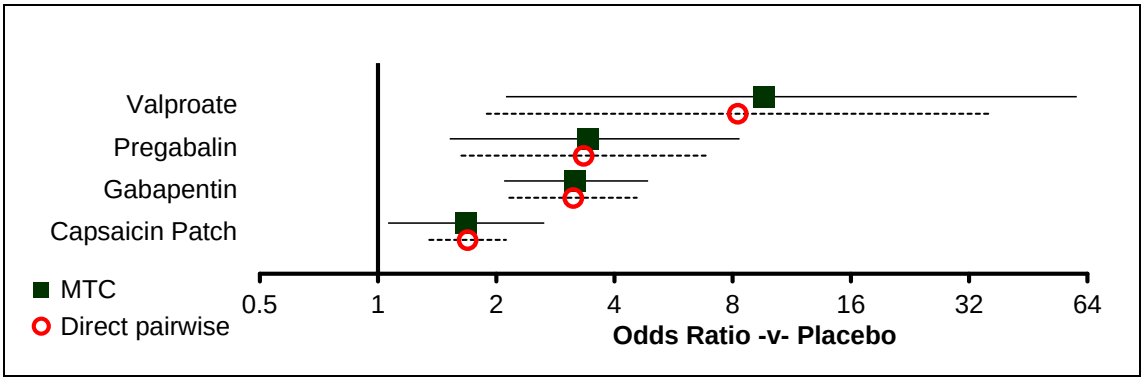

Figure 3 PGIC (at least moderate improvement) - 8 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 4 PGIC (at least moderate improvement) - 8 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (5, 5)
Capsaicin Patch	0.001	4 (3, 4)
Gabapentin	0.044	3 (1, 3)
Pregabalin	0.102	2 (1, 4)
Valproate	0.853	1 (1, 3)

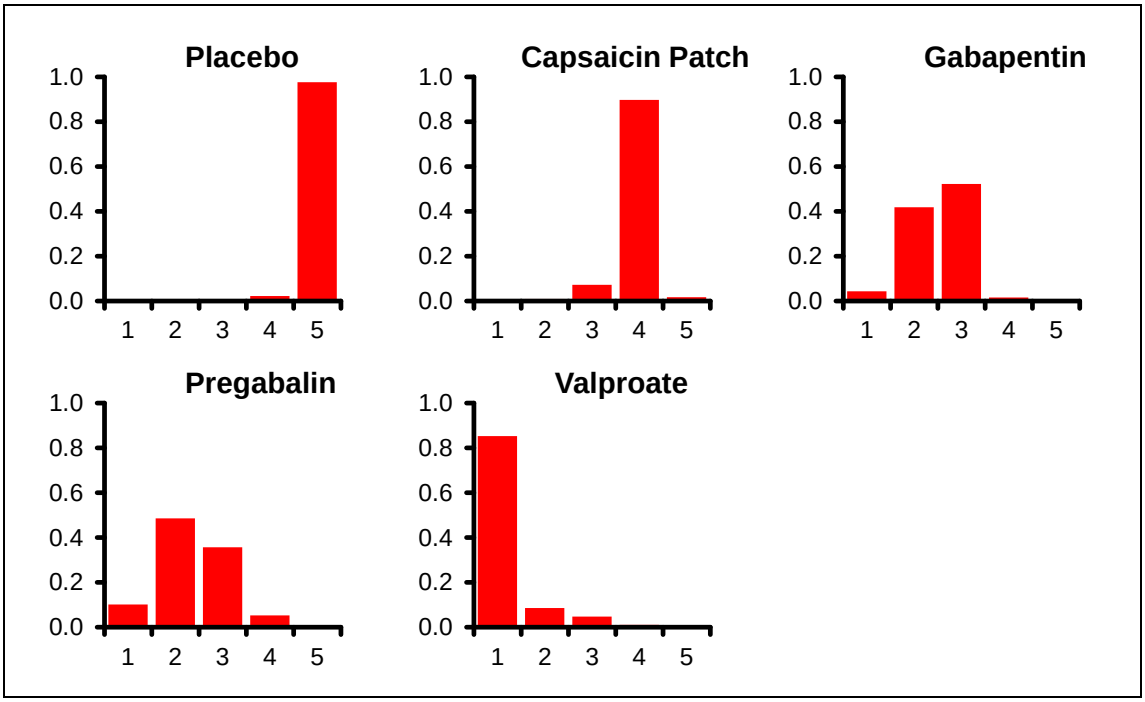

Figure 4 PGIC (at least moderate improvement) - 8 weeks - rank probability histograms

Table 5 PGIC (at least moderate improvement) - 8 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
16.59 (compared to 18 data-points)	102.227	88.295	13.932	116.159	0.000 (95%CrI: 0.000, 0.462)

Table 6 PGIC (at least moderate improvement) - 8 weeks - notes

- Random-effects model was used.
- 30000 burn-ins and 50000 iterations.
- Model convergence: autocorrelation relatively poor for valproate because of small numbers of events in placebo arm.

Summary GRADE profile 1c: Network meta-analysis for PGIC (at least moderate improvement) (84 +/- 14 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
PGIC – at least moderate improvement (follow up 84 days)	8 RCTs[a] n=3157	very serious[1]	not serious[2]	not serious[3]	serious[4]	low	Critical

[1] 5 studies do not report the method of randomisation and half were unclear about allocation concealment; there is uncertainty about comparability at baseline between groups in 5 studies (particularly for use of concomitant drugs); during the studies, concomitant drug and rescue medication use was unclear in 5 studies; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for capsaicin patch or pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons with only one trial); no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there are no head-to-head trials; half of the 'links' in network include only 1 trial; wide confidence intervals around rankings in the network

[a] capsaicin patch (n=1543): Irving et al. (2011); Irving et al. (2012); concomitant drugs permitted if stable

lacosamide (n=119): Rauck et al. (2007); only SSRIs permitted but others were permitted during the trial if the investigator considered it necessary

lamotrigine (n=227): Simpson et al. (2003); concomitant drugs permitted if stable

Pregabalin (n=1268): Arezzo et al. (2008), Freynhagen et al. (2005),Tolle et al. (2008), van Seventer et al. (2006); concomitant drugs permitted if stable in one study but only SSRIs permitted in 3 studies

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

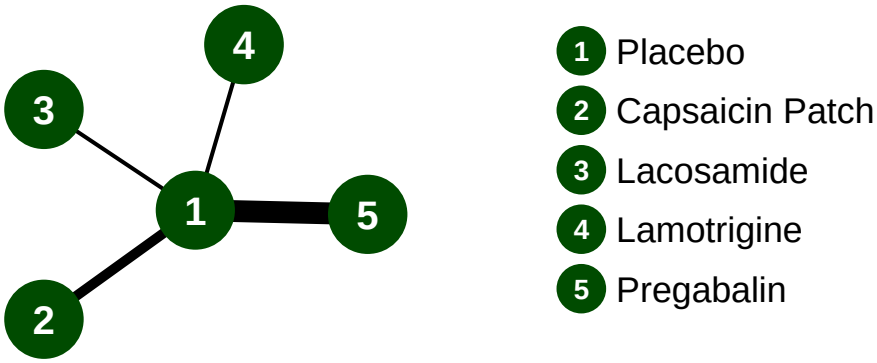

Figure 5 PGIC (at least moderate improvement) - 12 weeks - evidence network

Table 7 PGIC (at least moderate improvement) - 12 weeks - trials included in analysis

	Placebo	Capsaicin Patch	Lacosamide	Lamotrigine
Capsaicin Patch	2 RCTs[3,4] total n=1543			
Lacosamide	1 RCT[5] total n=119	-		
Lamotrigine	1 RCT[6] total n=227	-	-	
Pregabalin	4 RCTs[1,2,7,8] total n=1268	-	-	-

(1) Arezzo et al. (2008); (2) Freynhagen et al. (2005); (3) Irving et al. (2011); (4) Irving et al. (2012); (5) Rauck et al. (2007); (6) Simpson et al. (2003); (7) Tolle et al. (2008); (8) van Seventer et al. (2006)

Table 8 PGIC (at least moderate improvement) - 12 weeks - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Lacosamide	Lamotrigine	Pregabalin
Placebo		1.88 (1.50, 2.35)	2.04 (0.98, 4.24)	0.88 (0.48, 1.62)	2.07 (1.55, 2.77)
Capsaicin Patch	1.89 (1.37, 2.62)		-	-	-
Lacosamide	2.06 (0.92, 4.63)	1.09 (0.46, 2.59)		-	-
Lamotrigine	0.88 (0.44, 1.79)	0.47 (0.21, 1.01)	0.43 (0.15, 1.27)		-
Pregabalin	2.08 (1.51, 2.91)	1.10 (0.69, 1.76)	1.01 (0.42, 2.42)	2.36 (1.09, 5.15)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

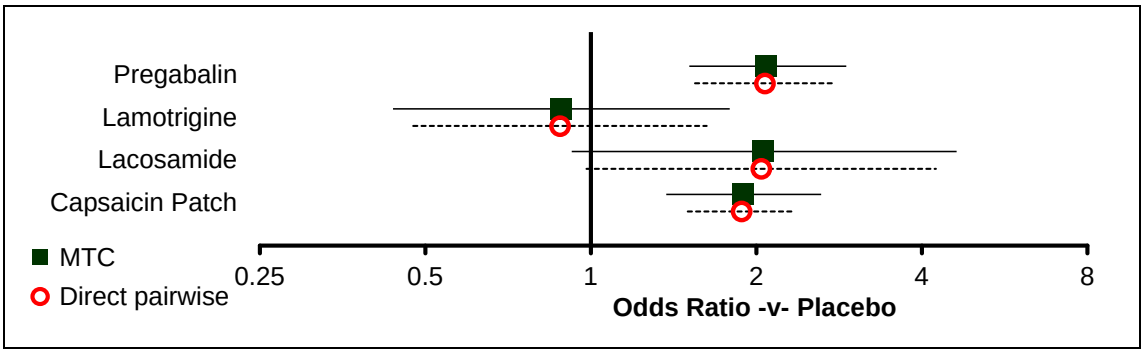

Figure 6 PGIC (at least moderate improvement) - 12 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 9 PGIC (at least moderate improvement) - 12 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	4 (3, 5)
Capsaicin Patch	0.175	2 (1, 3)
Lacosamide	0.439	2 (1, 4)
Lamotrigine	0.006	5 (3, 5)
Pregabalin	0.380	2 (1, 3)

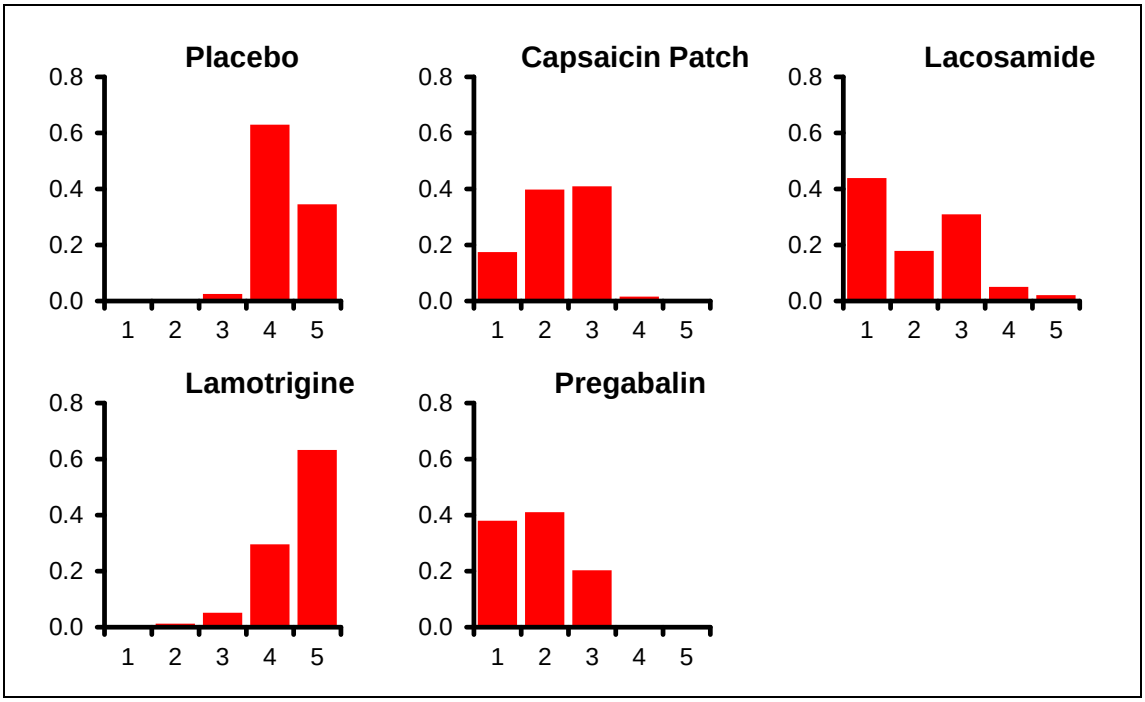

Figure 7 PGIC (at least moderate improvement) - 12 weeks - rank probability histograms

Table 10 PGIC (at least moderate improvement) - 12 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
17.45 (compared to 21 data-points)	123	109.254	13.746	136.746	0.000 (95%CrI: 0.000, 0.154)

Table 11 PGIC (at least moderate improvement) - 12 weeks - notes

- Random-effects model was used.
- 30000 burn-ins and 50000 iterations.
- Includes Rauck (2007) which reported outcomes at 70 days allowing us to include lacosamide into this network (adding this into the network does not make any dramatic changes to the results, but it does make us less certain

that pregabalin ranks in the top 2).

Summary GRADE profile 2a: Network meta-analysis for sleep interference on normalised 10-point scale (28 +/- 7d)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Sleep interference on normalised 10-point scale (follow up 28 days)	3 RCTs[a] n=326	very serious[1]	not serious[2]	not serious[3]	serious[4]	very low	Critical

[1] more than half of studies are crossover studies; it was unclear if groups were comparable in the others, particularly regarding concomitant drug use; during the study, there were differences in concomitant drug use between groups in one study (though the significance is unknown) and it was not clear if use was significantly different between groups in the other studies; concomitant drugs permitted varies across the studies in the network; inadequate length of follow-up (no more than 5 weeks for included studies)

[2] only 1 trial for each arm so no possibility of inconsistency between studies for a pairwise comparison; the network is not susceptible to inconsistency because the only loop is from a multi-armed trial

[3] all aspects of PICO conform to review protocol

[4] most 'links' in network include only 1 trial, wide confidence around rankings in the network

[a] **Placebo-controlled comparisons:**

Escitalopram (n=82): Otto et al. (2008); no concomitant drugs permitted

Gabapentin (n=196): Gordh et al. (2008) ; no concomitant drugs permitted

Head-to-head comparisons:

Gabapentin vs gabapentin+nortriptyline (n=96): Gilron et al. (2012); concomitant opioids permitted in stable doses but tricyclics, gabapentin, pregabalin excluded

Nortriptyline vs gabapentin+nortriptyline (n=100): Gilron et al. (2012); concomitant opioids permitted in stable doses but tricyclics, gabapentin, pregabalin excluded

Nortriptyline vs gabapentin (n=96): Gilron et al. (2012); concomitant opioids permitted in stable doses but tricyclics, gabapentin, pregabalin excluded

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial.

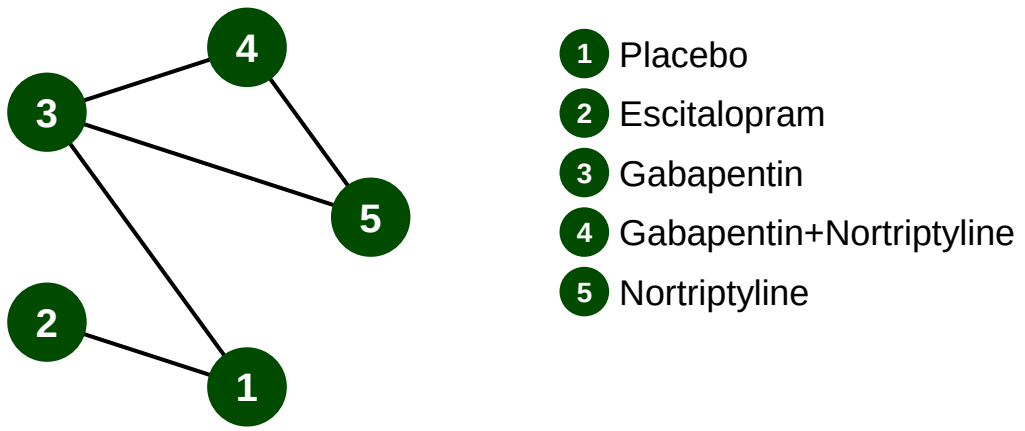

Figure 8 sleep interference - 4 weeks - evidence network

Table 12 sleep interference - 4 weeks - trials included in analysis

	Placebo	Escitalopram	Gabapentin	Gabapentin +Nortriptyline
Escitalopram	1 RCT[3] total n=82			
Gabapentin	1 RCT[2] total n=98	-		
Gabapentin +Nortriptyline	-	-	1 RCT[1] total n=96	
Nortriptyline	-	-	1 RCT[1] total n=96	1 RCT[1] total n=100

(1) Gilron et al. (2012); (2) Gordh et al. (2008); (3) Otto et al. (2008)

Table 13 sleep interference - 4 weeks - relative effectiveness of all pairwise combinations

	Placebo	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Nortriptyline
Placebo		-1.00 (-1.57, -0.43)	-0.39 (-0.95, 0.17)	-	-
Escitalopram	-1.00 (-1.57, -0.43)		-	-	-
Gabapentin	-0.39 (-0.96, 0.17)	0.61 (-0.20, 1.41)		-1.20 (-1.83, -0.57)	0.10 (-0.53, 0.73)
Gabapentin +Nortriptyline	-1.59 (-2.44, -0.75)	-0.60 (-1.61, 0.43)	-1.20 (-1.83, -0.58)		1.30 (0.69, 1.91)
Nortriptyline	-0.29 (-1.14, 0.55)	0.70 (-0.31, 1.73)	0.10 (-0.53, 0.73)	1.30 (0.69, 1.91)	

Values given are mean differences.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

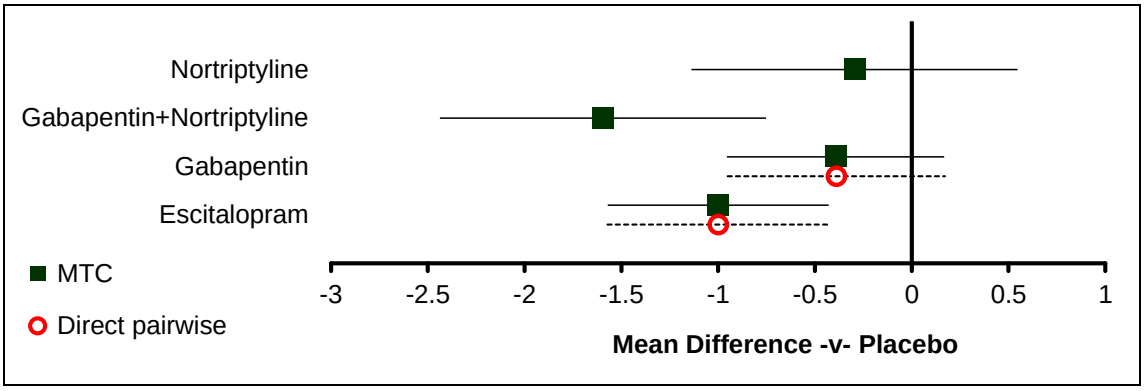

Figure 9 sleep interference - 4 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 14 peripheral - sleep interference - 4 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (3, 5)
Escitalopram	0.128	2 (1, 4)
Gabapentin	0.000	3 (2, 5)
Gabapentin+Nortriptyline	0.872	1 (1, 2)
Nortriptyline	0.000	4 (2, 5)

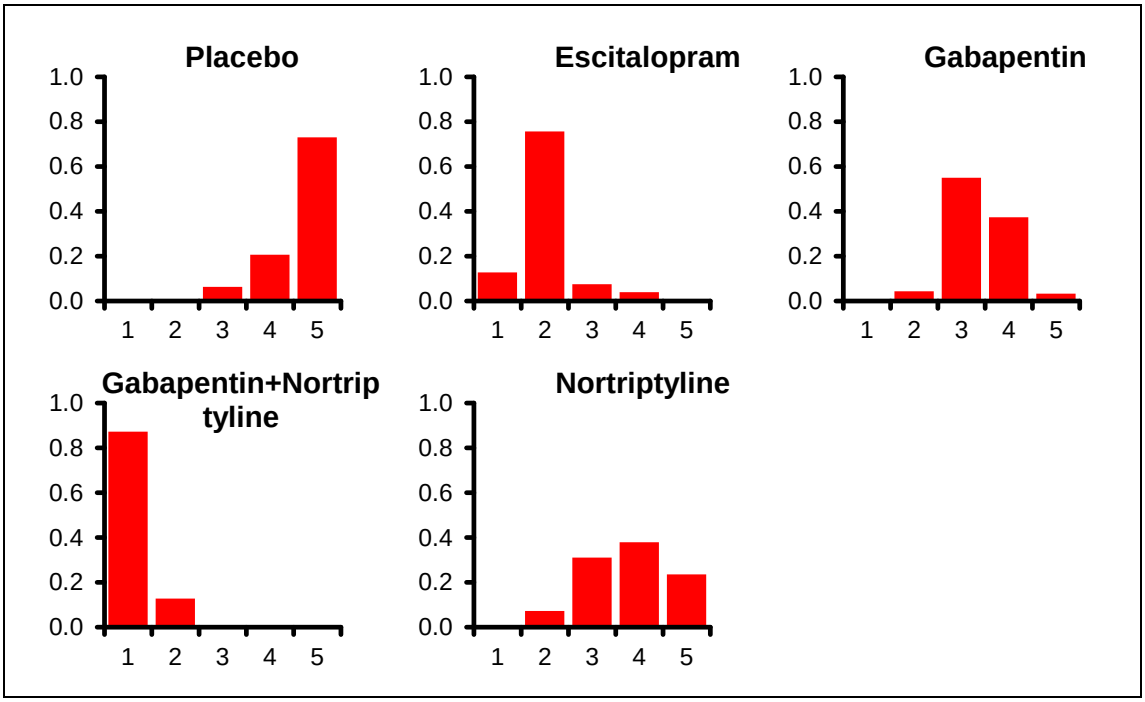

Figure 10 sleep interference - 4 weeks - rank probability histograms

Table 15 sleep interference - 4 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
6.998 (compared to 7 data-points)	-1.885	-8.883	6.998	5.114

Table 16 sleep interference - 4 weeks - notes

- Fixed-effects model was used.
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 2b: Meta-analysis for sleep interference on normalised 10-point scale (56 +/- 7d) – gabapentin vs placebo

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Effect/outcome	Quality	Importance
Sleep interference on normalised 10-point scale (follow up 56 days)	2 RCTs [a] n=360	serious[1]	not serious[2]	not serious[3]	not serious[4]	MD: -1.28 (95% CI: -1.69 to -0.88)	moderate	Critical

[1] 1 of the 2 studies does not report the method of randomisation and neither were clear about allocation concealment; there is uncertainty about SSRI usage at baseline between groups in 1 of the studies

[2] I^2 was 0% for the pairwise comparison which may indicate that any inconsistency might not be important

[3] all aspects of PICO conform to review protocol

[a] Gabapentin vs placebo (n=1543): Irving et al. (2011); Irving et al. (2012); concomitant tricyclic anti-depressants permitted in one but only SSRIs in the other

Abbreviations: CI, confidence interval; MD, mean difference; PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

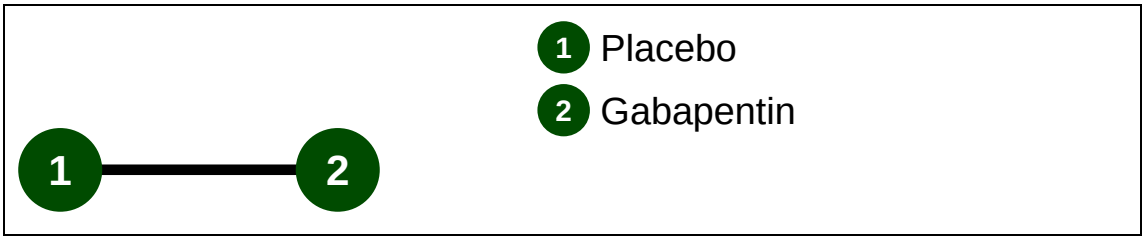

Figure 11 sleep interference - 8 weeks - evidence diagram

Table 17 sleep interference - 8 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
3.793 (compared to 4 data-points)	-1.69	-5.459	3.768	2.078	0.000 (95%CrI: 0.001, 21.137)

Table 18 sleep interference - 8 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
-

Summary GRADE profile 2c: Network meta-analysis for sleep interference on normalised 10-point scale (84 +/- 14d)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Sleep interference on normalised 10-point scale (follow up 84 days)	5 RCTs[a] n=1515	very serious[1]	not serious[2]	not serious[3]	serious[4]	Low	Critical

[1] one study used inadequate allocation concealment and 2 were unclear about allocation concealment; treatment groups were not comparable at baseline in two studies and it was unclear if groups were comparable in 3 of the others, particularly regarding concomitant drug use; during the study, there were differences in rescue medication usage in one study and it was not clear if there were differences between groups for concomitant and rescue medication usages in 2 other studies; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for duloxetine vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for topiramate vs placebo since the comparisons contains only one trial); no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there are no head-to-head trials; 1 of 2 'links' in network includes only 1 trial; confidence intervals for effect estimates against placebo appear small enough but confidence intervals around rankings are wide (both interventions could be ranked either 1 or 2)

[a] Duloxetine (n=1198): Gao et al. (2010), Raskin et al. (2005), Wernicke et al. (2006), Yasuda et al. (2011); most did not permit concomitant pain medications but one was unclear

Topiramate (n=317): Raskin et al. (2004); only SSRIs permitted

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

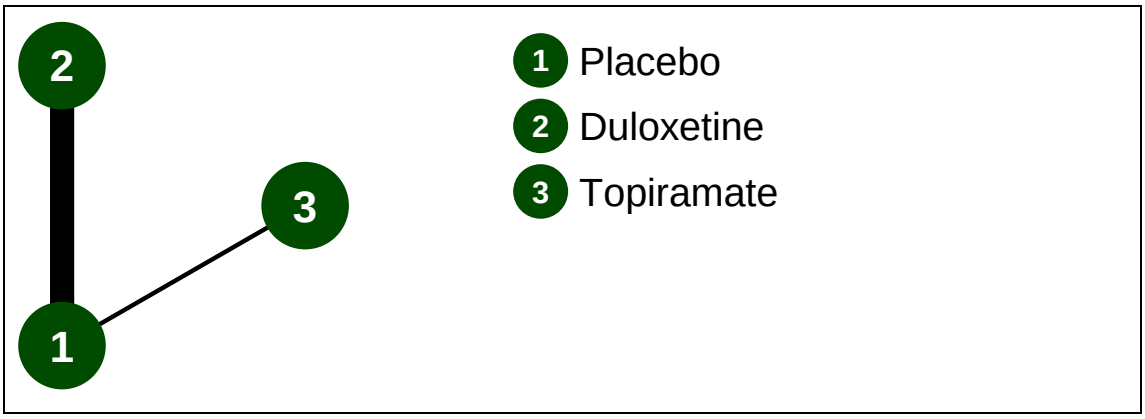

Figure 12 sleep interference - 12 weeks - evidence network

Table 19 sleep interference - 12 weeks - trials included in analysis

	Placebo	Duloxetine
Duloxetine	4 RCTs[1,3,4,5] total n=1198	
Topiramate	1 RCT[2] total n=317	-

(1) Gao et al. (2010); (2) Raskin et al. (2004); (3) Raskin et al. (2005); (4) Wernicke et al. (2006); (5) Yasuda et al. (2011)

Table 20 sleep interference - 12 weeks - relative effectiveness of all pairwise combinations

	Placebo	Duloxetine	Topiramate
Placebo		-0.62 (-0.94, -0.31)	-1.00 (-1.64, -0.36)
Duloxetine	-0.62 (-1.02, -0.21)		-
Topiramate	-1.00 (-1.86, -0.14)	-0.38 (-1.34, 0.57)	

Values given are mean differences.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

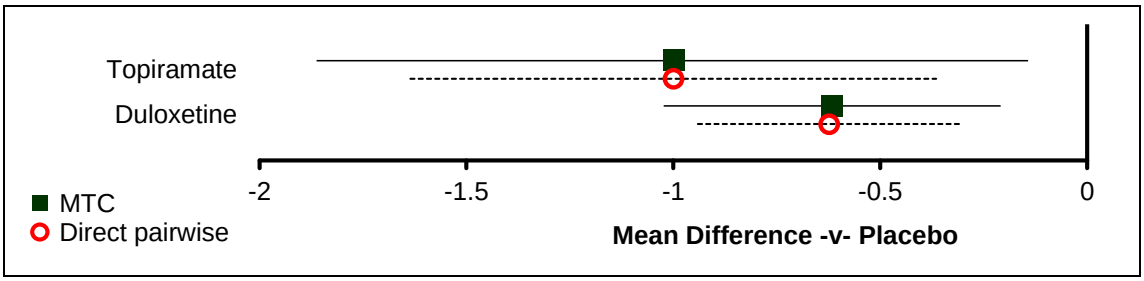

Figure 13 sleep interference - 12 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 21 sleep interference - 12 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.001	3 (3, 3)
Duloxetine	0.193	2 (1, 2)
Topiramate	0.806	1 (1, 2)

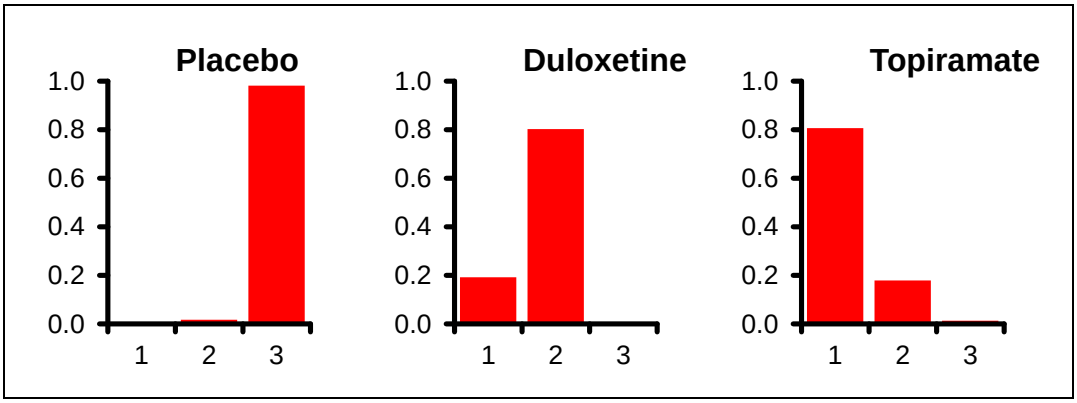

Figure 14 sleep interference - 12 weeks - rank probability histograms

Table 22 sleep interference - 12 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
10.88 (compared to 13 data-points)	-0.903	-9.653	8.75	7.847	0.000 (95%CrI: 0.000, 0.516)

Table 23 sleep interference - 12 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 3: Network meta-analysis for withdrawal due to adverse effects at any time point

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Withdrawal due to adverse effects at any time	75 RCTs[a] n=17063	very serious[2]	not serious[3]	not serious[4]	very serious[5]	Very low	Critical

[1] in just over half of the studies, groups were either not comparable or it was unclear if they were comparable at baseline; concomitant drugs permitted varies across the studies in the network

[2] it was not possible to assess heterogeneity for pairwise comparisons; there appears to be consistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] only a very small proportion of links in the network are connected with head-to-head trials; wide confidence intervals for effect estimates for the majority of interventions against placebo and around rankings in the network

[a] **placebo-controlled comparisons:**

amitriptyline (n=250): Graff-Radford et al. (2000), Kautio et al. (2008), Max et al. (1988), Vrethem et al. (1997); concomitant drugs permitted in one but it was unclear if they were permitted in the others

cannabis sativa extract (n=125): Nurmikko et al. (2007); concomitant drugs permitted

capsaicin cream (n=547): Donofrio & Capsaicin study (1992), Paice et al. (2000), Scheffler et al. (1991), Tandan et al. (1992), Watson & Evans (1992), Watson et al. (1993); concomitant drugs permitted but topical medications excluded in most

capsaicin patch (n=2738): Backonja et al. (2008), Clifford et al. (2012), Irving et al. (2011), Irving et al. (2012), Webster et al. (2010); concomitant drugs permitted but topical medications excluded in most

duloxetine (n=1692): Gao et al. (2010), Goldstein et al. (2005), Raskin et al. (2005), Wernicke et al. (2006), Yasuda et al. (2011); concomitant drugs not permitted in most except one study that was unclear

escitalopram (n=96): Otto et al. (2008); concomitant drugs not permitted

gabapentin (n=1054): Backonja et al. (1998), Gordh et al. (2008), Hahn et al. (2004), Rice & Maton (2001), Simpson (2001); concomitant drugs not permitted in three, permitted in two (only SSRIs in one and oxycodone was used as a rescue medication in another which is in the scope of the guideline for the use in NP so considered a concomitant medication)

imipramine (n=80): Sindrup et al. (2003); unclear if concomitant drugs permitted

lacosamide (n=1314): Rauck et al. (2007), Shaibani et al. (2009), Wymer et al. (2009), Ziegler et al. (2010); concomitant drugs were permitted in all but one (but anti-convulsants excluded in these)

lamotrigine (n=1207): Eisenberg et al. (2001), Luria et al. (2000), Rao et al. (2008), Simpson et al. (2000), Simpson et al. (2003), Vinik et al. (2007), Vinik et al. (2007); two studies did not permit concomitant drugs, one was unclear and the rest permitted concomitant drugs

levetiracetam (n=74): Holbech et al. (2011); concomitant drugs not permitted

lidocaine (n=56): Cheville et al. (2009); concomitant drugs not permitted

morphine (n=110): Khoromi et al. (2007); opioids, SSRIs, and tricylic anti-depressants not permitted but it appears some other medication for sciatica was permitted

nortriptyline (n=110): Khoromi et al. (2007); (as above)

nortriptyline+morphine (n=110): Khoromi et al. (2007); (as above)

oxcarbamazepine (n=493): Beydoun et al. (2006), Dogra et al. (2005); SSRIs only

oxycodone (n=159): Gimbel et al. (2003); unclear if concomitant drugs permitted

pregabalin (n=3840): Arezzo et al. (2008), Dworkin et al. (2003), Freynhagen et al. (2005), Guan et al. (2011), Lesser et al. (2004), Moon et al. (2010), Richter et al. (2005), Rosenstock et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Simpson et al. (2010); Stacey et al. (2008), Tolle et al. (2008), van Seventer et al. (2006); some concomitant drugs were permitted in all but one study which was unclear (however, SSRIs were the only drugs permitted in 7)

topiramate (n=1674): Khoromi et al. (2005), Raskin et al. (2004), Thienel et al. (2004); two studies

permitted concomitant drugs but only SSRIs in one and anti-convulsants were excluded in the other (the other study did not permit concomitant drugs) tramadol (n=257): Arbaiza & Vidal (2007), Harati et al. (1998), Sindrup et al. (1999); concomitant drugs were permitted in one, not permitted in one and unclear in the other valproate (n=145): Kochar et al. (2002), Kochar et al. (2004), Kochar et al. (2005); concomitant drugs not permitted in one, permitted in one and it was unclear if they were permitted in the other venlafaxine (n=355): Rowbotham et al. (2004), Sindrup et al. (2003), Tasmuth et al. (2002); concomitant drugs were not permitted in most but opioids were permitted in one **Head-to-head comparisons:** amitriptyline vs gabapentin (n=50): Morello et al. (1999); concomitant drugs not permitted amitriptyline vs nortriptyline (n=66): Watson et al. (1998); unclear if concomitant drugs permitted amitriptyline vs pregabalin (n=102): Bansal et al. (2009); concomitant drugs not permitted gabapentin vs gabapentin+oxycodone (n=338): Hanna et al. (2008); concomitant drugs permitted imipramine vs venlafaxine (n=80): Sindrup et al. (2003); unclear if concomitant drugs permitted nortriptyline+morphine vs nortriptyline, morphine vs nortriptyline+morphine vs nortriptyline, nortriptyline vs morphine (n=110): Khoromi et al. (2007); opioids, SSRIs, and tricylic anti-depressants not permitted but it appears some other medication for sciatica was permitted
Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

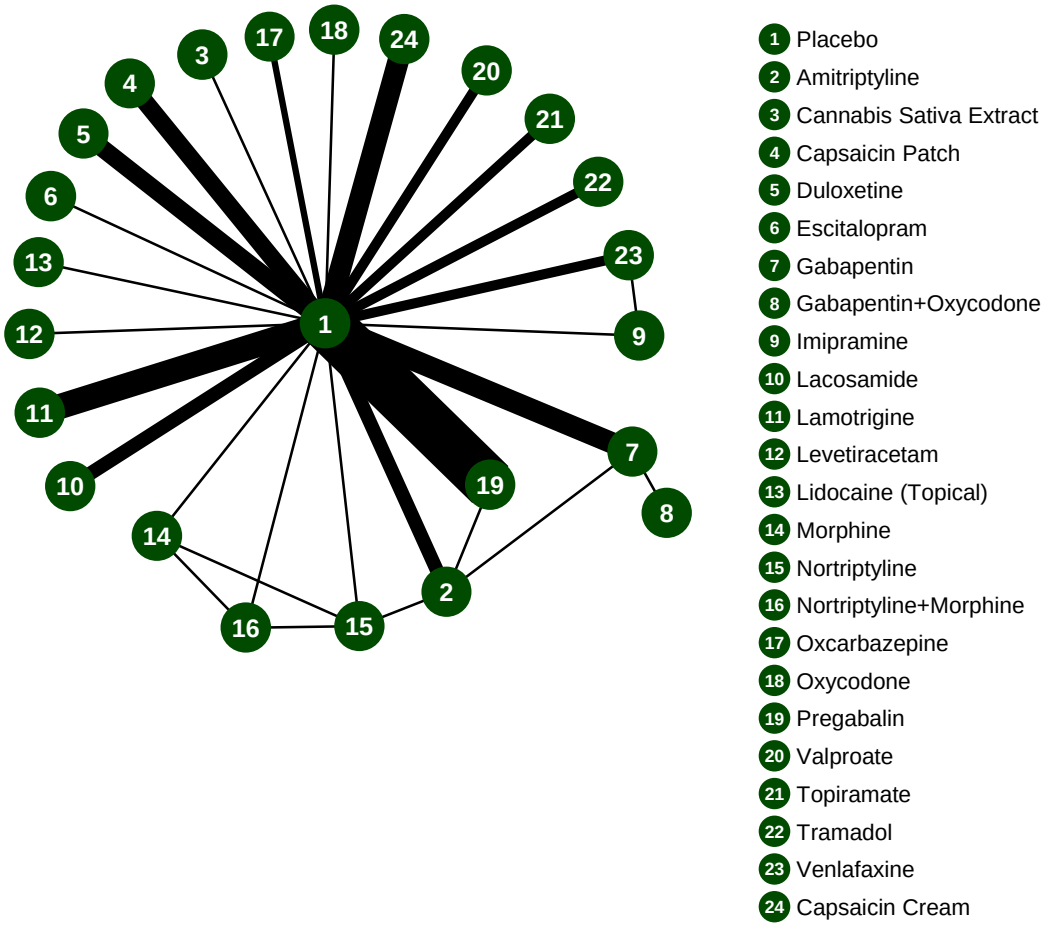

Figure 15 withdrawal due to adverse effects - evidence network

Table 24 withdrawal due to adverse effects - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Amitriptyline	4 RCTs[18,26,34,67] total n=250																						
Cannabis Sativa Extract	1 RCT[37] total n=125	-																					
Capsaicin Patch	5 RCTs[4,8,24,25,71] total n=2738	-	-																				
Duloxetine	5 RCTs[14,16,42,72,74] total n=1863	-	-	-																			
Escitalopram	1 RCT[38] total n=96	-	-	-	-																		
Gabapentin	6 RCTs[3,17,20,44,47,53] total n=1054	1 RCT[36] total n=50	-	-	-	-																	
Gabapentin +Oxycodone	-	-	-	-	-	-	1 RCT[21] total n=338																
Imipramine	1 RCT[58] total n=80	-	-	-	-	-	-	-															
Lacosamide	4 RCTs[43,52,73,75] total n=1314	-	-	-	-	-	-	-	-														
Lamotrigine	7 RCTs[12,33,40,54,55,65,66] total n=1207	-	-	-	-	-	-	-	-	-													
Levetiracetam	1 RCT[23] total n=74	-	-	-	-	-	-	-	-	-	-												

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Lidocaine (Topical)	1 RCT[7] total n=56	-	-	-	-	-	-	-	-	-	-	-											
Morphine	1 RCT[28] total n=110	-	-	-	-	-	-	-	-	-	-	-	-										
Nortriptyline	1 RCT[28] total n=110	1 RCT[70] total n=66	-	-	-	-	-	-	-	-	-	-	-	1 RCT[28] total n=110									
Nortriptyline +Morphine	1 RCT[28] total n=110	-	-	-	-	-	-	-	-	-	-	-	-	1 RCT[28] total n=110	1 RCT[28] total n=110								
Oxcarbazepine	2 RCTs[6,9] total n=493	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[15] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Pregabalin	14 RCTs[2,11,13,19,32,35,45,46,49,50,56,59,63,64] total n=3840	1 RCT[5] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Valproate	3 RCTs[29,30,31] total n=145	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Topiramate	3 RCTs[27,41,62] total n=1674	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	3 RCTs[1,22,57] total n=257	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	3 RCTs[48,58,61] total n=355	-	-	-	-	-	-	-	1 RCT[58] total	-	-	-	-	-	-	-	-	-	-	-	-	-	

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
									n=80														
Capsaicin Cream	6 RCTs[10,39,51,60,68,69] total n=547	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(1) Arbaiza & Vidal (2007); (2) Arezzo et al. (2008); (3) Backonja et al. (1998); (4) Backonja et al. (2008); (5) Bansal et al. (2009); (6) Beydoun et al. (2006); (7) Cheville et al. (2009); (8) Clifford et al. (2012); (9) Dogra et al. (2005); (10) Donofrio & Capsaicin study (1992); (11) Dworkin et al. (2003); (12) Eisenberg et al. (2001); (13) Freynhagen et al. (2005); (14) Gao et al. (2010); (15) Gimbel et al. (2003); (16) Goldstein et al. (2005); (17) Gordh et al. (2008); (18) Graff-Radford et al. (2000); (19) Guan et al. (2011); (20) Hahn et al. (2004); (21) Hanna et al. (2008); (22) Harati et al. (1998); (23) Holbech et al. (2011); (24) Irving et al. (2011); (25) Irving et al. (2012); (26) Kautio et al. (2008); (27) Khoromi et al. (2005); (28) Khoromi et al. (2007); (29) Kochar et al. (2002); (30) Kochar et al. (2004); (31) Kochar et al. (2005); (32) Lesser et al. (2004); (33) Luria et al. (2000); (34) Max et al. (1988); (35) Moon et al. (2010); (36) Morello et al. (1999); (37) Nurmikko et al. (2007); (38) Otto et al. (2008); (39) Paice et al. (2000); (40) Rao et al. (2008); (41) Raskin et al. (2004); (42) Raskin et al. (2005); (43) Rauck et al. (2007); (44) Rice & Maton (2001); (45) Richter et al. (2005); (46) Rosenstock et al. (2004); (47) Rowbotham et al. (1998); (48) Rowbotham et al. (2004); (49) Sabatowski et al. (2004); (50) Satoh et al. (2011); (51) Scheffler et al. (1991); (52) Shaibani et al. (2009); (53) Simpson (2001); (54) Simpson et al. (2000); (55) Simpson et al. (2003); (56) Simpson et al. (2010); (57) Sindrup et al. (1999); (58) Sindrup et al. (2003); (59) Stacey et al. (2008); (60) Tandan et al. (1992); (61) Tasmuth et al. (2002); (62) Thienel et al. (2004); (63) Tolle et al. (2008); (64) van Seventer et al. (2006); (65) Vinik et al. (2007); (66) Vinik et al. (2007); (67) Vrethem et al. (1997); (68) Watson & Evans (1992); (69) Watson et al. (1993); (70) Watson et al. (1998); (71) Webster et al. (2010); (72) Wernicke et al. (2006); (73) Wymer et al. (2009); (74) Yasuda et al. (2011); (75) Ziegler et al. (2010)

Table 25 withdrawal due to adverse effects - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amitriptyline	2.70 (1.15, 6.46)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cannabis Sativa Extract	7.08 (1.12, 69.34)	2.64 (0.34, 29.91)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Capsaicin Patch	1.09 (0.38, 3.18)	0.40 (0.10, 1.58)	0.15 (0.01, 1.30)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duloxetine	2.72 (1.48, 5.04)	1.01 (0.35, 2.89)	0.38 (0.04, 2.69)	2.52 (0.72, 8.38)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Escitalopram	7.18 (0.68, 216.50)	2.68 (0.21, 88.67)	1.03 (0.04, 46.68)	6.70 (0.49, 233.90)	2.65 (0.23, 83.30)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin	1.79 (0.93, 3.48)	0.67 (0.24, 1.83)	0.25 (0.02, 1.80)	1.65 (0.47, 5.65)	0.66 (0.27, 1.63)	0.25 (0.01, 2.91)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin +Oxycodone	5.93 (1.27, 28.42)	2.19 (0.39, 12.54)	0.82 (0.05, 9.41)	5.45 (0.84, 36.02)	2.19 (0.41, 11.74)	0.80 (0.02, 14.04)	3.31 (0.82, 13.69)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Imipramine	0.37 (0.01, 4.17)	0.14 (0.00, 1.82)	0.05 (0.00, 1.13)	0.34 (0.01, 4.78)	0.14 (0.00, 1.66)	0.05 (0.00, 1.62)	0.21 (0.01, 2.56)	0.06 (0.00, 1.12)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Lacosamide	2.46 (1.25, 4.92)	0.91 (0.31, 2.74)	0.35 (0.03, 2.50)	2.27 (0.63, 7.93)	0.91 (0.36, 2.28)	0.34 (0.01, 4.03)	1.38 (0.53, 3.59)	0.42 (0.08, 2.25)	6.67 (0.54, 252.80)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lamotrigine	2.08 (1.07, 4.20)	0.77 (0.26, 2.33)	0.29 (0.03, 2.12)	1.92 (0.54, 6.70)	0.77 (0.31, 1.94)	0.29 (0.01, 3.42)	1.17 (0.45, 3.04)	0.35 (0.06, 1.93)	5.63 (0.46, 209.90)	0.85 (0.33, 2.23)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Levetiracetam	13.07 (0.60, 7262.00)	4.89 (0.20, 2745.00)	1.91 (0.04, 1231.00)	12.30 (0.45, 6911.00)	4.84 (0.21, 2732.00)	1.87 (0.02, 1283.00)	7.34 (0.31, 4139.00)	2.30 (0.07, 1360.00)	43.56 (0.64, 44400.00)	5.35 (0.22, 2973.00)	6.31 (0.26, 3558.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lidocaine (Topical)	9.59 (0.38, 4395.00)	3.62 (0.13, 1725.00)	1.40 (0.03, 787.80)	8.94 (0.30, 4425.00)	3.56 (0.13, 1640.00)	1.37 (0.01, 843.50)	5.39 (0.20, 2515.00)	1.69 (0.04, 861.80)	31.39 (0.43, 28320.00)	3.93 (0.14, 1823.00)	4.62 (0.17, 2196.00)	0.73 (0.00, 623.20)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	6.90 (0.78, 96.33)	2.58 (0.26, 36.32)	0.96 (0.04, 23.96)	6.42 (0.56, 106.60)	2.55 (0.26, 37.82)	0.95 (0.02, 34.11)	3.87 (0.40, 57.86)	1.19 (0.08, 23.76)	20.17 (0.67, 1523.00)	2.81 (0.28, 42.95)	3.31 (0.33, 50.33)	0.50 (0.00, 32.84)	0.68 (0.00, 47.61)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	2.50 (0.28, 27.83)	0.93 (0.10, 10.39)	0.35 (0.02, 7.53)	2.32 (0.21, 31.61)	0.92 (0.10, 11.11)	0.34 (0.01, 10.41)	1.39 (0.15, 16.78)	0.43 (0.03, 7.14)	7.17 (0.26, 504.40)	1.02 (0.10, 12.43)	1.19 (0.12, 14.60)	0.18 (0.00, 10.14)	0.24 (0.00, 15.08)	0.36 (0.04, 2.46)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	5.38 (0.55, 76.50)	2.01 (0.19, 29.14)	0.75 (0.03, 19.20)	5.00 (0.40, 84.03)	1.98 (0.19, 30.21)	0.73 (0.01, 26.97)	3.01 (0.28, 45.42)	0.93 (0.06, 19.17)	15.49 (0.51, 1227.00)	2.20 (0.21, 34.09)	2.58 (0.24, 40.03)	0.39 (0.00, 25.63)	0.52 (0.00, 37.67)	0.78 (0.12, 4.71)	2.15 (0.29, 18.74)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Oxcarbazepine	4.08 (1.55, 11.09)	1.51 (0.41, 5.60)	0.57 (0.05, 4.68)	3.76 (0.89, 15.88)	1.50 (0.48, 4.82)	0.56 (0.02, 7.40)	2.28 (0.70, 7.49)	0.69 (0.11, 4.28)	11.14 (0.81, 450.50)	1.65 (0.50, 5.56)	1.96 (0.59, 6.48)	0.31 (0.00, 8.20)	0.42 (0.00, 12.54)	0.59 (0.04, 6.60)	1.63 (0.12, 17.76)	0.75 (0.04, 9.13)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxycodone	1.75 (0.32, 10.45)	0.65 (0.10, 4.70)	0.24 (0.01, 3.30)	1.61 (0.21, 12.73)	0.64 (0.11, 4.29)	0.24 (0.01, 4.71)	0.98 (0.16, 6.47)	0.30 (0.03, 3.12)	4.91 (0.23, 247.90)	0.71 (0.11, 4.86)	0.84 (0.13, 5.67)	0.13 (0.00, 4.94)	0.17 (0.00, 7.65)	0.25 (0.01, 4.26)	0.70 (0.04, 11.57)	0.32 (0.01, 5.80)	0.43 (0.06, 3.27)		N/A	N/A	N/A	N/A	N/A	N/A
Pregabalin	2.17 (1.47, 3.22)	0.80 (0.33, 1.94)	0.31 (0.03, 2.03)	2.00 (0.63, 6.08)	0.80 (0.38, 1.64)	0.30 (0.01, 3.29)	1.21 (0.56, 2.59)	0.37 (0.07, 1.79)	5.82 (0.50, 214.00)	0.88 (0.40, 1.94)	1.04 (0.47, 2.26)	0.17 (0.00, 3.76)	0.23 (0.00, 5.79)	0.31 (0.02, 2.87)	0.87 (0.08, 7.81)	0.40 (0.03, 3.99)	0.53 (0.18, 1.52)	1.24 (0.20, 7.13)		N/A	N/A	N/A	N/A	N/A
Valproate	3.60 (0.51, 46.19)	1.34 (0.16, 19.85)	0.51 (0.03, 11.86)	3.33 (0.36, 51.91)	1.33 (0.17, 18.11)	0.51 (0.01, 15.35)	2.02 (0.26, 28.19)	0.62 (0.05, 11.91)	10.67 (0.41, 756.20)	1.47 (0.18, 20.77)	1.73 (0.22, 24.12)	0.27 (0.00, 15.08)	0.36 (0.00, 23.91)	0.53 (0.02, 14.60)	1.47 (0.07, 39.69)	0.68 (0.03, 19.67)	0.89 (0.10, 13.23)	2.10 (0.15, 43.03)	1.66 (0.23, 22.09)		N/A	N/A	N/A	N/A
Topiramate	3.80 (1.80, 8.23)	1.41 (0.45, 4.45)	0.53 (0.05, 4.00)	3.50 (0.95, 12.83)	1.40 (0.53, 3.74)	0.53 (0.02, 6.28)	2.12 (0.78, 5.84)	0.64 (0.11, 3.61)	10.33 (0.81, 387.60)	1.54 (0.56, 4.33)	1.82 (0.65, 5.07)	0.29 (0.00, 7.10)	0.39 (0.00, 10.92)	0.55 (0.04, 5.52)	1.52 (0.12, 15.19)	0.70 (0.04, 7.72)	0.93 (0.27, 3.23)	2.17 (0.31, 14.25)	1.75 (0.75, 4.18)	1.05 (0.07, 8.52)		N/A	N/A	N/A
Tramadol	7.07 (1.92, 33.53)	2.64 (0.54, 15.43)	1.00 (0.07, 10.98)	6.57 (1.19, 41.61)	2.60 (0.62, 14.03)	0.98 (0.03, 16.44)	3.96 (0.91, 21.41)	1.21 (0.15, 10.72)	19.94 (1.18, 930.90)	2.88 (0.66, 15.52)	3.40 (0.78, 18.50)	0.53 (0.00, 17.96)	0.73 (0.00, 27.01)	1.03 (0.05, 14.77)	2.87 (0.18, 40.04)	1.33 (0.07, 20.43)	1.74 (0.33, 10.79)	4.08 (0.44, 40.38)	3.26 (0.84, 16.30)	1.96 (0.12, 23.88)	1.87 (0.41, 10.48)		N/A	N/A
Venlafaxine	2.73	1.01	0.38	2.52	1.01	0.38	1.52	0.46	7.33	1.11	1.31	0.20	0.28	0.40	1.10	0.51	0.67	1.57	1.26	0.76	0.72	0.38		N/

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
	(0.85, 9.79)	(0.24, 4.70)	(0.03, 3.70)	(0.52, 12.95)	(0.27, 4.13)	(0.01, 5.69)	(0.40, 6.47)	(0.07, 3.43)	(0.76, 250.50)	(0.28, 4.69)	(0.34, 5.50)	(0.00, 6.16)	(0.00, 9.18)	(0.02, 4.86)	(0.07, 13.23)	(0.03, 6.81)	(0.14, 3.30)	(0.18, 13.27)	(0.37, 4.78)	(0.05, 7.76)	(0.18, 3.14)	(0.06, 2.39)		A
Capsaicin Cream	6.10 (2.43, 16.88)	2.27 (0.63, 8.54)	0.86 (0.07, 7.15)	5.66 (1.35, 24.19)	2.25 (0.74, 7.32)	0.85 (0.03, 11.23)	3.42 (1.09, 11.33)	1.04 (0.17, 6.59)	16.76 (1.22, 674.10)	2.48 (0.78, 8.45)	2.93 (0.91, 9.91)	0.46 (0.00, 12.06)	0.63 (0.00, 18.84)	0.89 (0.05, 9.94)	2.44 (0.18, 26.98)	1.14 (0.07, 13.76)	1.50 (0.39, 6.13)	3.51 (0.46, 25.59)	2.82 (1.03, 8.39)	1.69 (0.12, 15.22)	1.61 (0.48, 5.67)	0.86 (0.14, 4.50)	2.24 (0.47, 10.52)	

Values given are hazard ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. Because it is not easily possible to derive analogous estimates of hazard ratios from a frequentist analysis of direct data only, the segment above and to the right of the shaded cells is left blank.

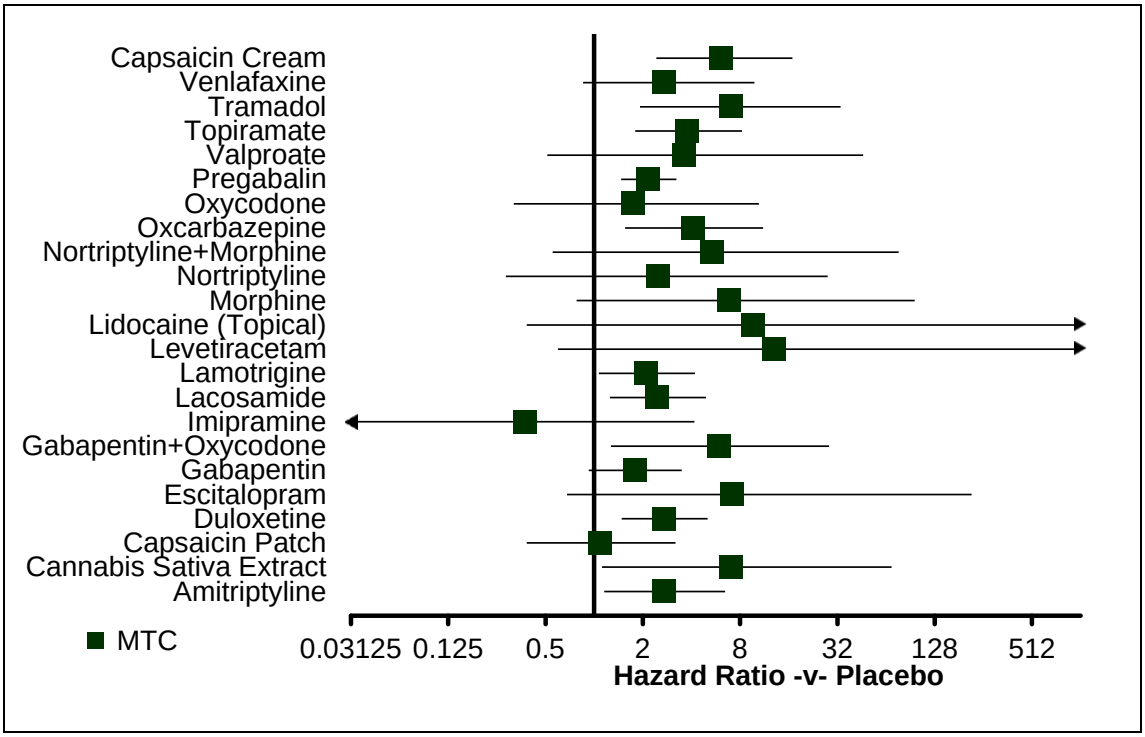

Figure 16 withdrawal due to adverse effects - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals)

Table 26 withdrawal due to adverse effects - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.045	3 (1, 6)
Amitriptyline	0.001	11 (4, 19)
Cannabis Sativa Extract	0.003	19 (4, 24)
Capsaicin Patch	0.092	4 (1, 14)
Duloxetine	0.000	12 (5, 18)
Escitalopram	0.011	19 (2, 24)
Gabapentin	0.003	7 (3, 15)
Gabapentin+Oxycodone	0.002	18 (5, 24)
Imipramine	0.639	1 (1, 15)
Lacosamide	0.000	10 (4, 18)
Lamotrigine	0.001	9 (3, 17)
Levetiracetam	0.014	22 (2, 24)
Lidocaine (Topical)	0.028	21 (1, 24)
Morphine	0.005	19 (3, 24)
Nortriptyline	0.053	11 (1, 22)
Nortriptyline+Morphine	0.013	18 (2, 24)
Oxcarbazepine	0.000	16 (6, 22)
Oxycodone	0.066	7 (1, 21)
Pregabalin	0.000	9 (5, 15)
Valproate	0.021	14 (2, 24)
Topiramate	0.000	15 (7, 21)
Tramadol	0.000	19 (8, 24)
Venlafaxine	0.002	12 (3, 21)
Capsaicin Cream	0.000	18 (10, 23)

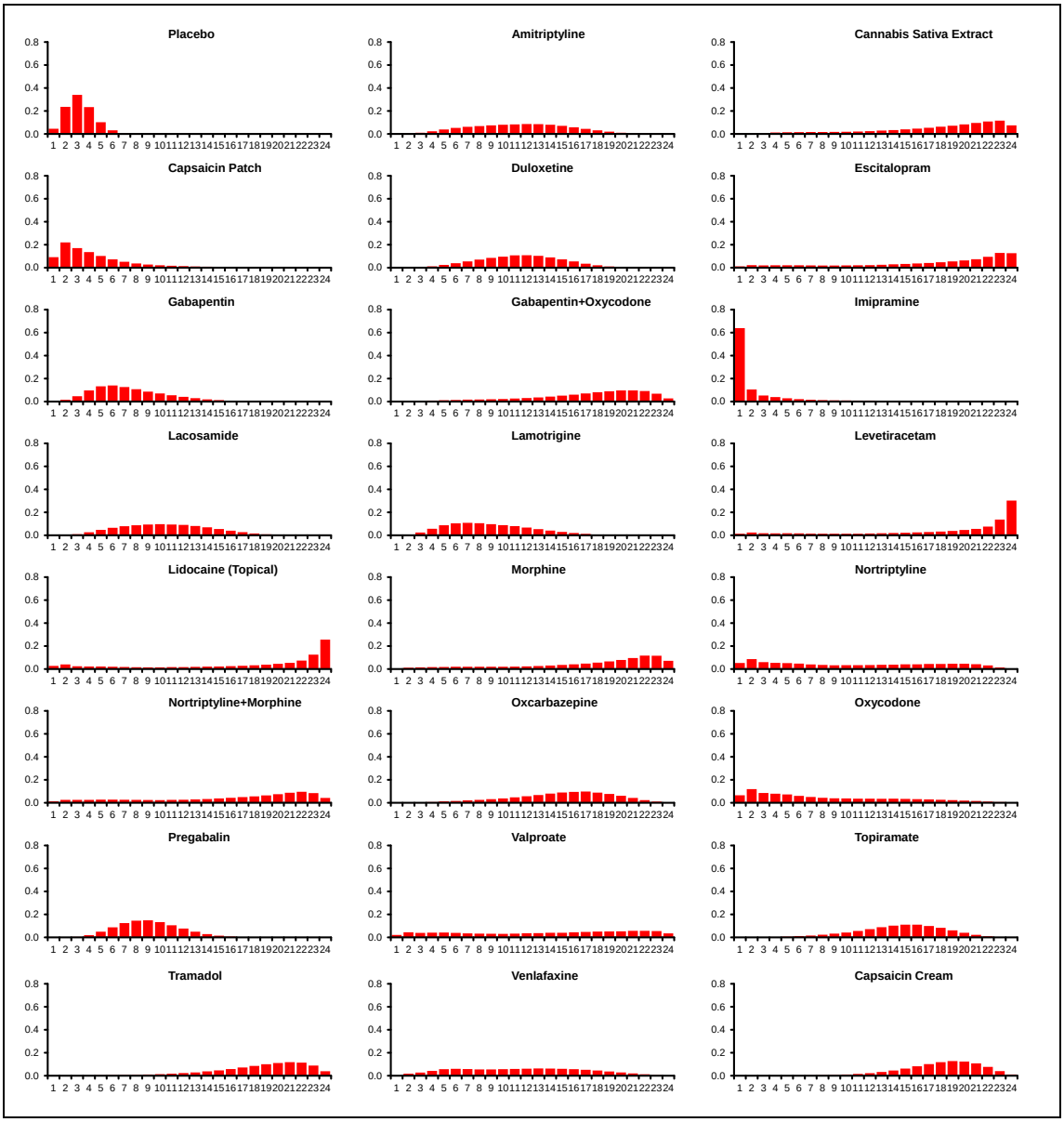

Figure 17 withdrawal due to adverse effects - rank probability histograms

Table 27 withdrawal due to adverse effects - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
176.7 (compared to 187 data-points)	798.607	661.961	136.646	935.253	0.328 (95%CrI: 0.197, 0.576)

Table 28 withdrawal due to adverse effects - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 10000 burn-ins and 50000 iterations.

- Model convergence: there was poor autocorrelation for lidocaine and levetiracetam since there were few studies and small events in the studies for these interventions.
- One of the Webster et al. (2010) studies was not included in this network as it had zero events in all study arms.

IMPORTANT OUTCOMES (profiles 4 to 6)

Summary GRADE profile 4a: Network meta-analysis for at least 30% pain relief (28 days +/-7 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 30% pain relief on any scale (follow up 28 days)	5 RCTs[a] n=775	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear if groups were comparable in 4 studies, particularly regarding concomitant drug use; during the study, most studies allowed concomitant drug use but it was not clear if use was different between groups in a number of studies; concomitant drugs permitted varies across the studies in the network; insufficient follow-up in 4 of the 5 studies

[2] I^2 was 0% for pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons with only one trial); no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] all but one 'link' in network include only 1 trial; no head-to-head trials; wide confidence intervals for the effect estimates of all interventions compared to placebo and for overall rankings within the network

[a]cannabis sativa extract (n=125): Nurmikko et al. (2007); concomitant drugs permitted

pregabalin (n=528): Lesser et al. (2004), Stacey et al. (2008); concomitant drugs apart from gabapentin and oxycodone permitted in one and only SSRIs permitted in the other

tramadol (n=90): Sindrup et al. (1999); unclear if any concomitant drugs permitted (study says a number of drugs tapered before study start but no details given)

capsaicin cream (n=32): Bernstein et al. (1989); concomitant drugs permitted

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

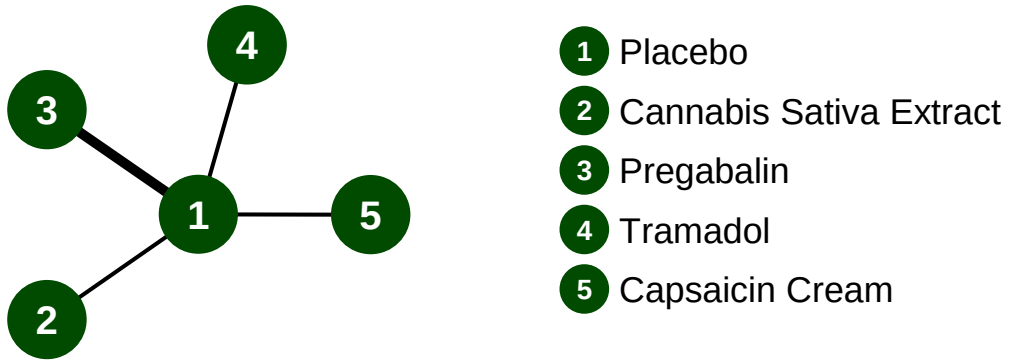

Figure 18 30% pain relief - 4 weeks - evidence network

Table 29 30% pain relief - 4 weeks - trials included in analysis

	Placebo	Cannabis Sativa Extract	Pregabalin	Tramadol
Cannabis Sativa Extract	1 RCT[3] total n=125			
Pregabalin	2 RCTs[2,5] total n=528	-		
Tramadol	1 RCT[4] total n=90	-	-	
Capsaicin Cream	1 RCT[1] total n=32	-	-	-

(1) Bernstein et al. (1989); (2) Lesser et al. (2004); (3) Nurmikko et al. (2007); (4) Sindrup et al. (1999); (5) Stacey et al. (2008); (6) van Seventer

Table 30 30% pain relief - 4 weeks - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Pregabalin	Tramadol	Capsaicin cream
Placebo		2.00 (0.81, 4.96)	3.75 (2.57, 5.48)	3.59 (1.25, 10.29)	5.57 (1.13, 27.52)
Cannabis Sativa Extract	2.04 (0.39, 11.11)		-	-	-
Pregabalin	3.80 (1.49, 9.92)	1.86 (0.27, 12.58)		-	-
Tramadol	3.74 (0.67, 22.32)	1.82 (0.16, 20.71)	0.98 (0.14, 7.24)		-
Capsaicin Cream	6.35 (0.78, 63.49)	3.12 (0.21, 51.52)	1.67 (0.17, 19.60)	1.72 (0.10, 29.89)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

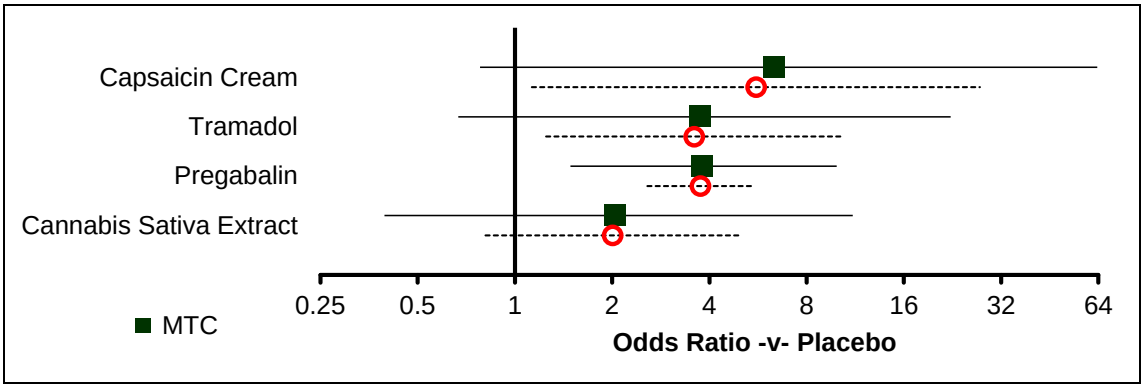

Figure 19 30% pain relief - 4 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 31 30% pain relief - 4 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (3, 5)
Cannabis Sativa Extract	0.057	4 (1, 5)
Pregabalin	0.152	2 (1, 4)
Tramadol	0.233	2 (1, 5)
Capsaicin Cream	0.558	1 (1, 5)

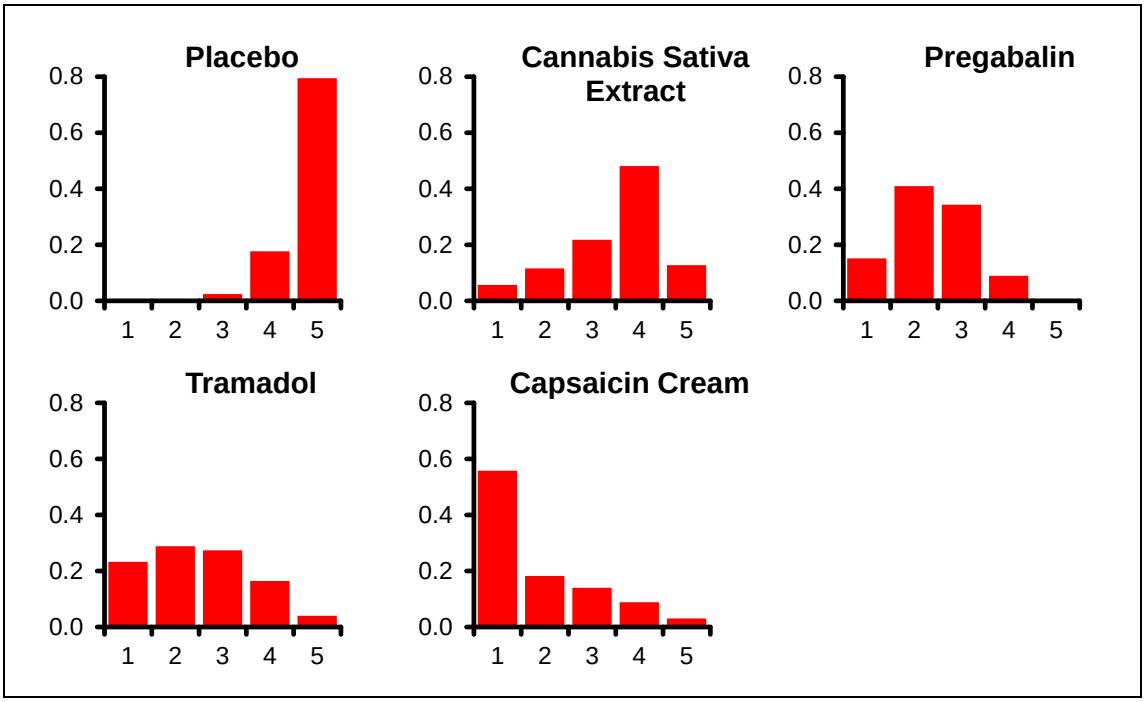

Figure 20 30% pain relief - 4 weeks - rank probability histograms

Table 32 30% pain relief - 4 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
11.86 (compared to 12 data-points)	62.771	51.805	10.965	73.736	0.000 (95%CrI: 0.000, 4.519)

Table 33 30% pain relief - 4 weeks - notes

- Random-effects model was used
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 4b: Network meta-analysis for at least 30% pain relief (56 days +/-7 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 30% pain relief on any scale (follow up 56 days)	5 RCTs[a] n=2247	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] 3 of 5 studies do not report the method of randomisation; treatment groups were not comparable at baseline in two studies and it was unclear if groups were comparable in one others; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for capsaicin patch vs placebo which may indicate that any inconsistency might not be important; however, I^2 was 80% for pregabalin vs placebo which may indicate considerable heterogeneity between the studies that make this comparison; appears to be consistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] no head-to-head comparisons; wide confidence intervals for the effect estimates of both interventions compared to placebo and for overall rankings within the network (most interventions could have any ranking)

[a] capsaicin patch (n=1529): Backonja et al. (2008), Irving et al (2012); concomitant drugs were permitted apart from topical medications

pregabalin (n=718): Dworkin et al. (2003), Guan et al. (2011), Moon et al. (2010); concomitant anti-depressants permitted in two (with the exception of anti-convulsants) but only SSRIs permitted in the other

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

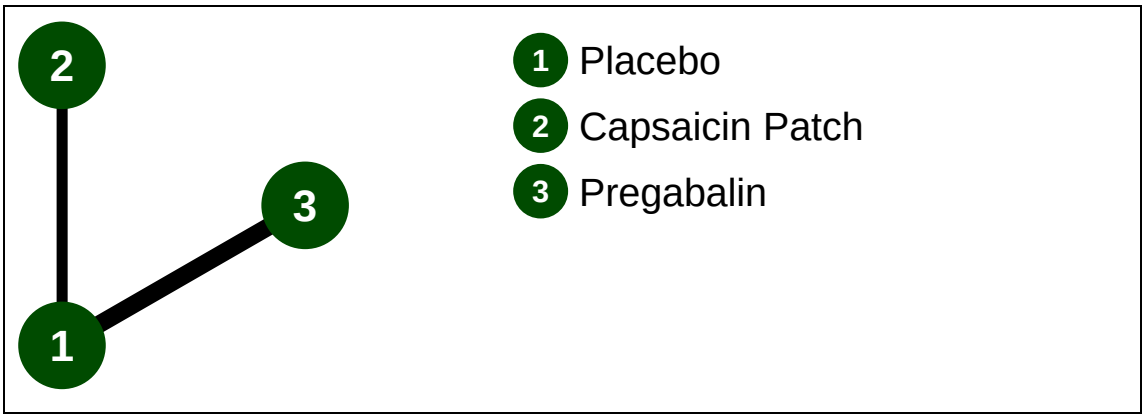

Figure 21 30% pain relief - 8 weeks - evidence network

Table 34 30% pain relief - 8 weeks - trials included in analysis

	Placebo	Capsaicin Patch
Capsaicin Patch	2 RCTs[1,4] total n=1529	
Pregabalin	3 RCTs[2,3,5] total n=718	-

(1) Backonja et al. (2008); (2) Dworkin et al. (2003); (3) Guan et al. (2011); (4) Irving et al. (2012); (5) Moon et al. (2010)

Table 35 30% pain relief - 8 weeks - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Pregabalin
Placebo		1.54 (1.25, 1.89)	2.20 (1.06, 4.59)
Capsaicin Patch	1.55 (0.29, 8.45)		-
Pregabalin	2.20 (0.55, 9.41)	1.42 (0.16, 13.00)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

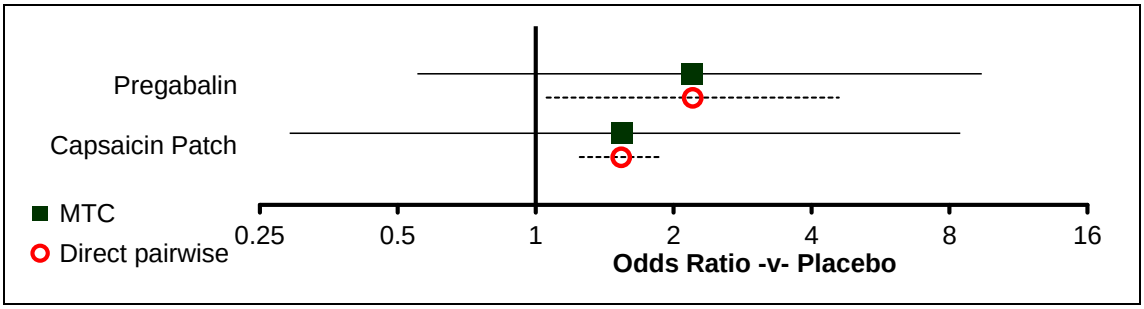

Figure 22 30% pain relief - 8 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 36 30% pain relief - 8 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.023	3 (2, 3)
Capsaicin Patch	0.270	2 (1, 3)
Pregabalin	0.707	1 (1, 3)

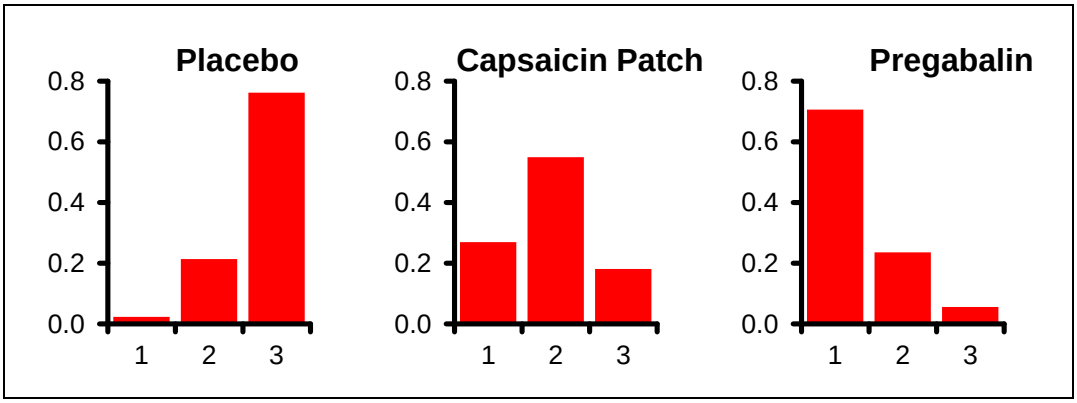

Figure 23 30% pain relief - 8 weeks - rank probability histograms

Table 37 30% pain relief - 8 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
10.69 (compared to 10 data-points)	65.961	55.902	10.058	76.019	0.003 (95%CrI: 0.010, 9.643)

Table 38 30% pain relief - 8 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 4c: Network meta-analysis for at least 30% pain relief (84 days +/-14 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 30% pain relief on any scale (follow up 84 days)	16 RCTs[a] n=5487	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] over half of studies do not report the method of randomisation; one study had inadequate allocation concealment while over half do not report about allocation concealment; treatment groups were not comparable at baseline in three studies and it was unclear if groups were comparable in eight; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 79% for pregabalin vs placebo which may indicate considerable heterogeneity between the studies that make this comparison, I^2 was 36% for duloxetine vs placebo which may suggest moderate heterogeneity in the studies;; no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there are no head-to-head trials; over half of links have only one trial; wide confidence intervals for the effect estimates of more than half of interventions compared to placebo and for overall rankings within the network

[a] cannabis sativa extract (n=30): Selvarajah et al. (2010); concomitant drugs permitted

capsaicin patch (n=2893): Backonja et al. (2008), Clifford et al. (2012), Irving et al. (2012), Irving et al. (2011), Webster et al. (2010), Webster et al. (2010); concomitant drugs except topical medications permitted (and no opioids in one study)

duloxetine (n=887): Gao et al. (2010), Wernicke et al. (2006), Yasuda et al. (2011); concomitant drugs not permitted in two and unclear in the other (the study only said that MAO inhibitors were permitted)

lacosamide (n=119): Rauck et al. (2007); SSRI only, however, excluded concomitant medications were permitted if the investigator considered them necessary

lamotrigine (n=227): Simpson et al. (2003); concomitant drugs permitted

pregabalin (n=1008): Freynhagen et al. (2005), Simpson et al. (2010), van Seventer et al. (2006); concomitant drugs permitted in all – two with the exception of anti-convulsants, two with the exception of gabapentin and SSRIs only in the fourth

topiramate (n=323): Raskin et al. (2004); SSRIs only

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

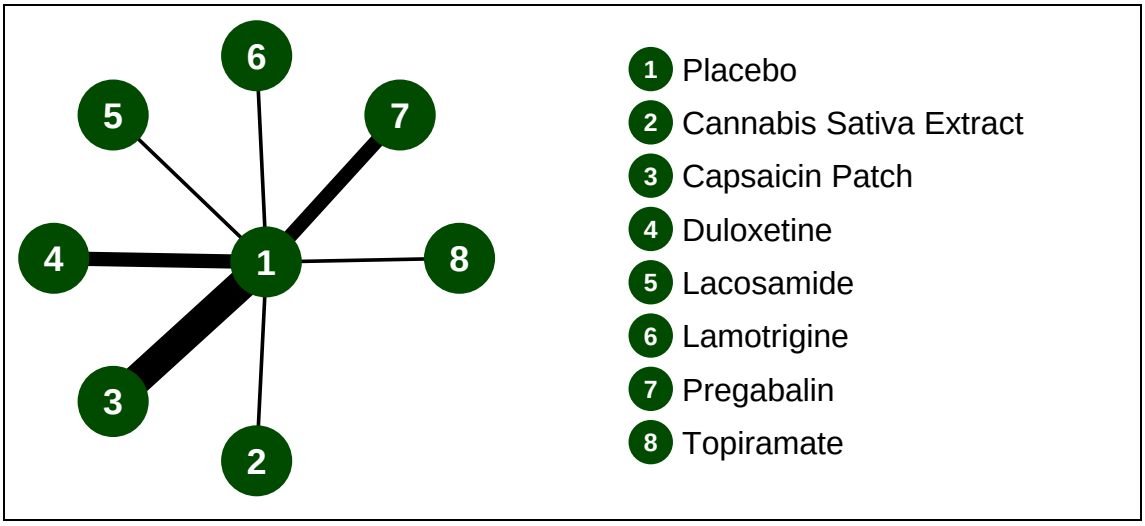

Figure 24 30% pain relief - 12 weeks - evidence network

Table 39 30% pain relief - 12 weeks - trials included in analysis

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Lacosamide	Lamotrigine	Pregabalin
Cannabis Sativa Extract	1 RCT[9] total n=30						
Capsaicin Patch	6 RCTs[1,2,5,6,13,14] total n=2893	-					
Duloxetine	3 RCTs[4,15,16] total n=887	-	-				
Lacosamide	1 RCT[8] total n=119	-	-	-			
Lamotrigine	1 RCT[10] total n=227	-	-	-	-		
Pregabalin	3 RCTs[3,11,12] total n=1008	-	-	-	-	-	
Topiramate	1 RCT[7] total n=323	-	-	-	-	-	-

(1) Backonja et al. (2008); (2) Clifford et al. (2012); (3) Freynhagen et al. (2005); (4) Gao et al. (2010); (5) Irving et al. (2011); (6) Irving et al. (2012); (7) Raskin et al. (2004); (8) Rauck et al. (2007); (9) Selvarajah et al. (2010); (10) Simpson et al. (2003); (11) Simpson et al. (2010); (12) van Seventer et al. (2006); (13) Webster et al. (2010); (14) Webster et al. (2010); (15) Wernicke et al. (2006); (16) Yasuda et al. (2011)

Table 40 30% pain relief - 12 weeks - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Lacosamide	Lamotrigine	Pregabalin	Topiramate
Placebo		0.76 (0.18, 3.24)	1.46 (1.25, 1.70)	2.17 (1.56, 3.01)	1.45 (0.70, 3.00)	2.06 (1.13, 3.77)	2.09 (0.95, 4.60)	1.81 (1.12, 2.91)
Cannabis Sativa Extract	0.74 (0.15, 3.56)		-	-	-	-	-	-
Capsaicin Patch	1.44 (1.10, 1.87)	1.95 (0.39, 9.87)		-	-	-	-	-
Duloxetine	2.20 (1.48, 3.25)	2.99 (0.59, 15.62)	1.53 (0.95, 2.46)		-	-	-	-
Lacosamide	1.46 (0.60, 3.62)	1.97 (0.31, 12.53)	1.01 (0.40, 2.62)	0.66 (0.25, 1.80)		-	-	-
Lamotrigine	2.09 (0.95, 4.73)	2.84 (0.49, 16.80)	1.45 (0.63, 3.44)	0.95 (0.39, 2.38)	1.43 (0.43, 4.84)		-	-
Pregabalin	2.02 (1.36, 3.21)	2.75 (0.55, 14.59)	1.40 (0.88, 2.42)	0.92 (0.53, 1.71)	1.39 (0.52, 3.84)	0.97 (0.40, 2.46)		-
Topiramate	1.81 (0.89, 3.75)	2.46 (0.45, 14.23)	1.26 (0.59, 2.75)	0.82 (0.37, 1.89)	1.25 (0.39, 3.96)	0.87 (0.29, 2.53)	0.90 (0.38, 2.01)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

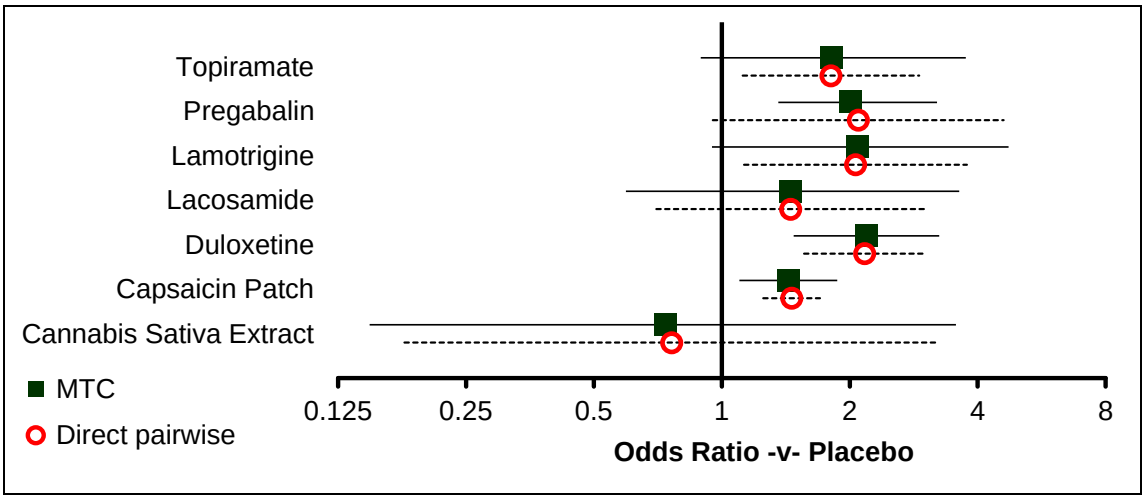

Figure 25 30% pain relief - 12 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 41 30% pain relief - 12 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	7 (6, 8)
Cannabis Sativa Extract	0.051	8 (1, 8)
Capsaicin Patch	0.001	5 (3, 7)
Duloxetine	0.255	2 (1, 5)
Lacosamide	0.095	5 (1, 8)
Lamotrigine	0.301	3 (1, 7)
Pregabalin	0.149	3 (1, 6)
Topiramate	0.149	4 (1, 7)

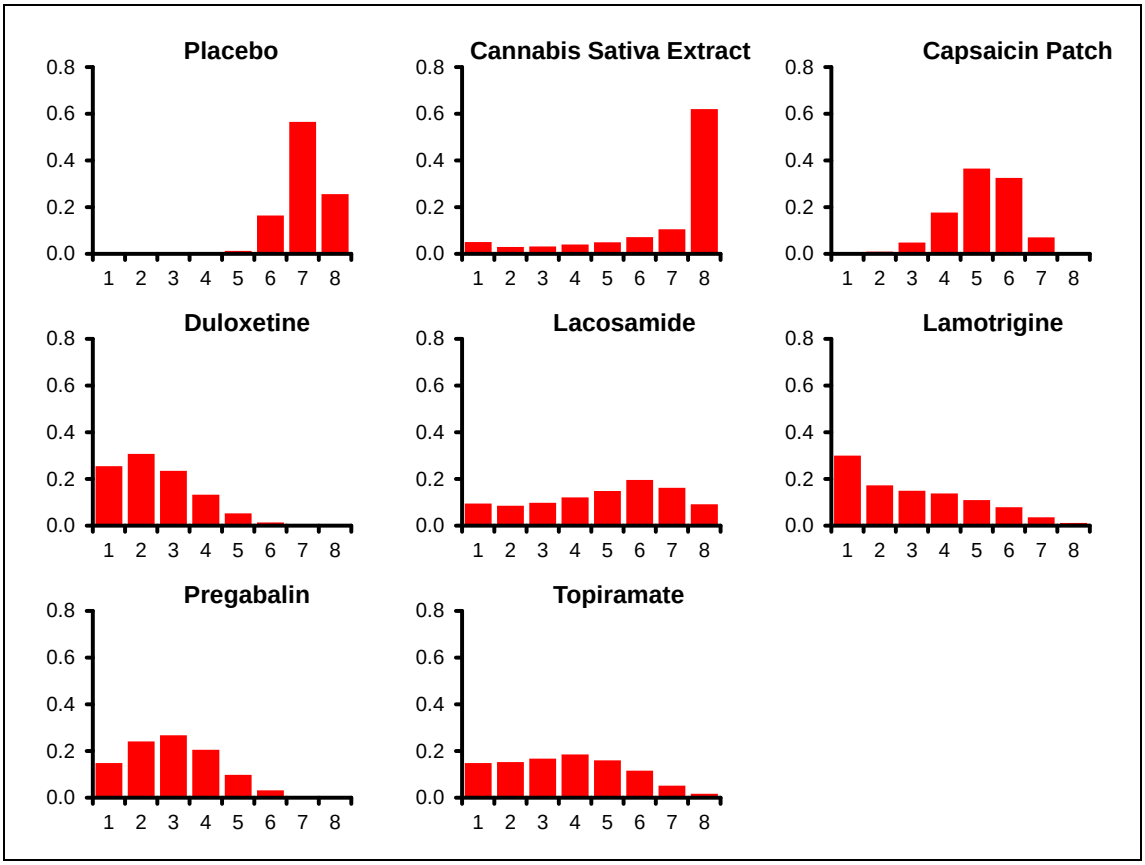

Figure 26 30% pain relief - 12 weeks - rank probability histograms

Table 42 30% pain relief - 12 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
43 (compared to 41 data-points)	249.325	217.812	31.513	280.837	0.003 (95%CrI: 0.001, 0.227)

Table 43 30% pain relief - 12 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
- Includes Rauck (2007) which reported outcomes at 70 days.

Summary GRADE profile 5a: Network meta-analysis for at least 50% pain relief (28 days +/-7 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 50% pain relief on any scale (follow up 28 days)	5 RCTs[a] n=845	very serious[1]	not serious[2]	not serious[3]	very serious[4]	very low	Important

[1] it was unclear if treatment groups were comparable at baseline in all studies, particularly for concomitant drug use; concomitant drugs permitted varies across the studies in the network; insufficient follow-up in all studies

[2] I^2 was 0% for pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons with only one trial); no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there is only one head-to-head trial; all but one 'link' in network includes only 1 trial; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] **placebo-controlled comparisons:**

cannabis sativa extract (n=125): Nurmikko et al. (2007); concomitant drugs permitted

pregabalin (n=528): Lesser et al. (2004); Stacey et al. (2008); concomitant drugs permitted in one except gabapentin, oxycodone, local or topical anaesthetic, but SSRIs only in another studies

tramadol (n=90): Sindrup et al (1999); unclear if concomitant drugs permitted

Head-to-head comparisons:

amitriptyline vs pregabalin (n=102): Bansal et al. (2009); concomitant drugs not permitted

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

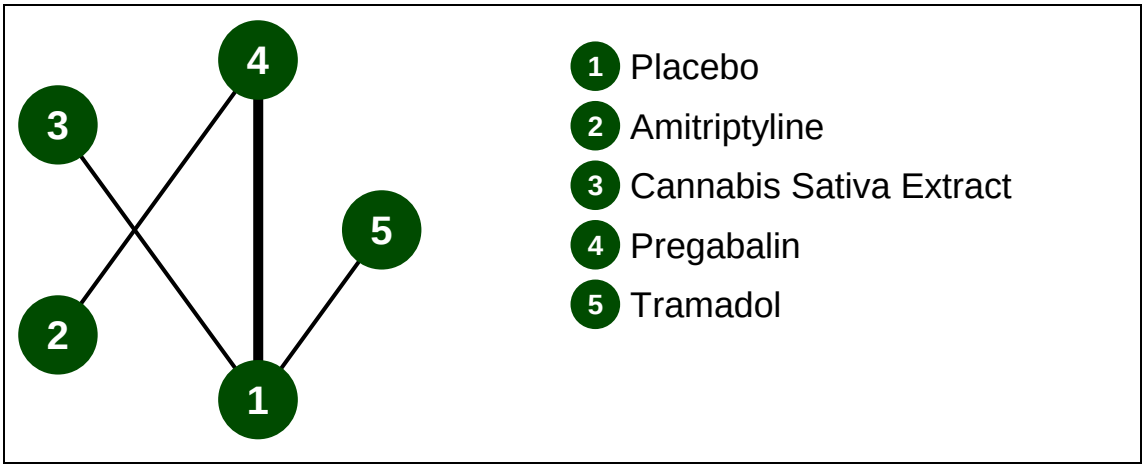

Figure 27 50% pain relief - 4 weeks - evidence network

Table 44 50% pain relief - 4 weeks - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Pregabalin
Amitriptyline	-			
Cannabis Sativa Extract	1 RCT[3] total n=125	-		
Pregabalin	2 RCTs[2,5] total n=528	1 RCT[1] total n=102	-	
Tramadol	1 RCT[4] total n=90	-	-	-

(1) Bansal et al. (2009); (2) Lesser et al. (2004); (3) Nurmikko et al. (2007); (4) Sindrup et al. (1999); (5) Stacey et al. (2008); (6) van Seventer

Table 45 50% pain relief - 4 weeks - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Pregabalin	Tramadol
Placebo		-	2.96 (0.99, 8.90)	3.67 (2.39, 5.63)	4.53 (1.17, 17.55)
Amitriptyline	2.20 (0.47, 10.11)		-	1.68 (0.74, 3.82)	-
Cannabis Sativa Extract	3.06 (0.69, 15.47)	1.40 (0.17, 12.81)		-	-
Pregabalin	3.75 (1.75, 8.09)	1.71 (0.46, 6.49)	1.22 (0.21, 6.50)		-
Tramadol	4.95 (0.92, 35.62)	2.27 (0.23, 26.20)	1.61 (0.16, 18.80)	1.31 (0.21, 10.80)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

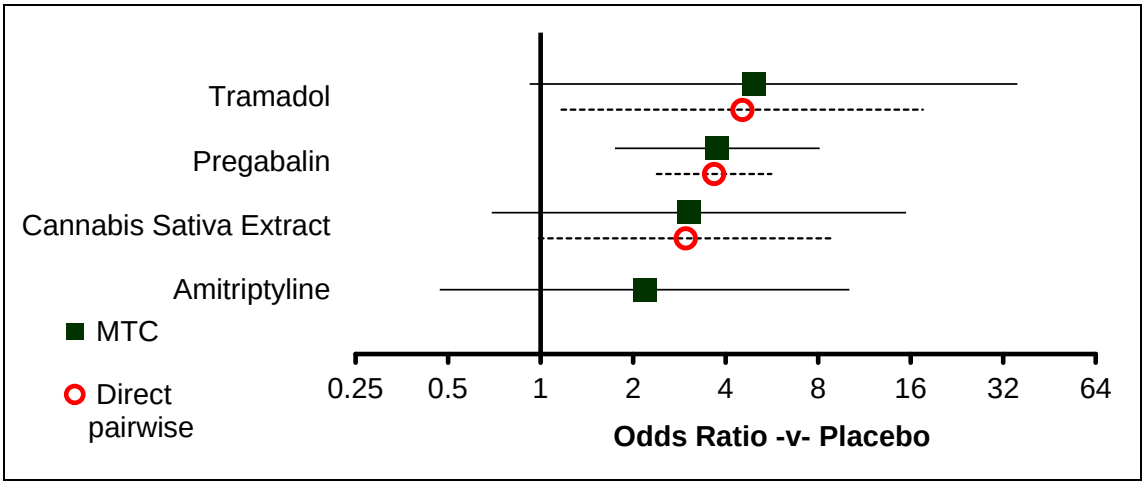

Figure 28 50% pain relief - 4 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 46 50% pain relief - 4 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (4, 5)
Amitriptyline	0.070	4 (1, 5)
Cannabis Sativa Extract	0.210	3 (1, 5)
Pregabalin	0.204	2 (1, 4)
Tramadol	0.516	1 (1, 4)

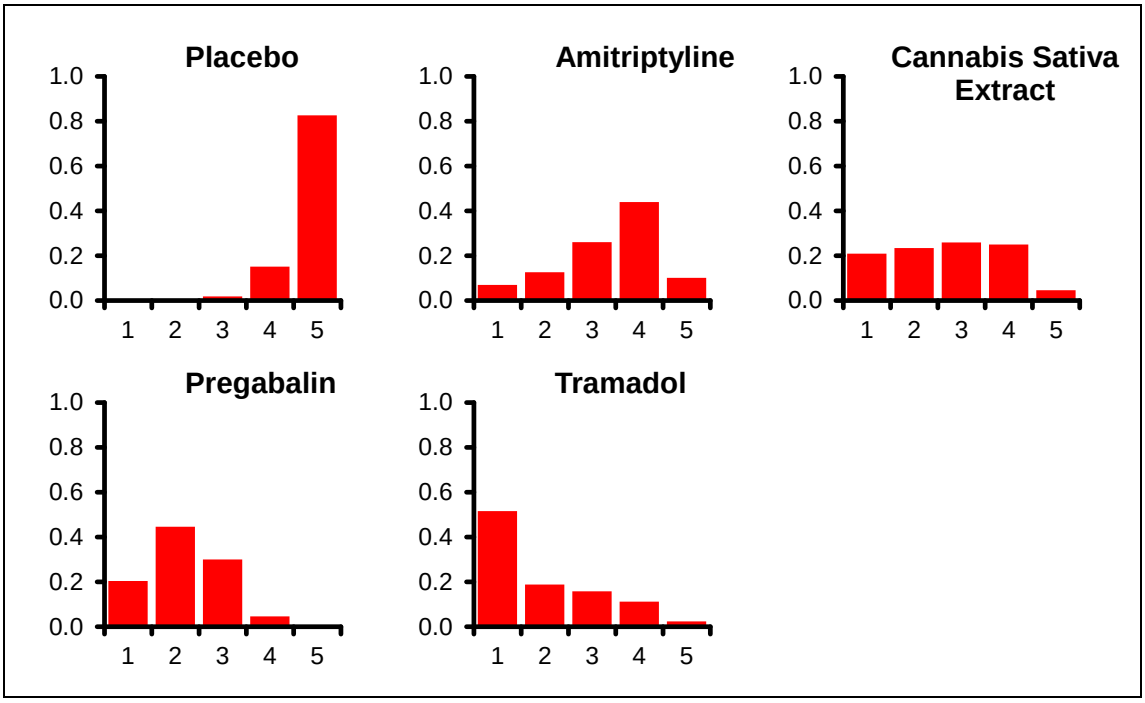

Figure 29 50% pain relief - 4 weeks - rank probability histograms

Table 47 50% pain relief - 4 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
10.9 (compared to 12 data-points)	62.456	52.121	10.335	72.791	0.000 (95%CrI: 0.000, 2.810)

Table 48 50% pain relief - 4 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 5b: Network meta-analysis for at least 50% pain relief (56 days +/-7 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 50% pain relief on any scale (follow up 56 days)	8 RCTs[a] n=2362	serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] groups were not comparable at baseline in one and it was unclear if treatment groups were comparable at baseline in 3; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons with only one trial); no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there is only one head-to-head trial; most 'links' in network include only 1 trial; wide confidence intervals for the effect estimates of most interventions compared to placebo (particularly for lamotrigine and nortriptyline which is likely due to small studies) and for overall rankings within the network

[a] **placebo-controlled comparisons:**

capsaicin patch (n=1127): Irving et al (2012); concomitant drugs except topical medications permitted

gabapentin (n=334): Rice & Maton (2001); concomitant drugs except anti-convulsants, opioids, and capsaicin permitted

lamotrigine (n=34): Luria et al. (2000); concomitant drugs not permitted

pregabalin (n=797): Dworkin et al. (2003); Moon et al. (2010); Rosenstock et al. (2004); Sabatowski et al. (2004); only SSRIs permitted in one but concomitant drugs permitted in the others with the exception of anti-convulsants two

Head-to-head comparisons:

nortriptyline vs gabapentin (n=70): Chandra et al. (2006); most concomitant drugs not permitted but unclear about anti-depressants

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

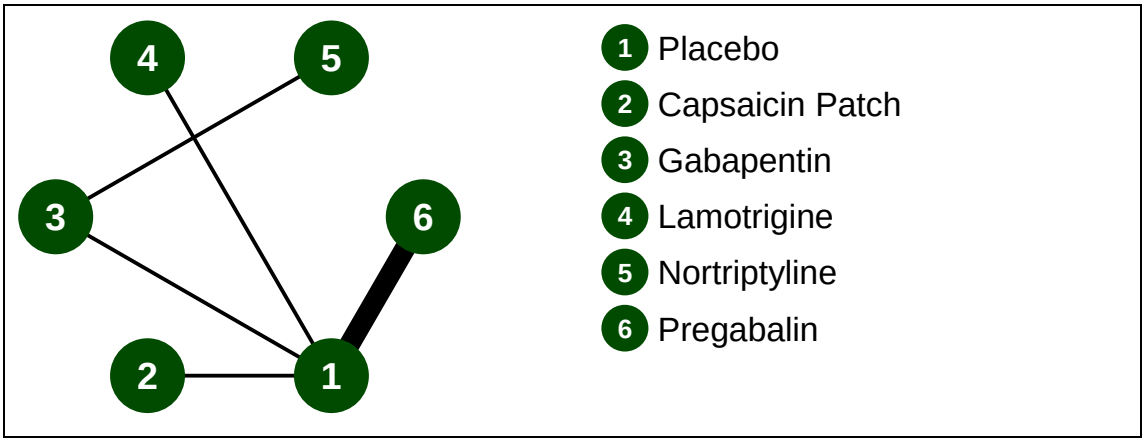

Figure 30 50% pain relief - 8 weeks - evidence network

Table 49 50% pain relief - 8 weeks - trials included in analysis

	Placebo	Capsaicin Patch	Gabapentin	Lamotrigine	Nortriptyline
Capsaicin Patch	1 RCT[3] total n=1127				
Gabapentin	1 RCT[6] total n=334	-			
Lamotrigine	1 RCT[4] total n=34	-	-		
Nortriptyline	-	-	1 RCT[1] total n=70	-	
Pregabalin	4 RCTs[2,5,7,8] total n=797	-	-	-	-

(1) Chandra et al. (2006); (2) Dworkin et al. (2003); (3) Irving et al. (2012); (4) Luria et al. (2000); (5) Moon et al. (2010); (6) Rice & Maton (2001); (7) Rosenstock et al. (2004); (8) Sabatowski et al. (2004)

Table 50 50% pain relief - 8 weeks - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Gabapentin	Lamotrigine	Nortriptyline	Pregabalin
Placebo		1.58 (1.20, 2.08)	2.71 (1.41, 5.20)	4.33 (0.91, 20.60)	-	3.13 (2.14, 4.56)
Capsaicin Patch	1.59 (0.82, 3.03)		-	-	-	-
Gabapentin	2.77 (1.25, 6.68)	1.75 (0.63, 5.15)		-	1.29 (0.42, 3.95)	-
Lamotrigine	4.84 (0.97, 30.66)	3.04 (0.54, 21.53)	1.74 (0.27, 13.36)		-	-
Nortriptyline	3.60 (0.79, 16.82)	2.28 (0.45, 11.92)	1.29 (0.36, 4.69)	0.75 (0.07, 6.93)		-
Pregabalin	3.20 (2.02, 5.15)	2.02 (0.92, 4.48)	1.15 (0.43, 2.96)	0.66 (0.10, 3.59)	0.88 (0.18, 4.35)	

Values given are odds ratios.

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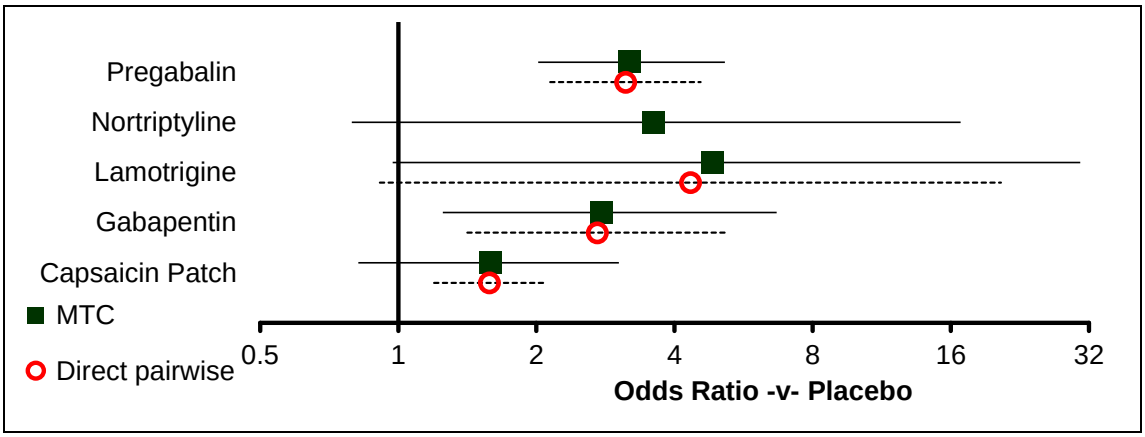

Figure 31 50% pain relief - 8 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 51 50% pain relief - 8 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	6 (5, 6)
Capsaicin Patch	0.005	5 (3, 6)
Gabapentin	0.053	3 (1, 5)
Lamotrigine	0.513	1 (1, 6)
Nortriptyline	0.304	2 (1, 6)
Pregabalin	0.124	3 (1, 4)

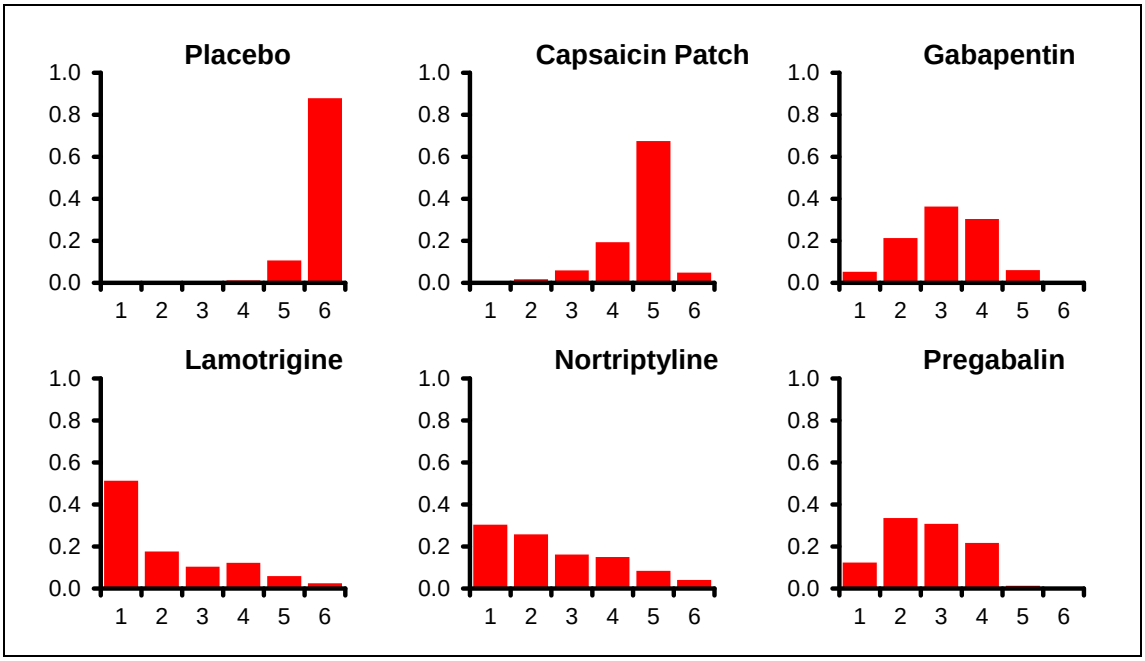

Figure 32 50% pain relief - 8 weeks - rank probability histograms

Table 52 50% pain relief - 8 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
15.26 (compared to 18 data-points)	96.181	81.962	14.219	110.401	0.000 (95%CrI: 0.000, 0.596)

Table 53 50% pain relief - 8 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
- McCleane (1999) was removed from the synthesis because both arms were zero.
- Model convergence: autocorrelation relatively poor for lamotrigine because of low event rates.

Summary GRADE profile 5c: Network meta-analysis for at least 50% pain relief (84 days +/-14 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 50% pain relief on any scale (follow up 84 days)	15 RCTs[a] n=5729	serious[1]	serious[2]	not serious[3]	serious[4]	Very low	Important

[1] group were not comparable at baseline in 2 studies and it was unclear if they were comparable in 7; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 74%, 53%, and 30% for pregabalin, duloxetine, and capsaicin patch vs placebo, respectively which may indicate considerable, substantial, and moderate heterogeneity, respectively; no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there are no head-to-head trials; wide confidence intervals for the overall ranking within the network

[a] capsaicin patch (n=1997): Irving et al. (2011), Irving et al. (2012), Webster et al. (2010), Webster et al. (2010); concomitant drugs except topical medications permitted

duloxetine (n= 1692): Gao et al. (2010), Goldstein et al. (2005), Raskin et al. (2005); Wernicke et al. (2006), Yasuda et al. (2011); concomitant drugs not permitted in four, but one of these is unclear about anti-depressant usage; unclear about concomitants in the other (the study only said that MAO inhibitors were permitted)

pregabalin (n=1717): Freynhagen et al. (2005), Satoh et al. (2011), Tolle et al. (2008), Simpson et al. (2010), van Seventer et al. (2006); unclear about concomitant drugs permitted in one but permitted in the remaining – two with the exception of anti-convulsants, two with the exception of gabapentin and SSRIs only in the two

topiramate (n=323): Raskin et al. (2004); SSRIs only

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

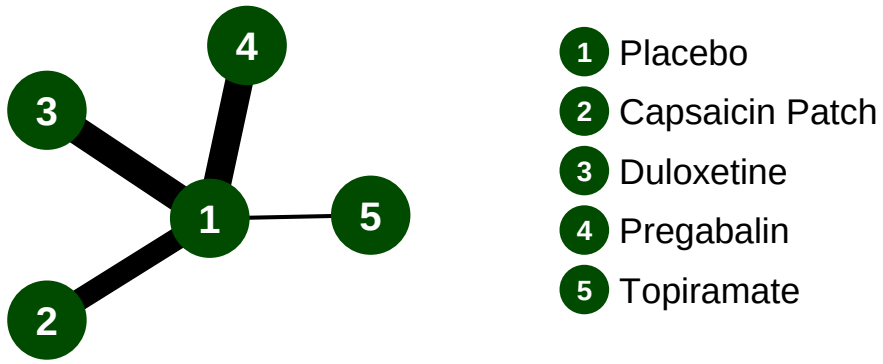

Figure 33 50% pain relief - 12 weeks - evidence network

Table 54 50% pain relief - 12 weeks - trials included in analysis

	Placebo	Capsaicin Patch	Duloxetine	Pregabalin
Capsaicin Patch	4 RCTs[4,5,12,13] total n=1997			
Duloxetine	5 RCTs[2,3,7,14,15] total n=1692	-		
Pregabalin	5 RCTs[1,8,9,10,11] total n=1717	-	-	
Topiramate	1 RCT[6] total n=323	-	-	-

(1) Freynhagen et al. (2005); (2) Gao et al. (2010); (3) Goldstein et al. (2005); (4) Irving et al. (2011); (5) Irving et al. (2012); (6) Raskin et al. (2004); (7) Raskin et al. (2005); (8) Satoh et al. (2011); (9) Simpson et al. (2010); (10) Tolle et al. (2008); (11) van Seventer et al. (2006); (12) Webster et al. (2010); (13) Webster et al. (2010); (14) Wernicke et al. (2006); (15) Yasuda et al. (2011)

Table 55 50% pain relief - 12 weeks - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Duloxetine	Pregabalin	Topiramate
Placebo		1.60 (1.29, 1.98)	2.27 (1.65, 3.13)	1.80 (1.05, 3.09)	1.98 (1.15, 3.39)
Capsaicin Patch	1.66 (1.15, 2.45)		-	-	-
Duloxetine	2.33 (1.71, 3.20)	1.41 (0.85, 2.28)		-	-
Pregabalin	1.75 (1.26, 2.54)	1.05 (0.64, 1.79)	0.75 (0.48, 1.23)		-
Topiramate	1.99 (0.91, 4.44)	1.20 (0.50, 2.90)	0.85 (0.37, 2.03)	1.15 (0.48, 2.67)	

Values given are odds ratios.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

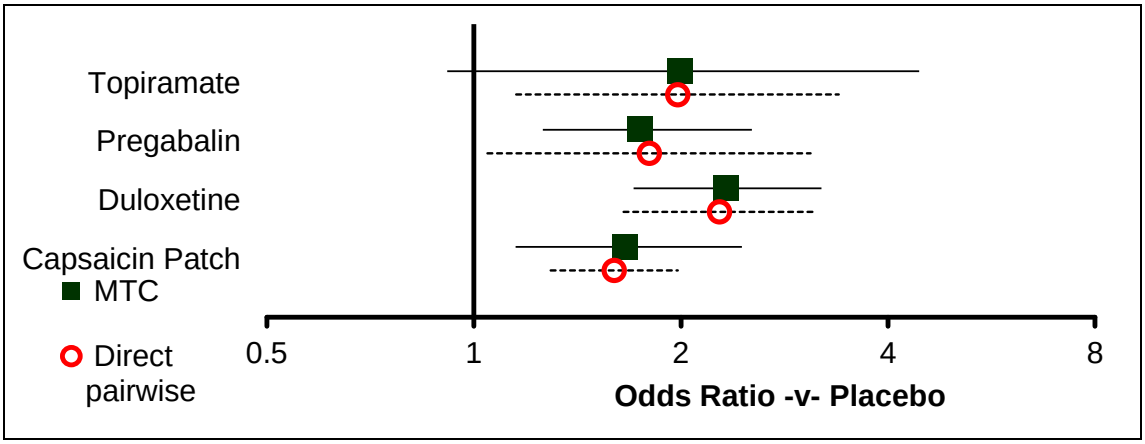

Figure 34 50% pain relief - 12 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 56 50% pain relief - 12 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (4, 5)
Capsaicin Patch	0.044	3 (1, 4)
Duloxetine	0.564	1 (1, 3)
Pregabalin	0.059	3 (1, 4)
Topiramate	0.333	2 (1, 5)

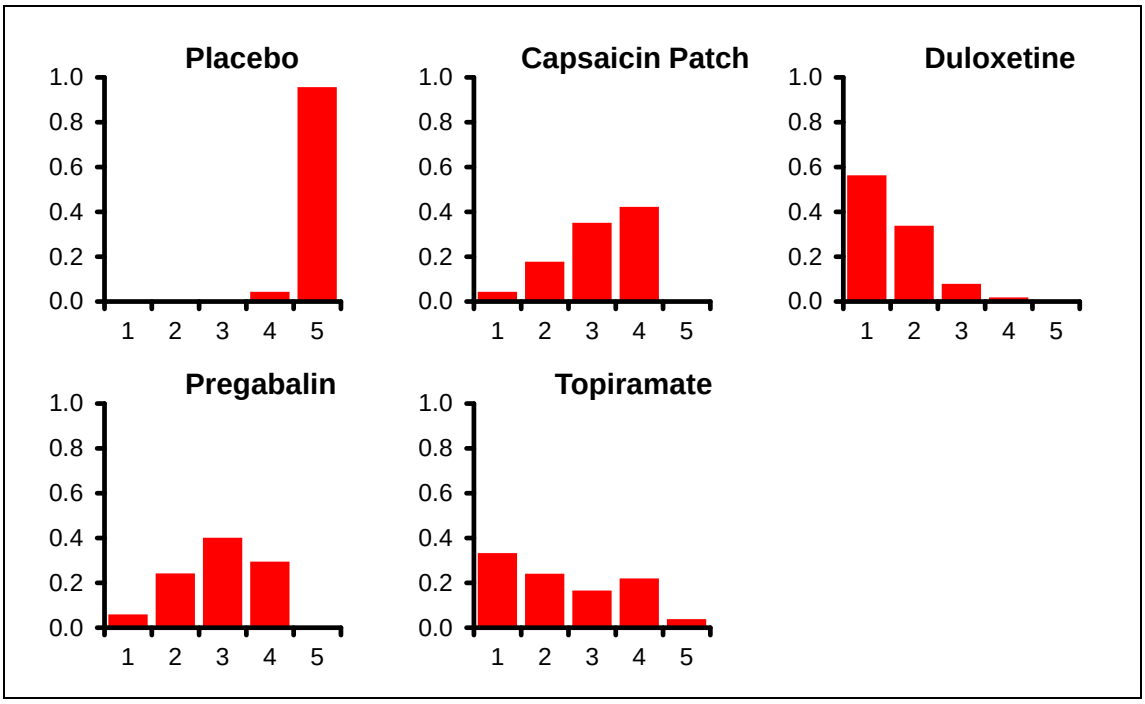

Figure 35 50% pain relief - 12 weeks - rank probability histograms

Table 57 50% pain relief - 12 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
45.91 (compared to 43 data-points)	259.343	229.073	30.269	289.612	0.000 (95%CrI: 0.002, 0.238)

Table 58 50% pain relief - 12 weeks - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 6a: Network meta-analysis for pain relief on normalised 10-point scale (28 +/- 7 days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Pain relief on normalised 10-point scale (follow up 28 days)	22 RCTs[a] n=3152	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] over half of the studies were unclear about allocation concealment; groups were not comparable at baseline in 2 studies and it was unclear if they were comparable in 17 others; over half of the studies had inadequate follow-up; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 83, 74, 76 and 29% for amitriptyline, gabapentin, pregabalin, tramadol vs placebo, respectively which may indicate substantial heterogeneity in the first 3 comparisons but might not be important in the last; there appears to be consistency between direct and indirect comparisons

[3] all aspects of PICO conform to review protocol

[4] the majority of links in the network are connected by only one study; wide confidence intervals in the overall rankings in the network

[a] **Placebo-controlled trials**

amitriptyline (n=88): Kalso et al. (1995), Vrethem et al. (1997) (both with and without diabetes); concomitant drugs allowed in one and unclear in one

cannabis sativa extract (n=125): Nurmikko et al. (2007); concomitant drugs permitted

escitalopram (n=82): Otto et al. (2008); concomitant drugs not permitted

gabapentin (n=620): Backonja et al. (1998), Gordh et al. (2008), Mishra et al. (2012), Rao et al. (2007), Rice & Maton (2001); concomitant drug not permitted in one and permitted in four (only tricyclics in one, SSRIs in another, most excluded from one but permitted if investigator considered necessary)

imipramine (n=64): Sindrup et al. (2003); unclear if concomitant drugs permitted

lamotrigine (n=125): Rao et al. (2008); concomitant drugs not permitted

lidocaine (n=28): Cheville et al. (2009); concomitant drugs not permitted

oxcarbazepine (n=146): Dogra et al. (2005); SSRIs only

oxycodone (n=159): Gimbel et al. (2003); unclear if concomitant drugs permitted

pregabalin (n=625): Guan et al. (2011), Lesser et al. (2004); SSRIs only

valproate (n=91): Kochar et al. (2002), Kochar et al. (2004); unclear if concomitant drugs permitted

topiramate (n=317): Raskin et al. (2004); SSRIs only

tramadol (n=176): Boureau et al. (2003), Sindrup et al. (1999); unclear if concomitant drugs permitted in one and not permitted in the other

venlafaxine (n=64): Sindrup et al. (2003); unclear if concomitant drugs permitted

Head-to-head trials

gabapentin+nortriptyline vs gabapentin (n=96): Gilron et al. (2012); concomitant opioids permitted in stable doses but tricyclics, gabapentin, pregabalin excluded

gabapentin+oxycodone vs gabapentin (n=328): Hanna et al. (2008); concomitant drugs permitted

nortriptyline vs gabapentin (n=96): Gilron et al. (2012); concomitant opioids permitted in stable doses but tricyclics, gabapentin, pregabalin excluded

nortriptyline vs gabapentin+nortriptyline (n=100): Gilron et al. (2012); concomitant opioids permitted in stable doses but tricyclics, gabapentin, pregabalin excluded

venlafaxine vs imipramine (n=64): Sindrup et al. (2003); unclear if concomitant drugs permitted

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

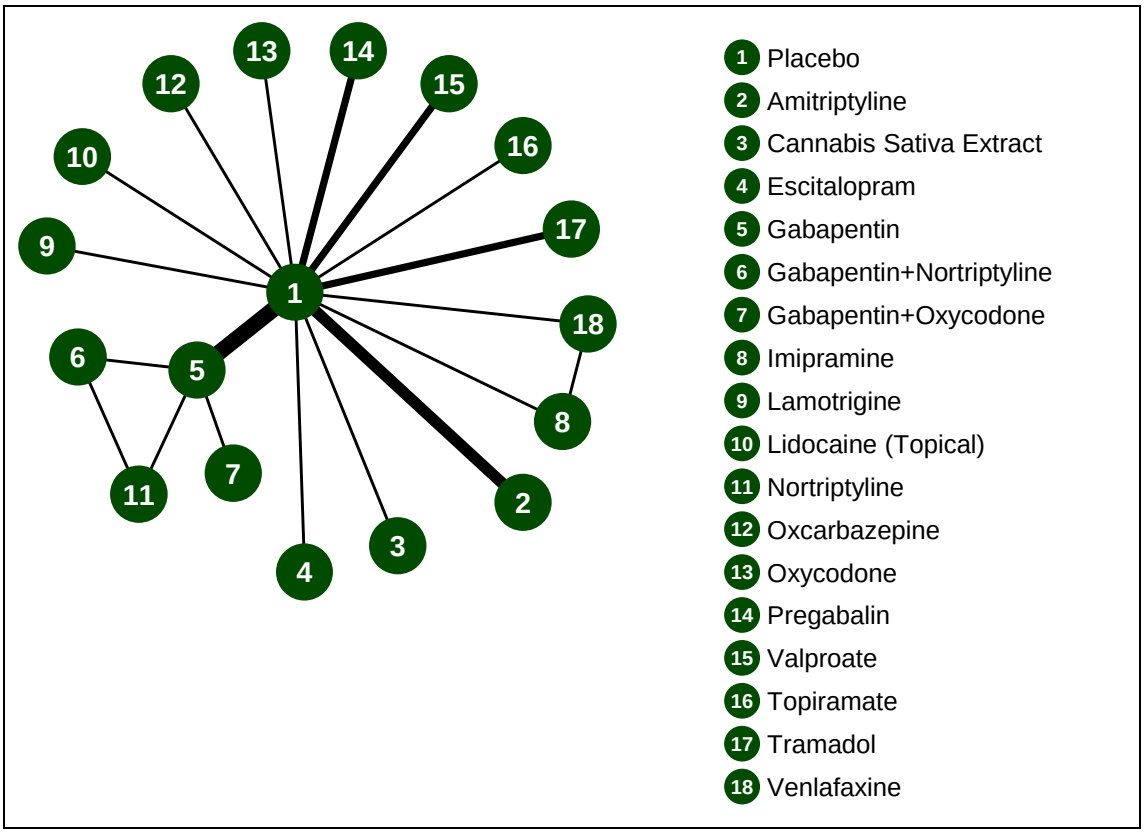

Figure 36 pain (continuous) - 4 weeks - evidence network

Table 59 pain (continuous) - 4 weeks - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Lidocaine (Topical)	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol
Amitriptyline	3 RCTs[10,22,22] total n=88																
Cannabis Sativa Extract	1 RCT[14] total n=125	-															
Escitalopram	1 RCT[15] total n=82	-	-														
Gabapentin	4 RCTs[1,7,16,19] total n=620	-	-	-													
Gabapentin +Nortriptyline	-	-	-	-	1 RCT[5] total n=96												
Gabapentin +Oxycodone	-	-	-	-	1 RCT[9] total n=328	-											
Imipramine	1 RCT[21] total n=64	-	-	-	-	-	-										
Lamotrigine	1 RCT[17] total n=125	-	-	-	-	-	-	-									
Lidocaine (Topical)	1 RCT[3] total n=28	-	-	-	-	-	-	-	-								
Nortriptyline	-	-	-	-	1 RCT[5] total n=96	1 RCT[5] total n=100	-	-	-	-							
Oxcarbazepine	1 RCT[4] total n=146	-	-	-	-	-	-	-	-	-	-						

	Placebo	Amitriptyline	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Lidocaine (Topical)	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol
Oxycodone	1 RCT[6] total n=159	-	-	-	-	-	-	-	-	-	-	-					
Pregabalin	2 RCTs[8,13] total n=625	-	-	-	-	-	-	-	-	-	-	-	-				
Valproate	2 RCTs[11,12] total n=91	-	-	-	-	-	-	-	-	-	-	-	-	-			
Topiramate	1 RCT[18] total n=317	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Tramadol	2 RCTs[2,20] total n=176	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Venlafaxine	1 RCT[21] total n=64	-	-	-	-	-	-	1 RCT[21] total n=64	-	-	-	-	-	-	-	-	-

(1) Backonja et al. (1998); (2) Boureau et al. (2003); (3) Cheville et al. (2009); (4) Dogra et al. (2005); (5) Gilron et al. (2012); (6) Gimbel et al. (2003); (7) Gordh et al. (2008); (8) Guan et al. (2011); (9) Hanna et al. (2008); (10) Kalso et al. (1995); (11) Kochar et al. (2002); (12) Kochar et al. (2004); (13) Lesser et al. (2004); (14) Nurmikko et al. (2007); (15) Otto et al. (2008); (16) Rao et al. (2007); (17) Rao et al. (2008); (18) Raskin et al. (2004); (19) Rice & Maton (2001); (20) Sindrup et al. (1999); (21) Sindrup et al. (2003); (22) Vrethem et al. (1997)

Table 60 pain (continuous) - 4 weeks - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Lidocaine (Topical)	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Placebo		-1.51 (-2.64, -0.38)	-1.10 (-1.72, -0.48)	-1.00 (-1.59, -0.41)	-0.70 (-1.17, -0.22)	-	-	-1.30 (-2.06, -0.54)	0.35 (-0.34, 1.04)	0.10 (-0.81, 1.01)	-	-0.72 (-1.20, -0.24)	-0.70 (-1.16, -0.24)	-0.51 (-0.93, -0.09)	-1.34 (-2.01, -0.66)	-0.18 (-0.51, 0.16)	-1.18 (-1.83, -0.53)	-1.00 (-1.76, -0.24)
Amitriptyline	-1.53 (-2.37, -0.67)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cannabis Sativa Extract	-1.10 (-2.47, 0.27)	0.42 (-1.20, 2.03)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	-1.01 (-2.37, 0.36)	0.52 (-1.10, 2.13)	0.10 (-1.84, 2.04)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	-0.73 (-1.35, -0.06)	0.80 (-0.25, 1.87)	0.38 (-1.13, 1.92)	0.28 (-1.21, 1.82)		-0.90 (-1.44, -0.36)	-0.80 (-1.22, -0.38)	-	-	-	-0.30 (-0.84, 0.24)	-	-	-	-	-	-	-
Gabapentin +Nortriptyline	-1.62 (-3.12, -0.11)	-0.10 (-1.82, 1.64)	-0.52 (-2.54, 1.53)	-0.62 (-2.64, 1.43)	-0.90 (-2.25, 0.45)		-	-	-	-	0.60 (0.17, 1.03)	-	-	-	-	-	-	-
Gabapentin +Oxycodone	-1.53 (-2.97, -0.05)	0.00 (-1.67, 1.70)	-0.43 (-2.41, 1.61)	-0.53 (-2.48, 1.49)	-0.80 (-2.11, 0.51)	0.10 (-1.80, 1.99)		-	-	-	-	-	-	-	-	-	-	-
Imipramine	-1.30 (-2.74, 0.14)	0.23 (-1.45, 1.89)	-0.20 (-2.19, 1.80)	-0.29 (-2.28, 1.69)	-0.57 (-2.17, 0.98)	0.33 (-1.78, 2.39)	0.23 (-1.85, 2.26)		-	-	-	-	-	-	-	-	-	0.30 (-0.56, 1.16)
Lamotrigine	0.35 (-1.08, 1.76)	1.88 (0.21, 3.52)	1.46 (-0.53, 3.41)	1.36 (-0.62, 3.32)	1.08 (-0.51, 2.61)	1.98 (-0.11, 4.01)	1.88 (-0.18, 3.89)	1.65 (-0.39, 3.67)		-	-	-	-	-	-	-	-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Lidocaine (Topical)	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Lidocaine (Topical)	0.10 (-1.42, 1.62)	1.63 (-0.12, 3.36)	1.20 (-0.85, 3.26)	1.10 (-0.93, 3.13)	0.82 (-0.85, 2.46)	1.72 (-0.43, 3.84)	1.62 (-0.49, 3.72)	1.40 (-0.70, 3.50)	-0.25 (-2.33, 1.84)		-	-	-	-	-	-	-	-
Nortriptyline	-1.02 (-2.51, 0.50)	0.51 (-1.22, 2.24)	0.08 (-1.93, 2.14)	-0.02 (-2.03, 2.03)	-0.29 (-1.66, 1.05)	0.60 (-0.71, 1.92)	0.51 (-1.38, 2.39)	0.27 (-1.79, 2.37)	-1.37 (-3.41, 0.71)	-1.12 (-3.24, 1.04)		-	-	-	-	-	-	-
Oxcarbazepine	-0.72 (-2.04, 0.61)	0.81 (-0.77, 2.38)	0.39 (-1.52, 2.29)	0.28 (-1.61, 2.19)	0.01 (-1.49, 1.46)	0.91 (-1.11, 2.90)	0.81 (-1.18, 2.76)	0.58 (-1.37, 2.55)	-1.07 (-3.01, 0.89)	-0.81 (-2.83, 1.21)	0.30 (-1.72, 2.30)		-	-	-	-	-	-
Oxycodone	-0.70 (-2.02, 0.62)	0.82 (-0.74, 2.39)	0.40 (-1.51, 2.31)	0.30 (-1.60, 2.20)	0.02 (-1.47, 1.47)	0.92 (-1.09, 2.91)	0.82 (-1.17, 2.78)	0.59 (-1.36, 2.55)	-1.06 (-2.98, 0.89)	-0.80 (-2.81, 1.22)	0.32 (-1.69, 2.30)	0.02 (-1.86, 1.89)		-	-	-	-	-
Pregabalin	-0.55 (-1.37, 0.26)	0.98 (-0.21, 2.14)	0.55 (-1.05, 2.15)	0.46 (-1.14, 2.04)	0.18 (-0.89, 1.19)	1.07 (-0.64, 2.76)	0.98 (-0.72, 2.62)	0.75 (-0.90, 2.40)	-0.90 (-2.54, 0.74)	-0.65 (-2.38, 1.08)	0.47 (-1.25, 2.16)	0.17 (-1.39, 1.74)	0.15 (-1.40, 1.70)		-	-	-	-
Valproate	-1.42 (-2.76, -0.15)	0.11 (-1.48, 1.61)	-0.32 (-2.25, 1.53)	-0.41 (-2.32, 1.42)	-0.69 (-2.20, 0.70)	0.21 (-1.84, 2.14)	0.11 (-1.90, 2.00)	-0.12 (-2.10, 1.78)	-1.77 (-3.71, 0.12)	-1.52 (-3.54, 0.44)	-0.40 (-2.43, 1.53)	-0.70 (-2.60, 1.10)	-0.71 (-2.61, 1.10)	-0.87 (-2.44, 0.62)		-	-	-
Topiramate	-0.18 (-1.48, 1.12)	1.35 (-0.21, 2.88)	0.92 (-0.97, 2.81)	0.82 (-1.06, 2.70)	0.55 (-0.92, 1.97)	1.45 (-0.55, 3.40)	1.35 (-0.62, 3.27)	1.12 (-0.82, 3.06)	-0.53 (-2.44, 1.39)	-0.28 (-2.27, 1.72)	0.84 (-1.16, 2.80)	0.54 (-1.32, 2.39)	0.53 (-1.33, 2.37)	0.37 (-1.16, 1.90)	1.24 (-0.54, 3.12)		-	-
Tramadol	-1.24 (-2.31, -0.24)	0.28 (-1.10, 1.59)	-0.14 (-1.89, 1.55)	-0.24 (-1.98, 1.43)	-0.51 (-1.80, 0.66)	0.38 (-1.49, 2.16)	0.29 (-1.56, 2.01)	0.05 (-1.75, 1.80)	-1.60 (-3.37, 0.14)	-1.35 (-3.21, 0.49)	-0.22 (-2.10, 1.55)	-0.52 (-2.25, 1.13)	-0.54 (-2.25, 1.10)	-0.69 (-2.04, 0.59)	0.17 (-1.47, 1.83)	-1.06 (-2.76, 0.56)		-
Venlafaxine	-1.00 (-2.44, 0.44)	0.53 (-1.14, 2.19)	0.10 (-1.89, 2.09)	0.00 (-1.99, 1.99)	-0.28 (-1.87, 1.28)	0.62 (-1.48, 2.69)	0.53 (-1.55, 2.56)	0.30 (-1.20, 1.79)	-1.35 (-3.37, 0.69)	-1.10 (-3.19, 1.00)	0.02 (-2.07, 2.09)	-0.28 (-2.25, 1.68)	-0.30 (-2.26, 1.66)	-0.45 (-2.10, 1.20)	0.42 (-1.48, 2.40)	-0.82 (-2.76, 1.12)	0.24 (-1.49, 2.05)	

Values given are mean differences.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus

	Placebo	Amitriptyline	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Lidocaine (Topical)	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.																		

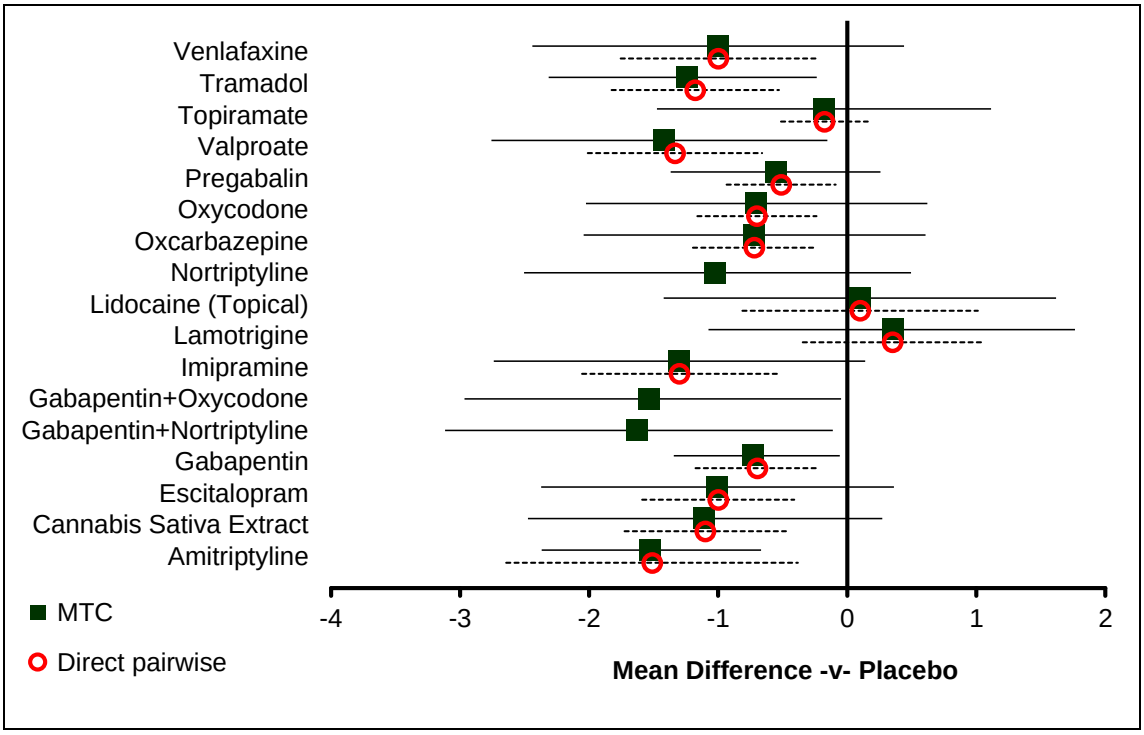

Figure 37 pain (continuous) - 4 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 61 pain (continuous) - 4 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	16 (13, 18)
Amitriptyline	0.101	4 (1, 11)
Cannabis Sativa Extract	0.058	7 (1, 17)
Escitalopram	0.043	8 (1, 17)
Gabapentin	0.000	11 (6, 15)
Gabapentin+Nortriptyline	0.228	4 (1, 14)
Gabapentin+Oxycodone	0.178	4 (1, 15)
Imipramine	0.107	6 (1, 16)
Lamotrigine	0.001	17 (8, 18)
Lidocaine (Topical)	0.002	16 (5, 18)
Nortriptyline	0.026	8 (1, 17)
Oxcarbazepine	0.016	11 (2, 18)
Oxycodone	0.015	11 (2, 18)
Pregabalin	0.001	12 (5, 17)
Valproate	0.132	5 (1, 15)
Topiramate	0.003	15 (5, 18)
Tramadol	0.048	6 (1, 14)
Venlafaxine	0.041	8 (1, 17)

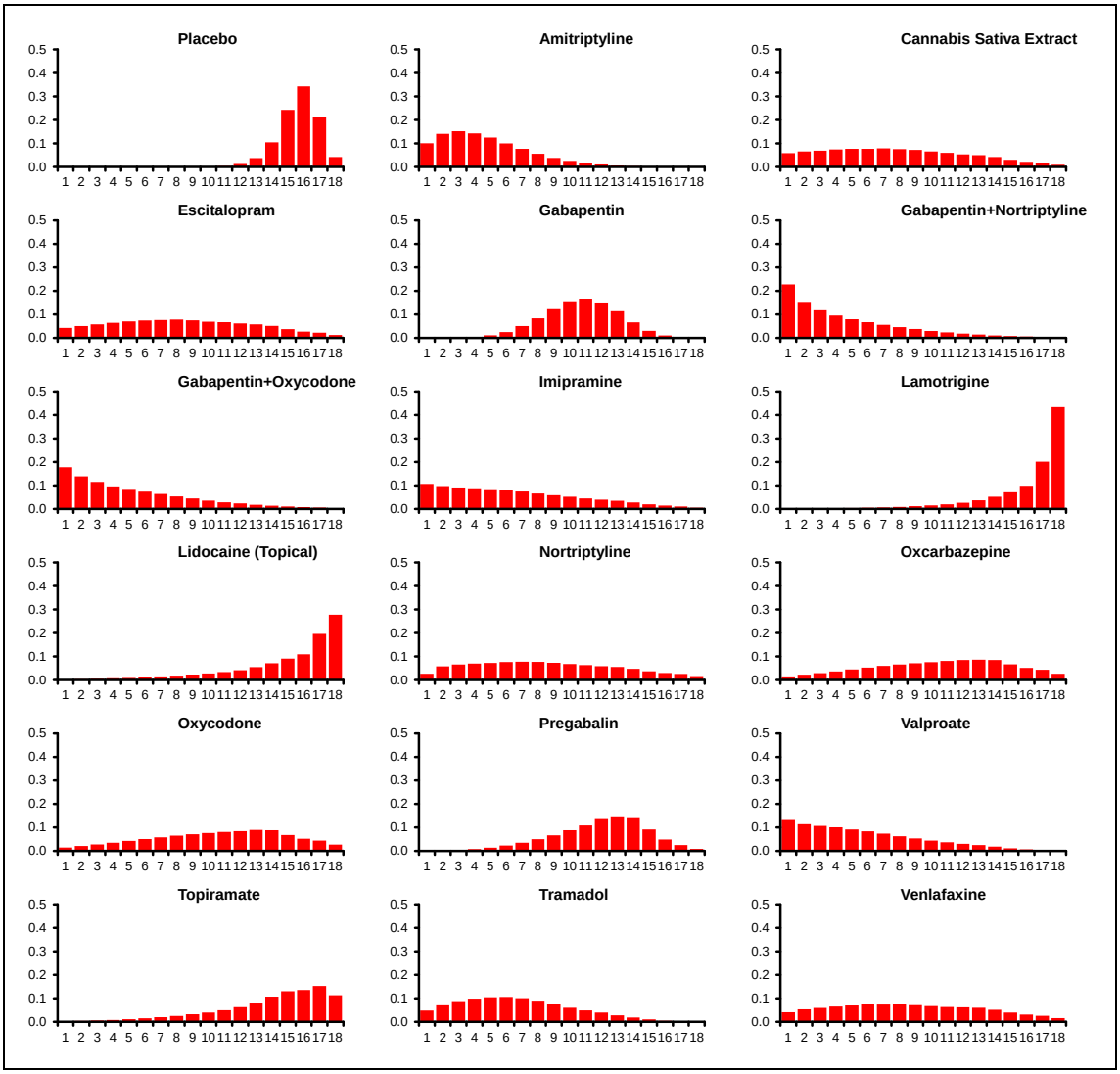

Figure 38 pain (continuous) - 4 weeks - rank probability histograms

Table 62 pain (continuous) - 4 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
51.72 (compared to 51 data-points)	-12.51	-61.005	48.496	35.986	0.240 (95%CrI: 0.081, 1.138)

Table 63 pain (continuous) - 4 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
- Vrethem (1997) reported this outcome separately in those with and without diabetes – both arms are included here since the study did not report this outcome for both of these groups separately.

Summary GRADE profile 6b: Network meta-analysis for pain relief on normalised 10-point scale (56 +/- 7d)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Pain relief on normalised 10-point scale (follow up 56 days)	17 RCTs[a] n=2750	very serious[1]	serious[2]	not serious[3]	serious[4]	very low	Important

[1] over half of the studies were unclear about allocation concealment; groups were not comparable at baseline in 4 studies and it was unclear if they were comparable in 7 others; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 90 for pregabalin vs placebo which may indicate considerable heterogeneity; I^2 was 41% for gabapentin vs placebo which may indicate moderate inconsistency; there did not appear to be differences between indirect and direct comparisons

[3] all aspects of PICO conform to review protocol

[4] the majority of links in the network are connected by only one study; only one head-to-head trial; wide confidence intervals in the overall ranking in the network

[a] **Placebo-controlled trials**

amitriptyline (n=24): Graff-Radford et al. (2000), unclear if concomitant drugs were permitted in one

gabapentin (n=632): Backonja et al. (1998), Rice & Maton (2001), Rowbotham et al. (1998); concomitant drugs permitted (but only SSRIs in one)

lamotrigine (n=212): Eisenberg et al. (2001), Luria et al. (2000), Rao et al. (2008); concomitant drugs not permitted

oxcarbazepine (n=146): Dogra et al. (2005); SSRIs only

pregabalin (n=749): Guan et al. (2011), Moon et al. (2010), Sabatowski et al. (2004); concomitant drugs permitted (but only SSRIs in one)

valproate (n=40): Kochar et al. (2005); no concomitant drugs permitted

topiramate (n=317): Raskin et al. (2004); SSRIs only

capsaicin cream (n=20): Tandan et al. (1992); concomitant drugs other than topical medications permitted

Head-to-head trials

gabapentin+oxycodone vs gabapentin (n=328): Hanna et al. (2008); concomitant drugs permitted

nortriptyline vs gabapentin (n=70): Chandra et al. (2006); unclear if concomitant drugs permitted

capsaicin cream vs amitriptyline (n=212); Biesbroeck et al. (1995); concomitant drugs permitted except tricyclics and topical medications

amitriptyline vs gabapentin (n=44): Rintala et al. (2007); concomitant drugs were not permitted but oxycodone was used as a rescue medication (this is in the scope of the guideline for the use in NP so considered a concomitant medication)

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

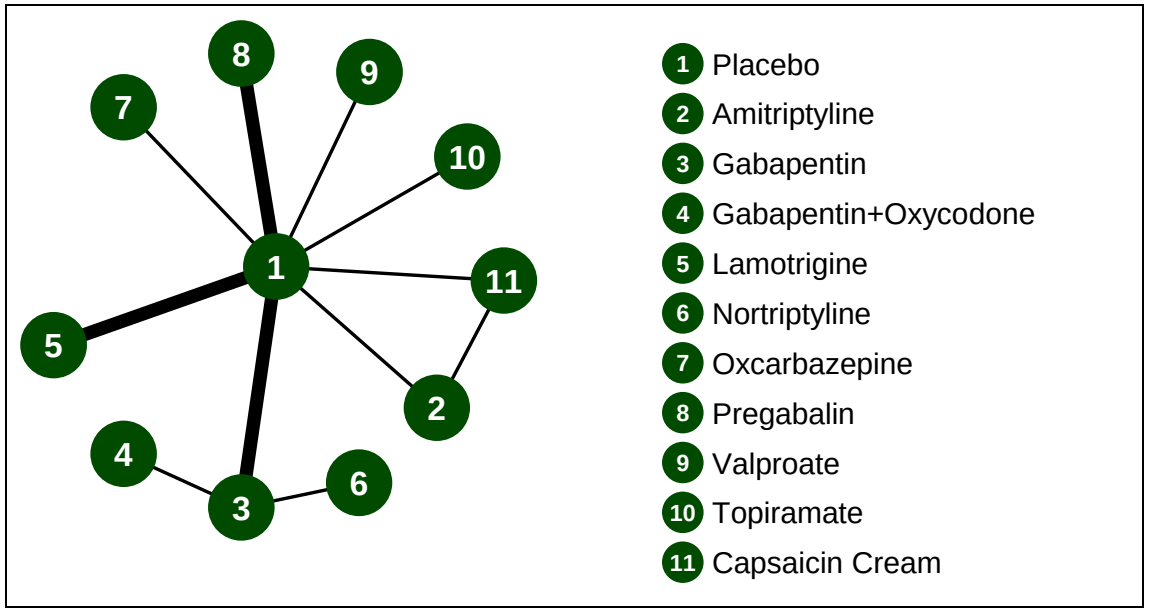

Figure 39 pain (continuous) - 8 weeks - evidence network

Table 64 pain (continuous) - 8 weeks - trials included in analysis

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Oxycodone	Lamotrigine	Nortriptyline	Oxcarbazepine	Pregabalin	Valproate	Topiramate
Amitriptyline	1 RCT[6] total n=24									
Gabapentin	3 RCTs[1,14,15] total n=632	-								
Gabapentin +Oxycodone	-	-	1 RCT[8] total n=328							
Lamotrigine	3 RCTs[5,10,12] total n=212	-	-	-						
Nortriptyline	-	-	1 RCT[3] total n=70	-	-					
Oxcarbazepine	1 RCT[4] total n=146	-	-	-	-	-				
Pregabalin	3 RCTs[7,11,16] total n=749	-	-	-	-	-	-			
Valproate	1 RCT[9] total n=40	-	-	-	-	-	-	-		
Topiramate	1 RCT[13] total n=317	-	-	-	-	-	-	-	-	
Capsaicin Cream	1 RCT[17] total n=20	1 RCT[2] total n=212	-	-	-	-	-	-	-	-

(1) Backonja et al. (1998); (2) Biesbroeck et al. (1995); (3) Chandra et al. (2006); (4) Dogra et al. (2005); (5) Eisenberg et al. (2001); (6) Graff-Radford et al. (2000); (7) Guan et al. (2011); (8) Hanna et al. (2008); (9) Kochar et al. (2005); (10) Luria et al. (2000); (11) Moon et al. (2010); (12) Rao et al. (2008); (13) Raskin et al. (2004); (14) Rice & Maton (2001); (15) Rowbotham et al. (1998); (16) Sabatowski et al. (2004); (17) Tandan et al. (1992)

Table 65 pain (continuous) - 8 weeks - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Oxycodone	Lamotrigine	Nortriptyline	Oxcarbazepine	Pregabalin	Valproate	Topiramate	Capsaicin Cream
Placebo		-2.39 (-3.82, -0.96)	-1.29 (-1.68, -0.89)	-	-0.97 (-1.20, -0.74)	-	-0.92 (-1.60, -0.24)	-0.92 (-1.70, -0.13)	-2.54 (-3.57, -1.51)	-0.66 (-1.14, -0.18)	-1.19 (-2.59, 0.21)
Amitriptyline	-2.00 (-3.37, -0.65)		-	-	-	-	-	-	-	-	0.30 (0.22, 0.38)
Gabapentin	-1.28 (-1.95, -0.59)	0.72 (-0.78, 2.26)		-0.80 (-1.31, -0.29)	-	-0.21 (-1.05, 0.63)	-	-	-	-	-
Gabapentin +Oxycodone	-2.08 (-3.45, -0.66)	-0.08 (-2.00, 1.89)	-0.80 (-2.02, 0.42)		-	-	-	-	-	-	-
Lamotrigine	-0.89 (-1.68, -0.10)	1.10 (-0.44, 2.70)	0.38 (-0.67, 1.42)	1.19 (-0.44, 2.79)		-	-	-	-	-	-
Nortriptyline	-1.48 (-3.01, 0.06)	0.52 (-1.52, 2.59)	-0.20 (-1.59, 1.18)	0.60 (-1.26, 2.43)	-0.58 (-2.32, 1.14)		-	-	-	-	-
Oxcarbazepine	-0.92 (-2.23, 0.38)	1.08 (-0.78, 2.98)	0.35 (-1.12, 1.82)	1.16 (-0.76, 3.04)	-0.03 (-1.55, 1.49)	0.56 (-1.45, 2.57)		-	-	-	-
Pregabalin	-0.98 (-1.65, -0.33)	1.02 (-0.48, 2.53)	0.30 (-0.68, 1.23)	1.10 (-0.48, 2.62)	-0.08 (-1.13, 0.93)	0.50 (-1.19, 2.16)	-0.06 (-1.53, 1.40)		-	-	-
Valproate	-2.54 (-4.04, -1.04)	-0.54 (-2.57, 1.49)	-1.27 (-2.92, 0.37)	-0.46 (-2.53, 1.58)	-1.65 (-3.36, 0.05)	-1.06 (-3.23, 1.09)	-1.62 (-3.61, 0.36)	-1.57 (-3.21, 0.08)		-	-
Topiramate	-0.66 (-1.87, 0.56)	1.34 (-0.46, 3.17)	0.61 (-0.79, 1.99)	1.42 (-0.46, 3.24)	0.23 (-1.22, 1.68)	0.82 (-1.15, 2.77)	0.26 (-1.51, 2.06)	0.31 (-1.05, 1.71)	1.88 (-0.05, 3.82)		-
Capsaicin Cream	-1.58 (-2.93, -0.22)	0.41 (-0.56, 1.48)	-0.31 (-1.81, 1.23)	0.49 (-1.45, 2.45)	-0.68 (-2.26, 0.88)	-0.10 (-2.15, 1.97)	-0.66 (-2.52, 1.23)	-0.60 (-2.09, 0.93)	0.96 (-1.06, 3.02)	-0.92 (-2.72, 0.91)	

Values given are mean differences.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

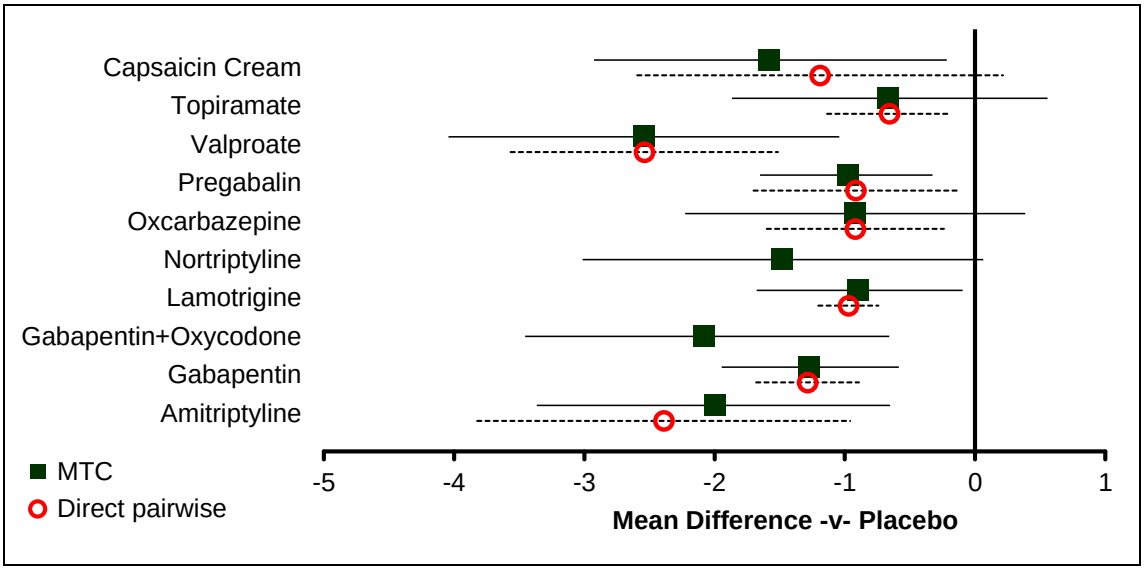

Figure 40 pain (continuous) - 8 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 66 pain (continuous) - 8 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	11 (9, 11)
Amitriptyline	0.170	3 (1, 8)
Gabapentin	0.000	6 (3, 9)
Gabapentin+Oxycodone	0.205	3 (1, 8)
Lamotrigine	0.001	8 (4, 10)
Nortriptyline	0.058	5 (1, 10)
Oxcarbazepine	0.009	8 (2, 11)
Pregabalin	0.001	7 (4, 10)
Valproate	0.526	1 (1, 7)
Topiramate	0.003	9 (3, 11)
Capsaicin Cream	0.028	4 (1, 10)

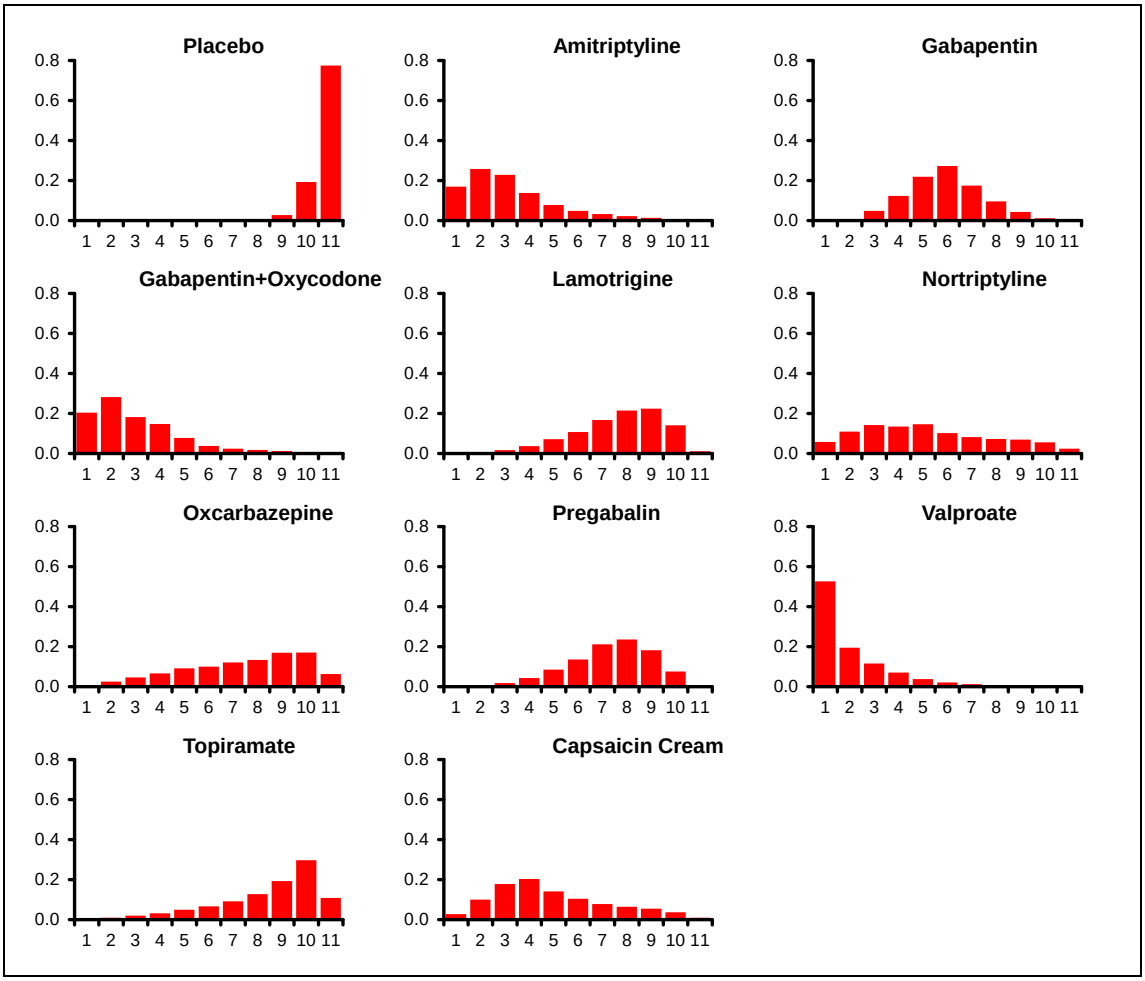

Figure 41 pain (continuous) - 8 weeks - rank probability histograms

Table 67 pain (continuous) - 8 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
35.76 (compared to 36 data-points)	-12.141	-45.695	33.554	21.413	0.170 (95%CrI: 0.051, 1.005)

Table 68 pain (continuous) - 8 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.

Summary GRADE profile 6c: Network meta-analysis for pain relief on normalised 10-point scale (84 +/- 14days)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Pain relief on normalised 10-point scale (follow up 84 days)	13 RCTs[a] n=2833	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] over half of the studies were unclear about allocation concealment; groups were not comparable at baseline in 2 studies and it was unclear if they were comparable in 7 others; baseline severity and concomitant drugs permitted varies across the studies in the network

[2] I^2 was 89% for pregabalin vs placebo which may indicate considerable heterogeneity and 27% for valproate vs placebo which may indicate that any inconsistency might not be important; no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] there are no head-to-head trials; the majority of links in the network are connected by only one study; wide confidence intervals for the overall ranking in the network

[a] cannabis sativa extract (n=30): Selvarajah et al. (2010); concomitant drugs permitted

duloxetine (n=1352): Goldstein et al. (2005), Raskin et al. (2005), Wernicke et al. (2006), Yasuda et al. (2011); concomitant drugs not permitted in 3 and unclear if permitted in the other

lacosamide (n=119): Rauck et al. (2007); only SSRIs permitted but others were permitted during the trial if the investigator considered it necessary

lamotrigine (n=125): Rao et al. (2008); concomitant drugs not permitted

oxcarbazepine (n=146): Dogra et al. (2005); SSRIs only

pregabalin (n=665): Simpson et al. (2010), van Seventer et al. (2006); concomitant drugs permitted in both but anti-convulsants excluded in one

valproate (n=79): Agrawal et al. (2009), Kochar et al. (2004); concomitant drugs not permitted and unclear in the other

topiramate (n=317): Raskin et al. (2004); SSRIs only

[all compared to placebo]

Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitors.

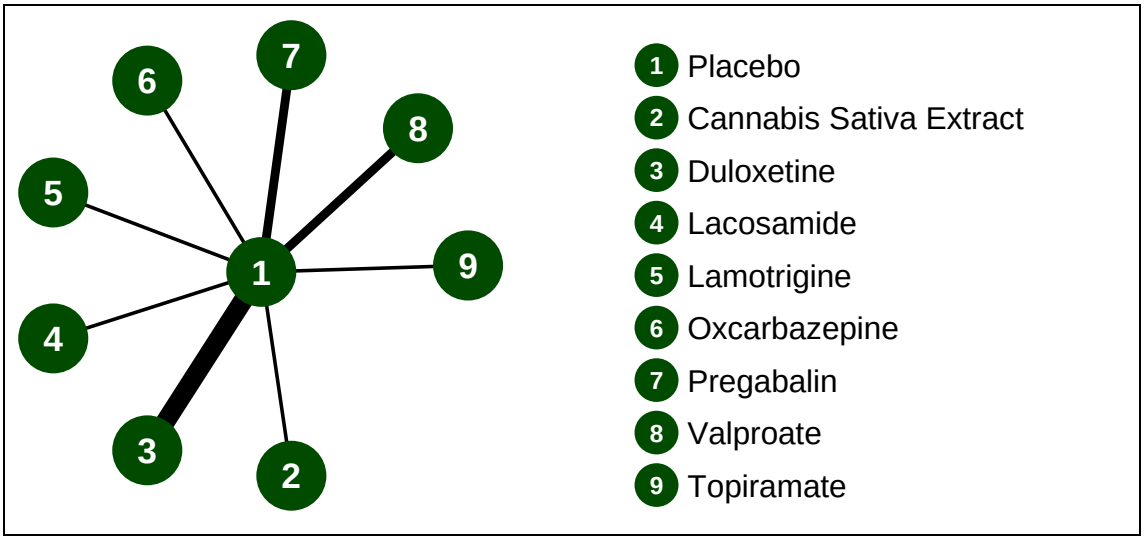

Figure 42 pain (continuous) - 12 weeks - evidence network

Table 69 pain (continuous) - 12 weeks - trials included in analysis

	Placebo	Cannabis Sativa Extract	Duloxetine	Lacosamide	Lamotrigine	Oxcarbazepine	Pregabalin	Valproate
Cannabis Sativa Extract	1 RCT[9] total n=30							
Duloxetine	4 RCTs[3,7,12,13] total n=1352	-						
Lacosamide	1 RCT[8] total n=119	-	-					
Lamotrigine	1 RCT[5] total n=125	-	-	-				
Oxcarbazepine	1 RCT[2] total n=146	-	-	-	-			
Pregabalin	2 RCTs[10,11] total n=665	-	-	-	-	-		
Valproate	2 RCTs[1,4] total n=79	-	-	-	-	-	-	
Topiramate	1 RCT[6] total n=317	-	-	-	-	-	-	-

(1) Agrawal et al. (2009); (2) Dogra et al. (2005); (3) Goldstein et al. (2005); (4) Kochar et al. (2004); (5) Rao et al. (2008); (6) Raskin et al. (2004); (7) Raskin et al. (2005); (8) Rauck et al. (2007); (9) Selvarajah et al. (2010); (10) Simpson et al. (2010); (11) van Seventer et al. (2006); (12) Wernicke et al. (2006); (13) Yasuda et al. (2011)

Table 70 pain (continuous) - 12 weeks - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Duloxetine	Lacosamide	Lamotrigine	Oxcarbazepine	Pregabalin	Valproate	Topiramate
Placebo		0.40 (-1.52, 2.32)	-0.99 (-1.23, -0.75)	-0.90 (-1.72, -0.08)	-0.15 (-1.32, 1.02)	-0.82 (-1.61, -0.03)	-0.59 (-1.32, 0.14)	-0.56 (-2.77, 1.64)	-0.67 (-1.23, -0.11)
Cannabis Sativa Extract	0.40 (-1.77, 2.55)		-	-	-	-	-	-	-
Duloxetine	-1.01 (-1.49, -0.54)	-1.41 (-3.62, 0.81)		-	-	-	-	-	-
Lacosamide	-0.90 (-2.17, 0.36)	-1.31 (-3.78, 1.21)	0.11 (-1.24, 1.46)		-	-	-	-	-
Lamotrigine	-0.15 (-1.67, 1.36)	-0.55 (-3.18, 2.08)	0.86 (-0.73, 2.45)	0.75 (-1.21, 2.72)		-	-	-	-
Oxcarbazepine	-0.82 (-2.07, 0.42)	-1.22 (-3.70, 1.29)	0.19 (-1.14, 1.52)	0.08 (-1.70, 1.85)	-0.67 (-2.64, 1.28)		-	-	-
Pregabalin	-0.62 (-1.33, 0.02)	-1.03 (-3.30, 1.24)	0.39 (-0.46, 1.18)	0.28 (-1.17, 1.68)	-0.48 (-2.15, 1.16)	0.19 (-1.25, 1.58)		-	-
Valproate	-0.22 (-1.37, 0.84)	-0.63 (-3.08, 1.79)	0.79 (-0.46, 1.96)	0.68 (-1.04, 2.32)	-0.07 (-1.98, 1.77)	0.60 (-1.11, 2.22)	0.41 (-0.90, 1.68)		-
Topiramate	-0.67 (-1.79, 0.44)	-1.07 (-3.49, 1.37)	0.34 (-0.88, 1.55)	0.23 (-1.46, 1.91)	-0.52 (-2.39, 1.37)	0.15 (-1.51, 1.82)	-0.05 (-1.32, 1.29)	-0.45 (-1.97, 1.17)	

Values given are mean differences.

The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

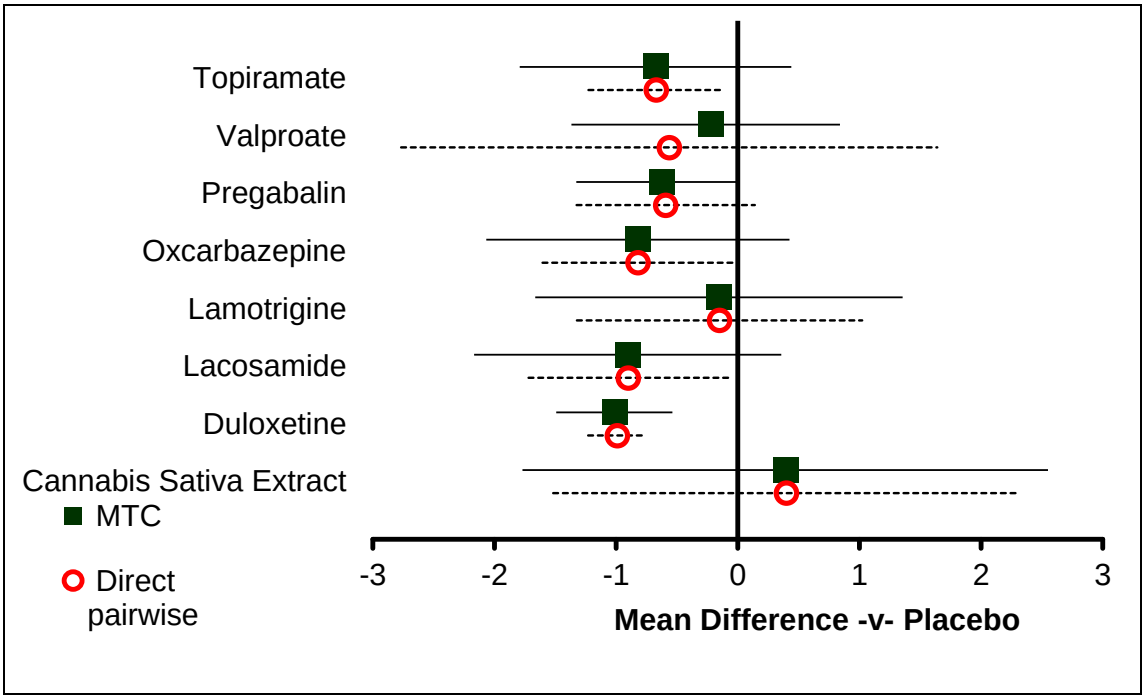

Figure 43 pain (continuous) - 12 weeks - relative effect of all options compared with placebo

(solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 71 pain (continuous) - 12 weeks - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	7 (5, 9)
Cannabis Sativa Extract	0.056	9 (1, 9)
Duloxetine	0.211	2 (1, 5)
Lacosamide	0.272	3 (1, 8)
Lamotrigine	0.061	7 (1, 9)
Oxcarbazepine	0.217	3 (1, 8)
Pregabalin	0.037	4 (1, 7)
Valproate	0.028	6 (1, 9)
Topiramate	0.120	4 (1, 9)

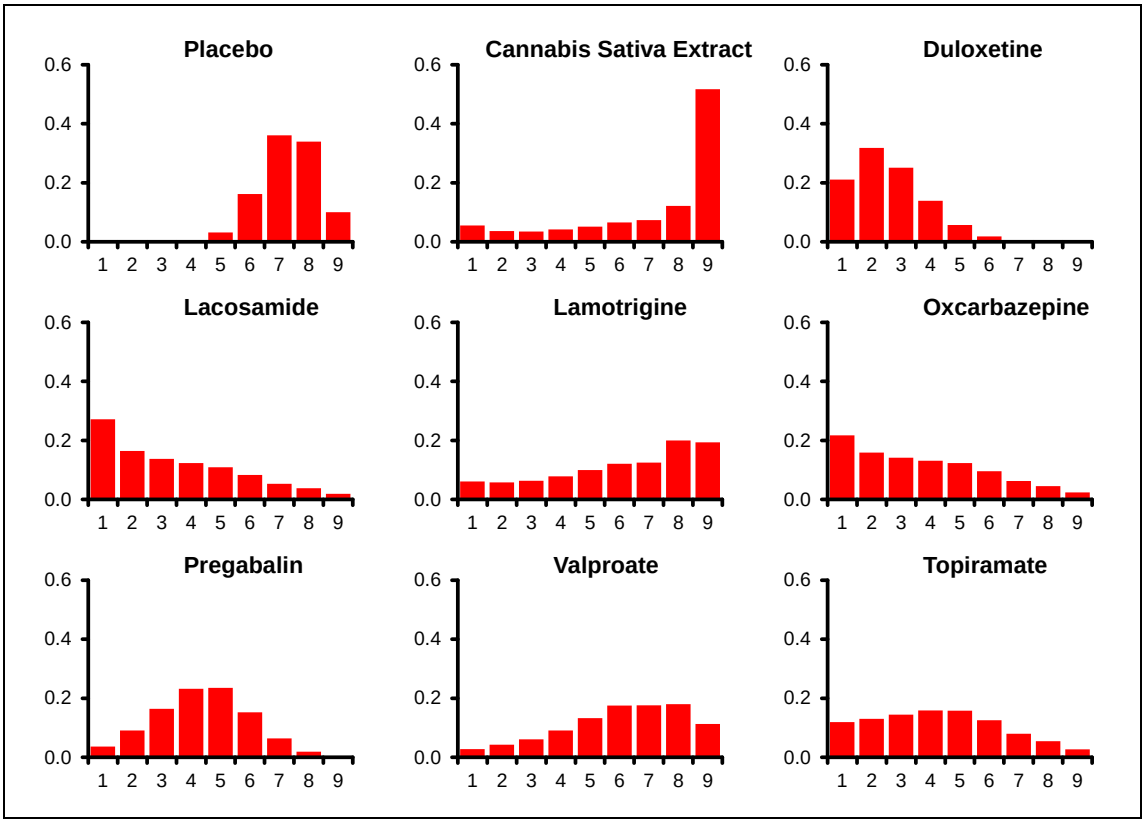

Figure 44 pain (continuous) - 12 weeks - rank probability histograms

Table 72 pain (continuous) - 12 weeks - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
33.78 (compared to 33 data-points)	4.445	-24.741	29.186	33.631	0.137 (95%CrI: 0.042, 0.698)

Table 73 pain (continuous) - 12 weeks - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.