Appendix G GRADE profiles and results for 'all neuropathic pain'

Outcome	Profile ID	Follow-up (days)	Number of RCTs	Interventions
Critical				
Patient-reported global improvement[1] (at least moderate improvement)	1a (pg2)	28 +/- 7	4	cannabis sativa extract, levetiracetam, pregabalin, tramadol
	1b (pg6)	56 +/- 7	8	capsaicin patch, duloxetine, gabapentin, pregabalin, valproate
	1c (see Appendix H)	84 +/- 14	8	capsaicin patch, lacosamide, lamotrigine, pregabalin
Sleep interference – normalised 10-point scale[2]	2a (pg11)	28 +/- 7	4	cannabis sativa extract, escitalopram, gabapentin, gabapentin+nortriptyline, nortriptyline
	2b (see Appendix H)	56 +/- 7	2	gabapentin
	2c (pg14)	84 +/- 14	6	duloxetine, pregabalin, topiramate
Withdrawal due to adverse effects	3 (pg19)	All time points	91	23 (see below)
Specific adverse effects	3a-t	All time points	See Appendix J	
Important				
30% pain relief	4a (pg31)	28 +/- 7	7	cannabis sativa extract, capsaicin cream, gabapentin, levetiracetam, pregabalin, tramadol
	4b (pg36)	56 +/- 7	5	amitriptyline, capsaicin patch, gabapentin, pregabalin
	4c (pg40)	84 +/- 14	18	cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate
50% pain relief	5a (pg44)	28 +/- 7	8	amitriptyline, cannabis sativa extract, gabapentin, levetiracetam, morphine, pregabalin, tramadol
	5b (see Appendix H)	56 +/- 7	7	gabapentin, lamotrigine, nortriptyline, pregabalin
	5c (pg48)	84 +/- 14	16	capsaicin patch, duloxetine, pregabalin, topiramate
30% and 50% pain relief	6 (pg52)	All time points	49	17 (see below)
Pain relief – normalised 10-point scale	7a (pg66)	28 +/- 7	30	21 (see below)
	7b (pg77)	56 +/- 7	21	13 (see below)
	7c (pg85)	84 +/- 14	15	10 (see below)

[1] measured using the 7-point PGIC (patient-reported global impression of change) tool

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

(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: Network meta-analysis for patient-reported global improvement (at least moderate improvement) – 28 +/- 7 days

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Patient-reported global improvement – at least moderate improvement (28 +/-7 days)	4 RCTs[a] n=412	very serious[1]	not applicable[2]	not serious[3]	very serious[4]	Very low	Critical

[1] treatment groups were not comparable at baseline in one study and 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 and it was not clear if use was 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; also, 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 'links' in network include only 1 trial; no head-to-head trials; wide confidence intervals for effect estimates of most compared to placebo and for overall rankings within the network (all interventions ranked from 1 to 5)

[a] cannabis sativa extract (n=66): Rog et al. (2005); concomitant drugs permitted

levetiracetam (n=72): Finnerup et al. (2009); concomitant drugs permitted

pregabalin (n=252): Lesser et al. (2004); only SSRIs permitted

tramadol (n=22): Norrbrink (2009); concomitant drugs permitted

[all compared to placebo]

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

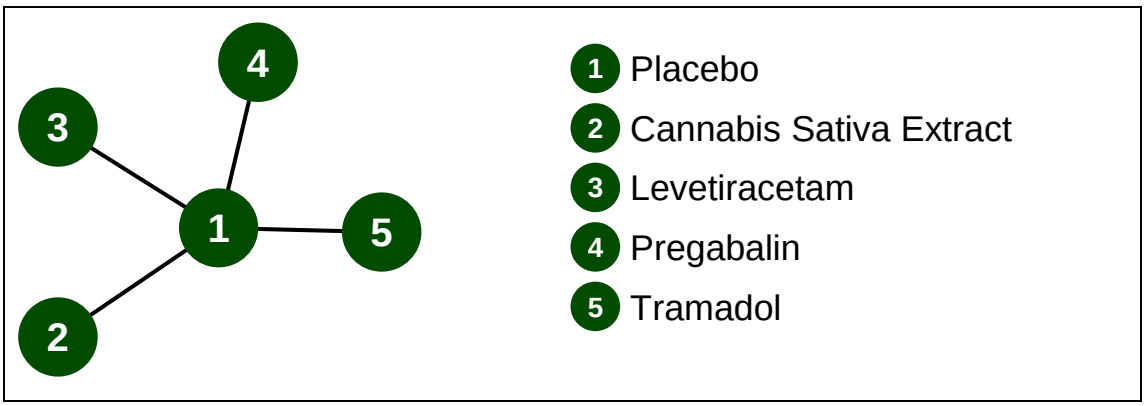


Figure 1 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - evidence network

Table 1 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - trials included in analysis

	Placebo	Cannabis Sativa Extract	Levetiracetam	Pregabalin
Cannabis Sativa Extract	1 RCT[4] total n=66			
Levetiracetam	1 RCT[1] total n=72	-		
Pregabalin	1 RCT[2] total n=252	-	-	
Tramadol	1 RCT[3] total n=22	-	-	-

(1) Finnerup et al. (2009); (2) Lesser et al. (2004); (3) Norrbrink & Lundeberg (2009); (4) Rog et al. (2005)

Table 2 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Levetiracetam	Pregabalin	Tramadol
Placebo		2.52 (0.69, 9.20)	1.00 (0.06, 16.63)	5.20 (2.94, 9.19)	11.12 (0.52, 236.75)
Cannabis Sativa Extract	2.67 (0.74, 11.46)		-	-	-
Levetiracetam	1.00 (0.02, 39.93)	0.37 (0.01, 18.24)		-	-
Pregabalin	5.28 (3.01, 9.52)	1.98 (0.42, 8.07)	5.29 (0.13, 223.70)		-
Tramadol	23.18 (1.31, 10440.00)	8.85 (0.34, 4351.00)	26.69 (0.22, 23600.00)	4.40 (0.23, 1986.00)	

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.

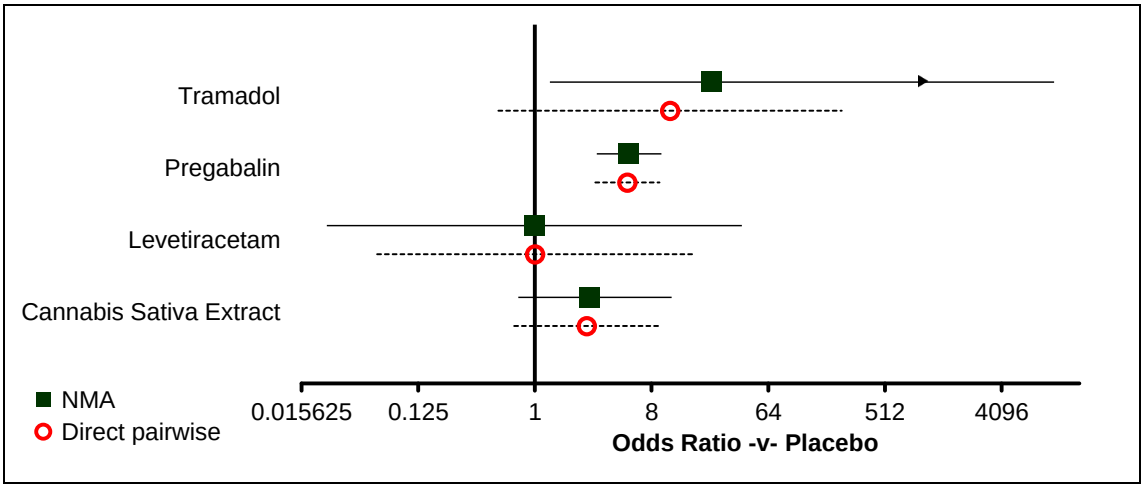


Figure 2 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 3 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	4 (3, 5)
Cannabis Sativa Extract	0.041	3 (1, 5)
Levetiracetam	0.063	4 (1, 5)
Pregabalin	0.139	2 (1, 4)
Tramadol	0.757	1 (1, 4)

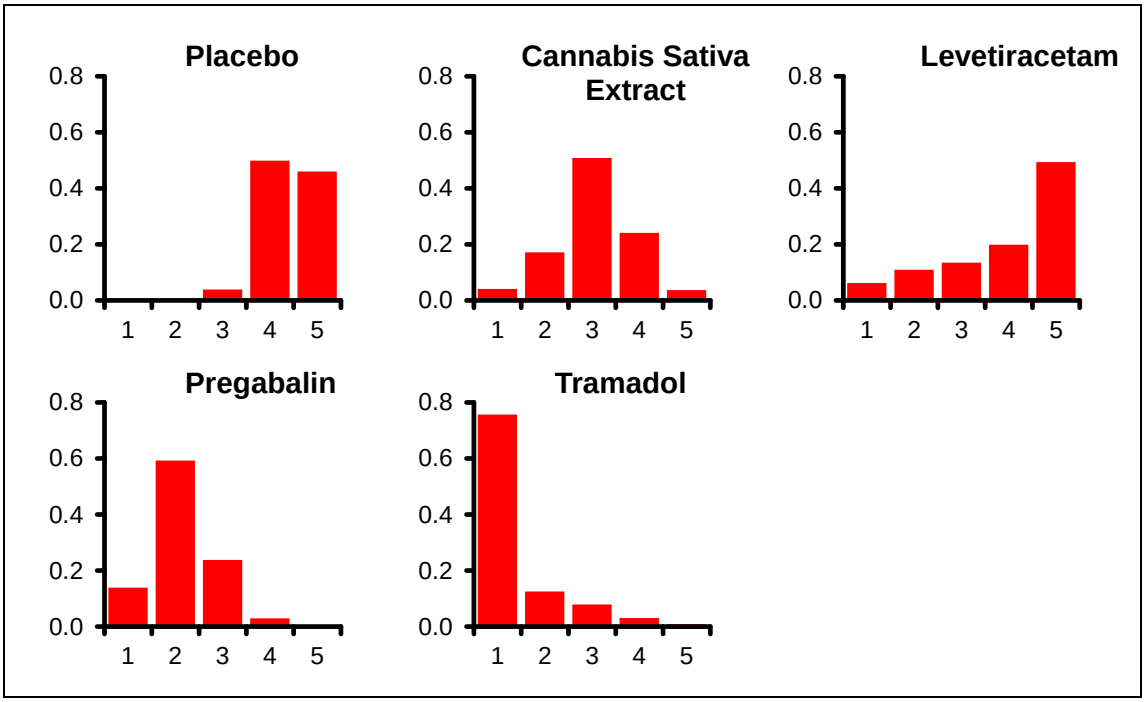


Figure 3 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - rank probability histograms

Table 4 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
11.76 (compared to 9 data-points)	41.127	33.515	7.612	48.739

Table 5 Patient-reported global improvement (at least moderate improvement) - 28 +/- 7 days - notes

- Fixed-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: autocorrelation for tramadol was relatively poor because of small study size and zero events in the placebo arm.

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

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Patient-reported global improvement – at least moderate improvement (56 +/-7 days)	8 RCTs[a] n=1525	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Critical

[1] half of the studies were unclear 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 (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; most links in the network contain only one trial; wide confidence intervals for effect estimates compared to placebo for 3 of 5 interventions, but particularly for duloxetine and valproate which are likely due to very small study sizes causing uncertainty of the ranking within the network

[a] Capsaicin Patch (n=416): Irving et al. (2011); concomitant drugs permitted if stable

Duloxetine (n=48): Vranken et al. (2011); concomitant drugs permitted if stable except antidepressants

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 anticonvulsants 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.

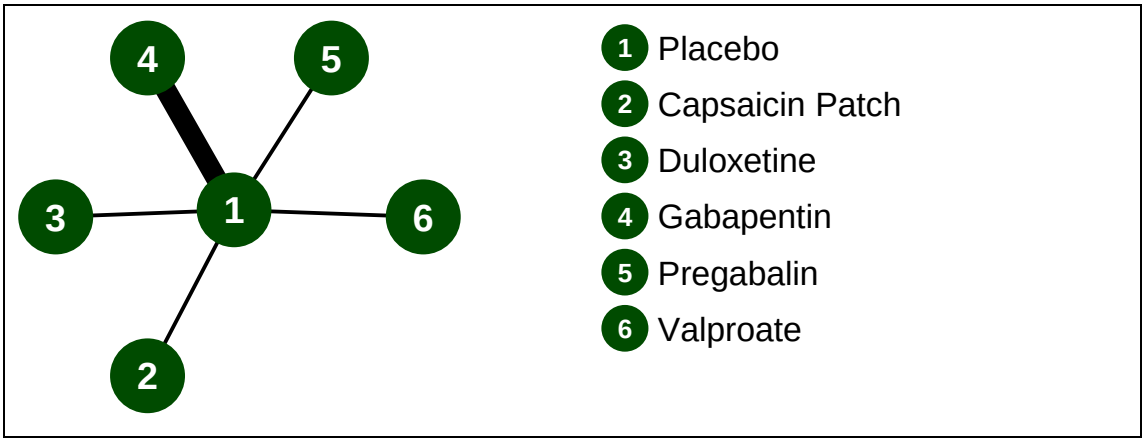


Figure 4 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - evidence network

Table 6 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - trials included in analysis

	Placebo	Capsaicin Patch	Duloxetine	Gabapentin	Pregabalin
Capsaicin Patch	1 RCT[2] total n=416				
Duloxetine	1 RCT[8] total n=48	-			
Gabapentin	4 RCTs[1,4,5,7] total n=778	-	-		
Pregabalin	1 RCT[6] total n=238	-	-	-	
Valproate	1 RCT[3] total n=45	-	-	-	-

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

Table 7 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Duloxetine	Gabapentin	Pregabalin	Valproate
Placebo		1.59 (1.04, 2.45)	13.82 (0.72, 265.52)	3.14 (2.16, 4.56)	3.34 (1.63, 6.83)	8.23 (1.89, 35.83)
Capsaicin Patch	1.61 (0.65, 3.86)		-	-	-	-
Duloxetine	27.73 (1.60, 16140.00)	17.66 (0.87, 10760.00)		-	-	-
Gabapentin	3.19 (1.94, 5.29)	1.98 (0.73, 5.58)	0.11 (0.00, 2.08)		-	-
Pregabalin	3.39 (1.31, 9.38)	2.13 (0.58, 8.25)	0.12 (0.00, 2.56)	1.07 (0.36, 3.29)		-
Valproate	9.48 (1.90, 61.06)	5.88 (0.94, 46.96)	0.32 (0.00, 9.69)	2.96 (0.55, 20.62)	2.77 (0.41, 23.05)	

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.

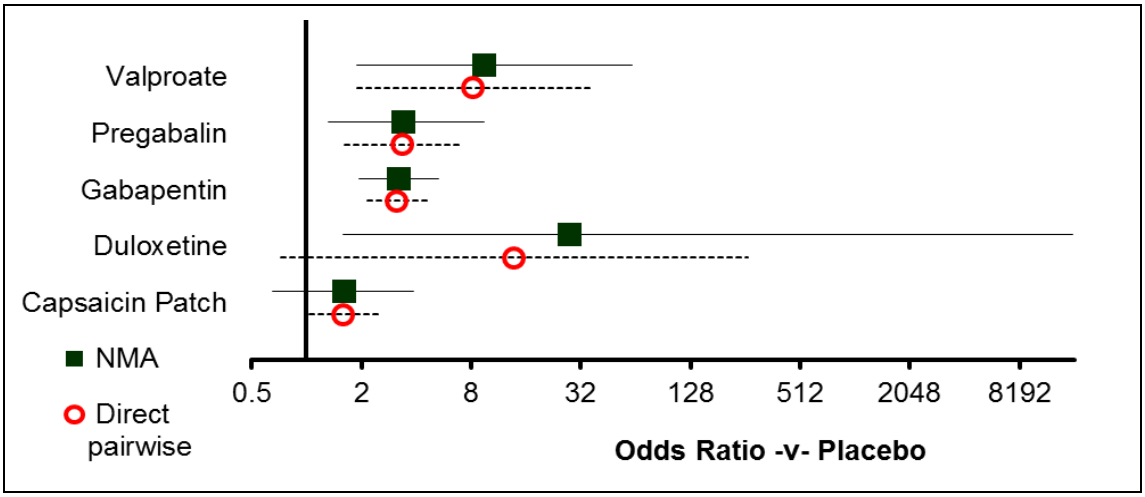


Figure 5 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 8 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	6 (5, 6)
Capsaicin Patch	0.002	5 (3, 6)
Duloxetine	0.705	1 (1, 5)
Gabapentin	0.006	3 (2, 5)
Pregabalin	0.020	3 (2, 5)
Valproate	0.267	2 (1, 4)

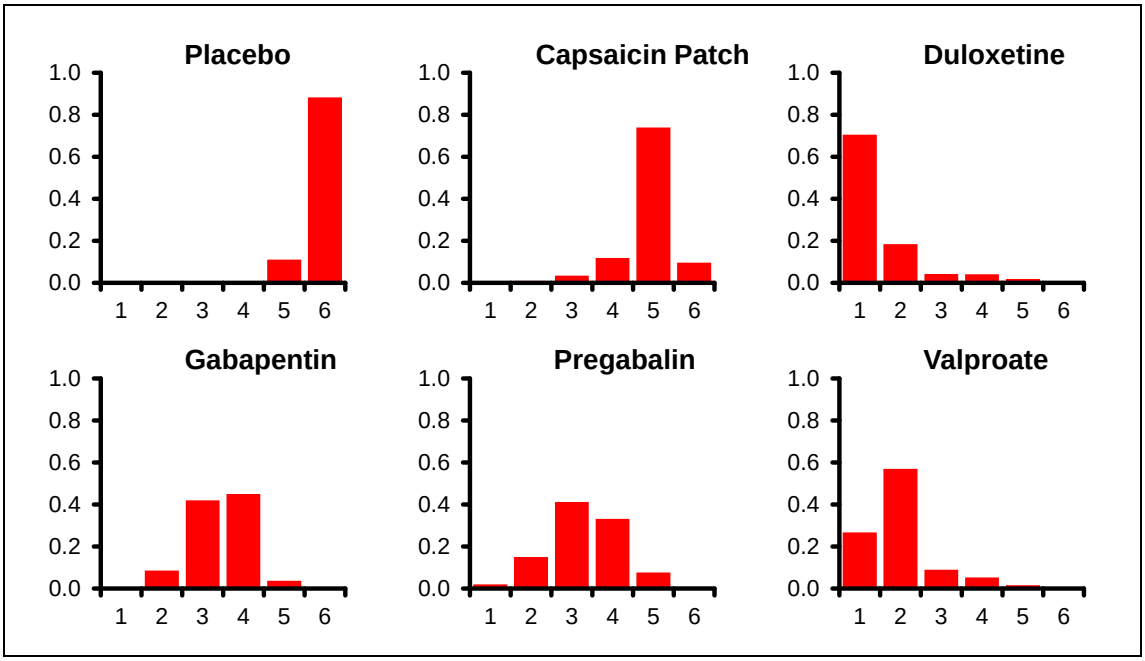


Figure 6 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - rank probability histograms

Table 9 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
17.39 (compared to 18 data-points)	94.672	79.729	14.942	109.614	0.000 (95%CI: 0.000, 0.927)

Table 10 Patient-reported global improvement (at least moderate improvement) - 56 +/- 7 days - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- Model convergence: autocorrelation relatively poor for duloxetine and valproate because of small numbers of events in placebo arm.
- Both duloxetine and valproate have a high median ranking but the study sizes are relatively small and there are large credible intervals around the estimates for these drugs. The considerable uncertainty about the true effect of these drugs and how they rank overall in the network is reflected in the size of the confidence intervals around the rankings.

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

Please see Appendix H (peripheral pain) for this outcome (only studies with peripheral pain reported this outcome at this time point).

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)	4 RCTs [a] n=489	very serious[1]	not serious[2]	not serious[3]	serious[4]	Low	Critical

[1] more than half of studies are crossover studies; treatment groups were not comparable at baseline in one study and 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] all 'links' in network include only 1 trial, wide confidence intervals around rankings in the network

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

Cannabis sativa extract (n=65): Rog et al. (2005); concomitant amitriptyline or tricyclic anti-depressants permitted if in stable doses

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.

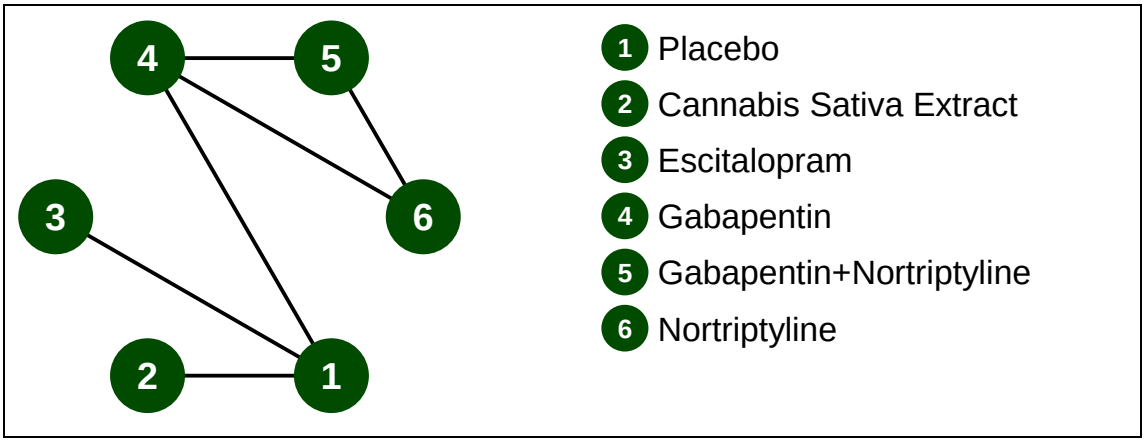


Figure 7 sleep interference - 28 +/- 7 days - evidence network

Table 11 sleep interference - 28 +/- 7 days - trials included in analysis

	Placebo	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline
Cannabis Sativa Extract	1 RCT[4] total n=65				
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); (4) Rog et al. (2005)

Table 12 sleep interference - 28 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Nortriptyline
Placebo		-1.74 (-2.40, -1.08)	-1.00 (-1.57, -0.43)	-0.39 (-0.95, 0.17)	-	-
Cannabis Sativa Extract	-1.74 (-2.40, -1.08)		-	-	-	-
Escitalopram	-1.00 (-1.57, -0.43)	0.74 (-0.13, 1.61)		-	-	-
Gabapentin	-0.39 (-0.96, 0.17)	1.35 (0.47, 2.22)	0.61 (-0.19, 1.41)		-1.20 (-1.83, -0.57)	0.10 (-0.53, 0.73)
Gabapentin +Nortriptyline	-1.60 (-2.44, -0.75)	0.14 (-0.92, 1.22)	-0.60 (-1.61, 0.42)	-1.20 (-1.83, -0.57)		1.30 (0.69, 1.91)
Nortriptyline	-0.30 (-1.13, 0.55)	1.44 (0.38, 2.52)	0.71 (-0.31, 1.72)	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.

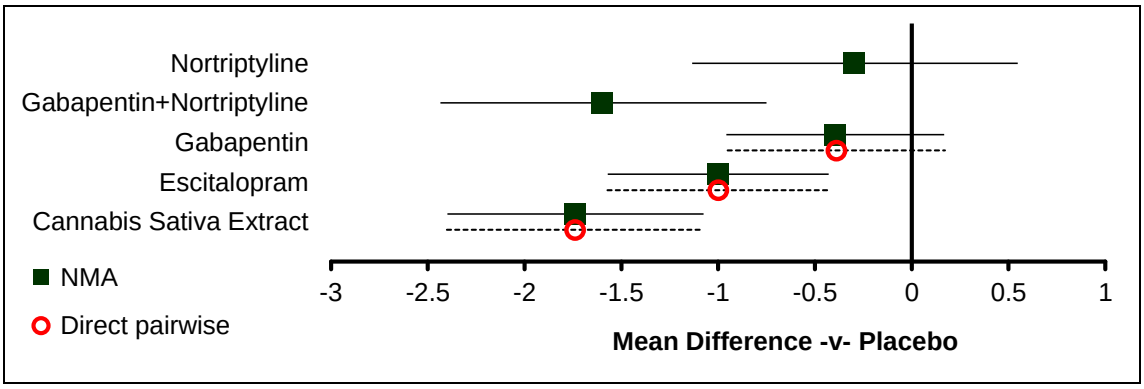


Figure 8 sleep interference - 28 +/- 7 days - relative effect of all options compared with placebo

(values less than 0 favour the treatment; values greater than 0 favour placebo; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 13 sleep interference - 28 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	6 (4, 6)
Cannabis Sativa Extract	0.593	1 (1, 3)
Escitalopram	0.016	3 (2, 5)
Gabapentin	0.000	4 (3, 6)
Gabapentin+Nortriptyline	0.391	2 (1, 3)
Nortriptyline	0.000	5 (3, 6)

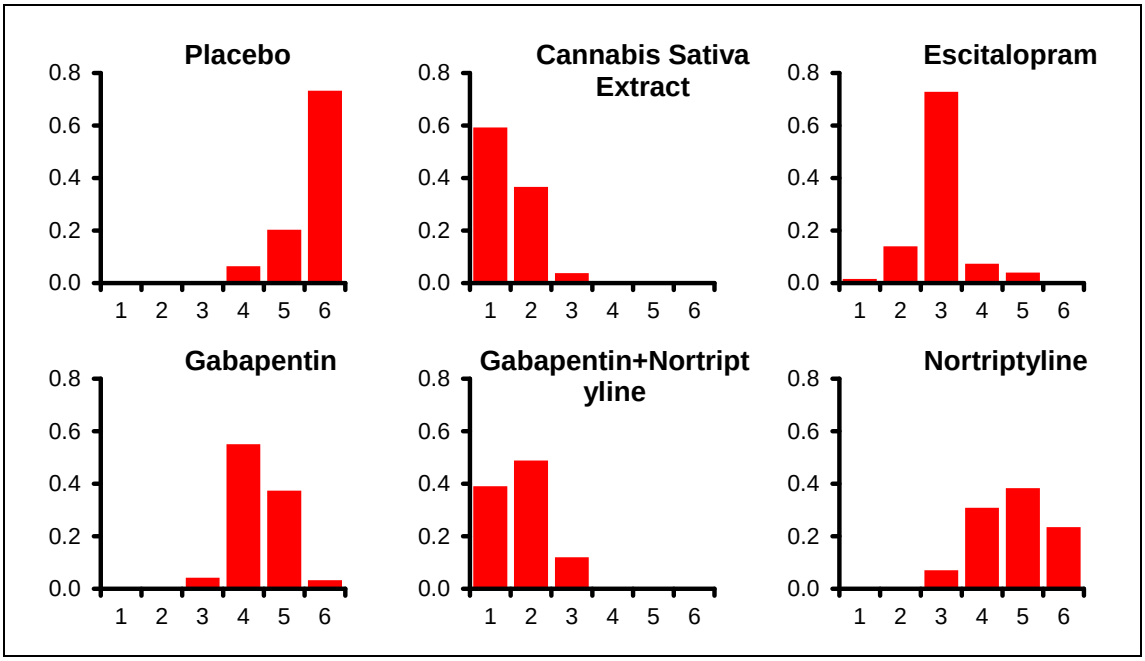


Figure 9 sleep interference - 28 +/- 7 days - rank probability histograms

Table 14 sleep interference - 28 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
8.996 (compared to 9 data-points)	-1.941	-10.937	8.995	7.054

Table 15 sleep interference - 28 +/- 7 days - 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)

Please see Appendix H (peripheral pain) for this outcome (only studies with peripheral pain reported this outcome at this time point).

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)	6 RCTs[a] n=1650	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 one study 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 3 other studies; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for placebo vs pregabalin 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; most 'links' in network include only 1 trial; confidence intervals for effect estimates against placebo appear small enough but confidence intervals around rankings are wide (all 3 interventions could be ranked from 1 to 3)

[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

Pregabalin (n=135): Siddall et al. (2006); concomitant medications were permitted in stable doses but gabapentin was excluded

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.

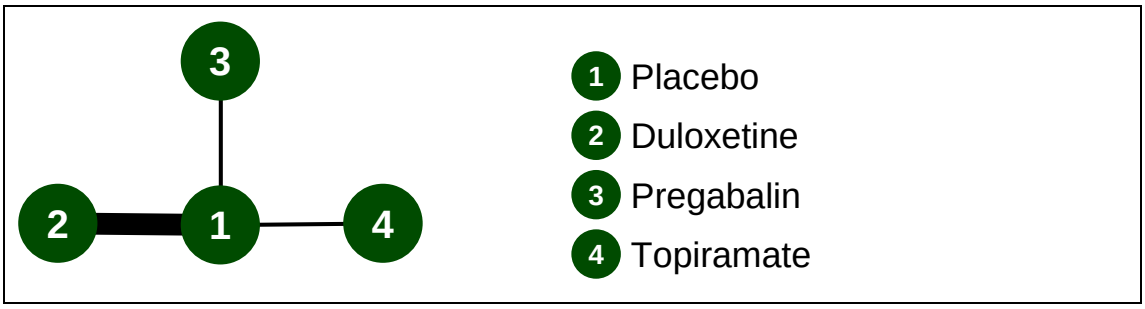


Figure 10 sleep interference - 84 +/- 14 days - evidence network

Table 16 sleep interference - 84 +/- 14 days - trials included in analysis

	Placebo	Duloxetine	Pregabalin
Duloxetine	4 RCTs[1,3,5,6] total n=1198		
Pregabalin	1 RCT[4] total n=135	-	
Topiramate	1 RCT[2] total n=317	-	-

(1) Gao et al. (2010); (2) Raskin et al. (2004); (3) Raskin et al. (2005); (4) Siddall et al. (2006); (5) Wernicke et al. (2006); (6) Yasuda et al. (2011)

Table 17 sleep interference - 84 +/- 14 days - relative effectiveness of all pairwise combinations

	Placebo	Duloxetine	Pregabalin	Topiramate
Placebo		-0.62 (-0.94, -0.31)	-1.16 (-2.05, -0.27)	-1.00 (-1.64, -0.36)
Duloxetine	-0.62 (-1.03, -0.20)		-	-
Pregabalin	-1.15 (-2.21, -0.09)	-0.52 (-1.67, 0.61)		-
Topiramate	-1.00 (-1.87, -0.14)	-0.38 (-1.35, 0.56)	0.15 (-1.22, 1.50)	

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.

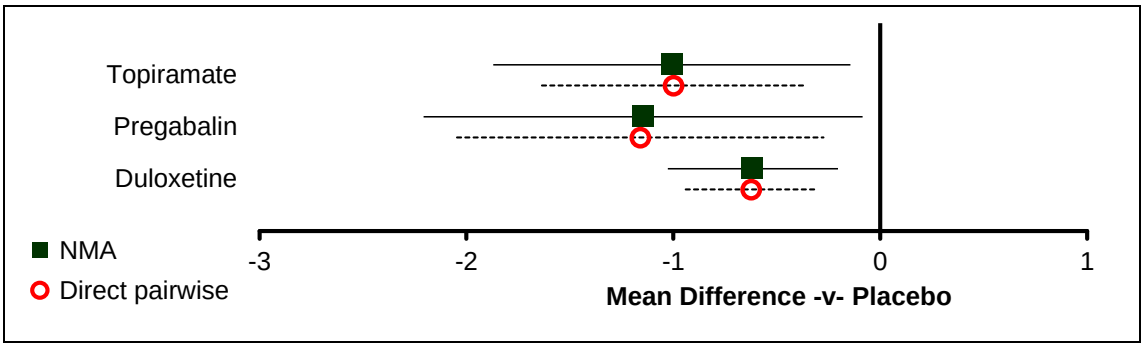


Figure 11 sleep interference - 84 +/- 14 days - relative effect of all options compared with placebo

(values less than 0 favour the treatment; values greater than 0 favour placebo; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 18 sleep interference - 84 +/- 14 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	4 (3, 4)
Duloxetine	0.043	3 (1, 3)
Pregabalin	0.568	1 (1, 3)
Topiramate	0.389	2 (1, 3)

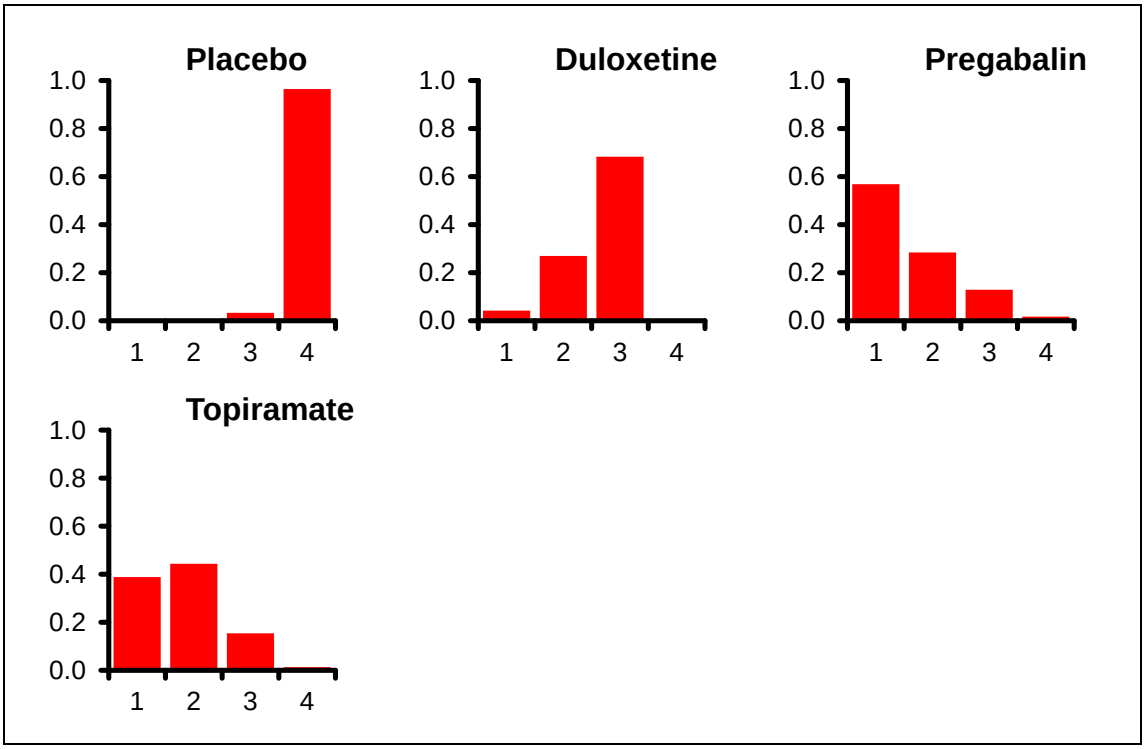


Figure 12 sleep interference - 84 +/- 14 days - rank probability histograms

Table 19 sleep interference - 84 +/- 14 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
12.88 (compared to 15 data-points)	0.213	-10.539	10.752	10.966	0.000 (95%CrI: 0.000, 0.530)

Table 20 sleep interference - 84 +/- 14 days - 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	91 RCTs[a] n=17274	very serious[1]	not serious[2]	not serious[3]	serious[4]	Very low	Critical

[1] in 66% of 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; one study was single-blind

[2] it was not possible to assess heterogeneity for pairwise comparisons; there appears to be consistency between direct and indirect estimates (the 'loops' in the network)

[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; confidence intervals around the hazard ratios were wide for the majority of interventions and were wide for the overall rankings within the network

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

amitriptyline (n=449): Cardenas et al. (2002), Graff-Radford et al. (2000), Kautio et al. (2008), Max et al. (1988), Rintala et al. (2007), Robinson et al. (2004), Vrethem et al. (1997); concomitant drugs permitted in 3 but it was unclear if they were permitted in the others

cannabis sativa extract (n=191): Nurmikko et al. (2007), Rog et al. (2005); 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=1918): Backonja et al. (2008), Clifford et al. (2012), Irving et al. (2011), Simpson et al. (2008), 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=1130): Backonja et al. (1998), Gordh et al. (2008), Hahn et al. (2004), Rice & Maton (2001), Rintala et al. (2007), Rowbotham et al. (1998), Simpson (2001); concomitant drugs not permitted in three, permitted in five (oxycodone was used as a rescue medication in one 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=1463): Breuer et al. (2007), Eisenberg et al. (2001), Finnerup et al. (2002), Luria et al. (2000), McCleane (1999), Rao et al. (2008), Simpson et al. (2000), Simpson et al. (2003), Vestergaard et al. (2001), Vinik et al. (2007), Vinik et al. (2007); five studies permitted concomitant drugs, four did not and the rest were unclear

levetiracetam (n=226): Falah et al. (2012), Finnerup et al. (2009), Holbech et al. (2011), Rossi et al. (2009); concomitant drugs not permitted in 3 studies but were permitted (apart from anti-depressants) in the other

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=4236): Arezzo et al. (2008), Dworkin et al. (2003), Freynhagen et al. (2005), Guan et al. (2011), Kim 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), Siddall et al. (2006), Simpson et al. (2010);

Stacey et al. (2008), Tolle et al. (2008), van Seventer et al. (2006), Vranken et al. (2008); 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=292): Arbaiza & Vidal (2007), Harati et al. (1998), Norrbrink & Lundeberg (2009), Sindrup et al. (1999); concomitant drugs were permitted in 2, 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=415): Rowbotham et al. (2004), Sindrup et al. (2003), Tasmuth et al. (2002), Yucel et al. (2005); concomitant drugs were not permitted in most but opioids were permitted in one

Head-to-head comparisons:

amitriptyline vs gabapentin (n=126): Morello et al. (1999), Rintala et al. (2007); concomitant drugs not permitted in both but oxycodone was used as a rescue medication in one (this is in the scope of the guideline for the use in NP so considered a concomitant medication)

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.

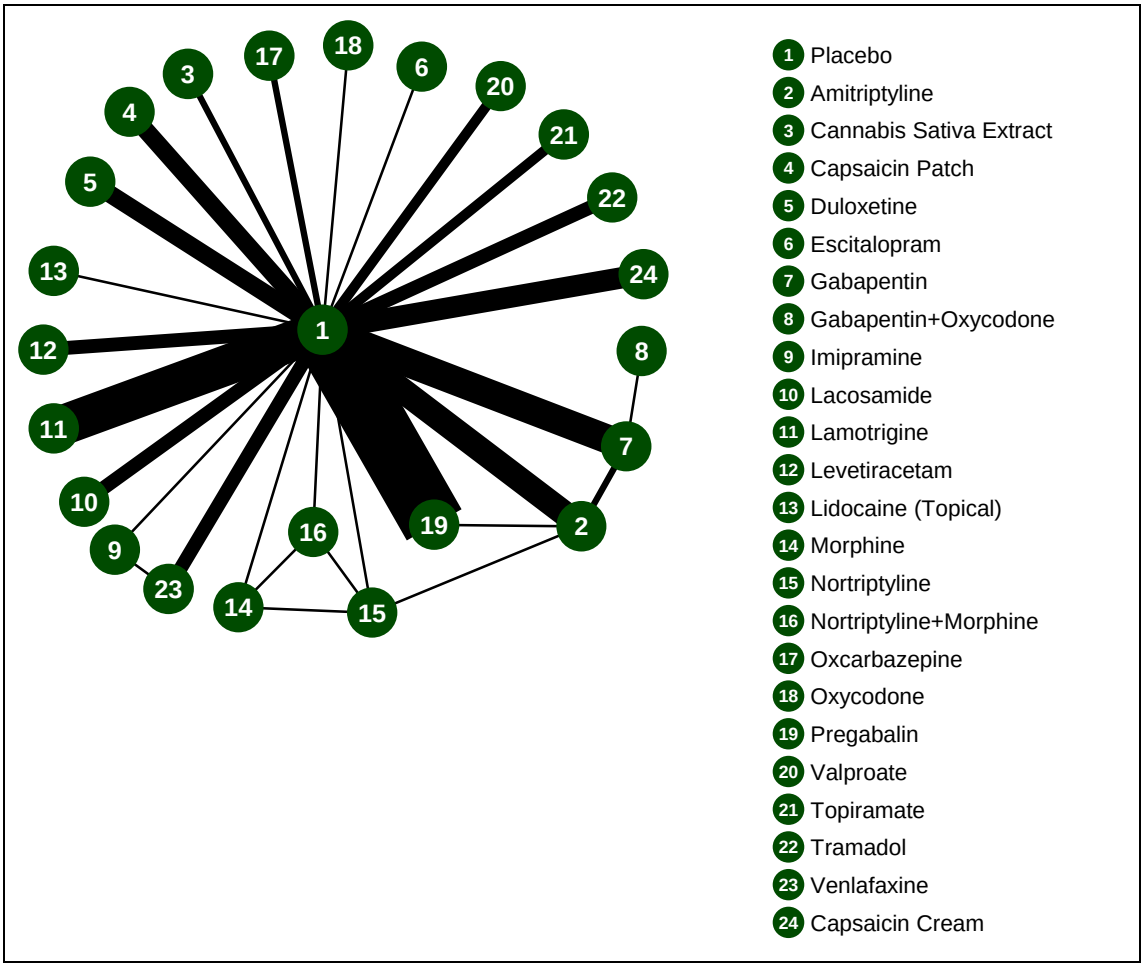


Figure 13 withdrawal due to adverse effects - evidence network

Table 21 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	7 RCTs[8,23,30,39,53,54,82] total n=449																						
Cannabis Sativa Extract	2 RCTs[44,55] total n=191	-																					
Capsaicin Patch	5 RCTs[4,10,29,68,86] total n=1918	-	-																				
Duloxetine	5 RCTs[19,21,49,87,89] total n=1692	-	-	-																			
Escitalopram	1 RCT[45] total n=96	-	-	-	-																		
Gabapentin	7 RCTs[3,22,25,51,53,58,65] total n=1130	2 RCTs[42,53] total n=126	-	-	-	-																	
Gabapentin +Oxycodone	-	-	-	-	-	-	1 RCT[26] total n=338																	
Imipramine	1 RCT[71] total n=80	-	-	-	-	-	-	-															
Lacosamide	4 RCTs[50,63,88,91] total n=1314	-	-	-	-	-	-	-	-														
Lamotrigine	11 RCTs[7,14,16,38,40,47,66,67,78,79,80] total n=1463	-	-	-	-	-	-	-	-	-													

	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
Levetiracetam	4 RCTs[15,17,28,57] total n=226	-	-	-	-	-	-	-	-	-	-												
Lidocaine (Topical)	1 RCT[9] total n=56	-	-	-	-	-	-	-	-	-	-	-											
Morphine	1 RCT[32] total n=110	-	-	-	-	-	-	-	-	-	-	-	-										
Nortriptyline	1 RCT[32] total n=110	1 RCT[85] total n=66	-	-	-	-	-	-	-	-	-	-	-	1 RCT[32] total n=110									
Nortriptyline +Morphine	1 RCT[32] total n=110	-	-	-	-	-	-	-	-	-	-	-	-	1 RCT[32] total n=110	1 RCT[32] total n=110								
Oxcarbazepine	2 RCTs[6,11] total n=493	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[20] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Pregabalin	17 RCTs[2,13,18,24,33,37,41,52,56,60,61,64,69,72,76,77,81] total n=4236	1 RCT[5] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Valproate	3 RCTs[34,35,36] total n=145	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Topiramate	3 RCTs[31,48,75]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			

	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
	total n=1674																						
Tramadol	4 RCTs[1,27,43,70] total n=292	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	4 RCTs[59,71,74,90] total n=415	-	-	-	-	-	-	-	1 RCT[71] total n=80	-	-	-	-	-	-	-	-	-	-	-	-	-	
Capsaici83ie*£IE x n Cream	6 RCTs[12,46,62,73,83,84] total n=547	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

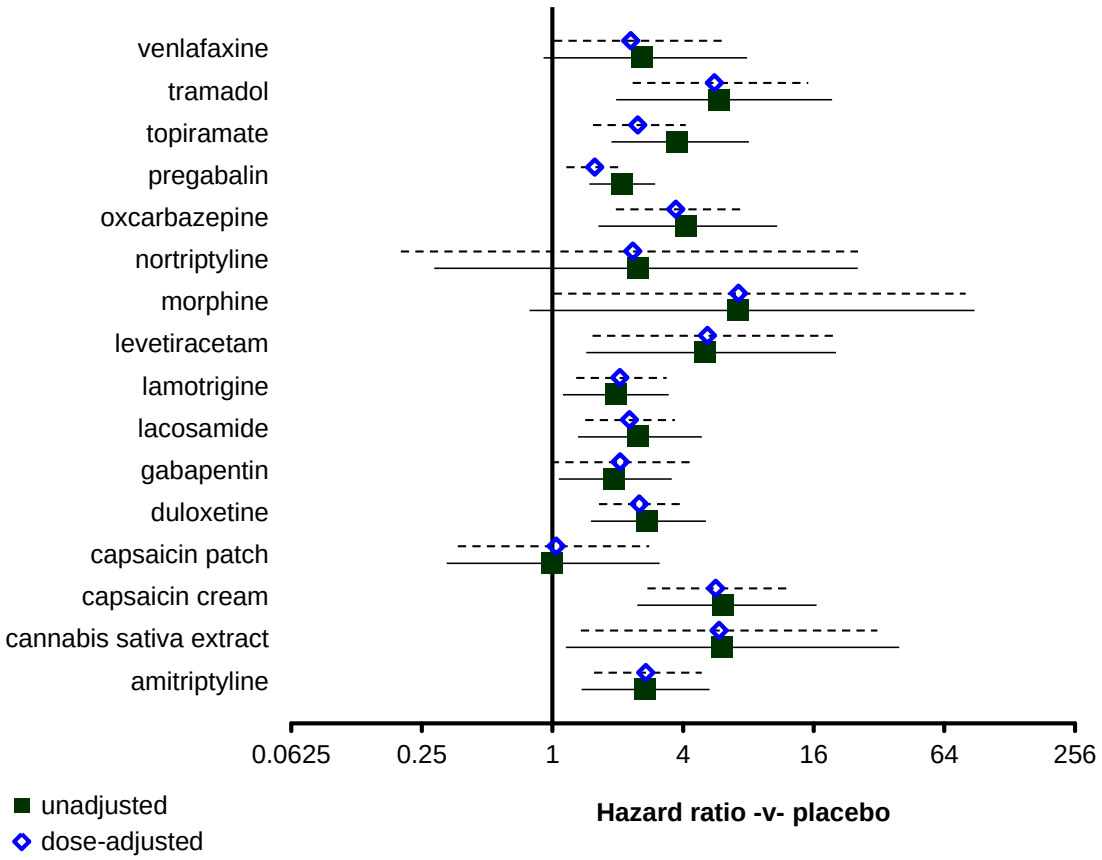
(1) Arbaiza & Vidal (2007); (2) Arezzo et al. (2008); (3) Backonja et al. (1998); (4) Backonja et al. (2008); (5) Bansal et al. (2009); (6) Beydoun et al. (2006); (7) Breuer et al. (2007); (8) Cardenas et al. (2002); (9) Cheville et al. (2009); (10) Clifford et al. (2012); (11) Dogra et al. (2005); (12) Donofrio & Capsaicin study (1992); (13) Dworkin et al. (2003); (14) Eisenberg et al. (2001); (15) Falah et al. (2012); (16) Finnerup et al. (2002); (17) Finnerup et al. (2009); (18) Freynhagen et al. (2005); (19) Gao et al. (2010); (20) Gimbel et al. (2003); (21) Goldstein et al. (2005); (22) Gordh et al. (2008); (23) Graff-Radford et al. (2000); (24) Guan et al. (2011); (25) Hahn et al. (2004); (26) Hanna et al. (2008); (27) Harati et al. (1998); (28) Holbech et al. (2011); (29) Irving et al. (2011); (30) Kautio et al. (2008); (31) Khoromi et al. (2005); (32) Khoromi et al. (2007); (33) Kim et al. (2011); (34) Kochar et al. (2002); (35) Kochar et al. (2004); (36) Kochar et al. (2005); (37) Lesser et al. (2004); (38) Luria et al. (2000); (39) Max et al. (1988); (40) McCleane (1999); (41) Moon et al. (2010); (42) Morello et al. (1999); (43) Norrbrink & Lundeberg (2009); (44) Nurmikko et al. (2007); (45) Otto et al. (2008); (46) Paice et al. (2000); (47) Rao et al. (2008); (48) Raskin et al. (2004); (49) Raskin et al. (2005); (50) Rauck et al. (2007); (51) Rice & Maton (2001); (52) Richter et al. (2005); (53) Rintala et al. (2007); (54) Robinson et al. (2004); (55) Rog et al. (2005); (56) Rosenstock et al. (2004); (57) Rossi et al. (2009); (58) Rowbotham et al. (1998); (59) Rowbotham et al. (2004); (60) Sabatowski et al. (2004); (61) Satoh et al. (2011); (62) Scheffler et al. (1991); (63) Shaibani et al. (2009); (64) Siddall et al. (2006); (65) Simpson (2001); (66) Simpson et al. (2000); (67) Simpson et al. (2003); (68) Simpson et al. (2008); (69) Simpson et al. (2010); (70) Sindrup et al. (1999); (71) Sindrup et al. (2003); (72) Stacey et al. (2008); (73) Tandan et al. (1992); (74) Tasmuth et al. (2002); (75) Thienel et al. (2004); (76) Tolle et al. (2008); (77) van Seventer et al. (2006); (78) Vestergaard et al. (2001); (79) Vinik et al. (2007); (80) Vinik et al. (2007); (81) Vranken et al. (2008); (82) Vrethem et al. (1997); (83) Watson & Evans (1992); (84) Watson et al. (1993); (85) Watson et al. (1998); (86) Webster et al. (2010); (87) Wernicke et al. (2006); (88) Wymer et al. (2009); (89) Yasuda et al. (2011); (90) Yucel et al. (2005); (91) Ziegler et al. (2010)

Table 22 withdrawal due to adverse effects - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis 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
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
Amitriptyline	2.68 (1.37, 5.31)		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 Extract	5.93 (1.22, 40.47)	2.21 (0.40, 16.66)		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	0.98 (0.32, 3.22)	0.37 (0.10, 1.41)	0.17 (0.02, 1.27)		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	2.74 (1.50, 5.14)	1.02 (0.41, 2.55)	0.46 (0.06, 2.57)	2.80 (0.75, 9.79)		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	7.52 (0.77, 240.50)	2.86 (0.26, 94.17)	1.30 (0.06, 54.76)	7.82 (0.59, 310.90)	2.76 (0.25, 92.68)		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	1.95 (1.07, 3.59)	0.73 (0.32, 1.67)	0.33 (0.04, 1.79)	1.97 (0.53, 7.03)	0.71 (0.30, 1.67)	0.26 (0.01, 2.77)		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	6.40 (1.46, 28.38)	2.38 (0.49, 11.92)	1.07 (0.09, 9.65)	6.44 (0.98, 40.77)	2.34 (0.47, 11.67)	0.81 (0.02, 13.33)	3.26 (0.85, 12.88)		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	0.35 (0.01, 3.50)	0.13 (0.00, 1.46)	0.06 (0.00, 1.01)	0.35 (0.01, 4.70)	0.13 (0.00, 1.45)	0.04 (0.00, 1.35)	0.18 (0.01, 1.95)	0.05 (0.00, 0.88)		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
Lacosamide	2.45 (1.28, 4.79)	0.92 (0.36, 2.37)	0.41 (0.05, 2.34)	2.49 (0.64, 8.89)	0.90 (0.36, 2.18)	0.32 (0.01, 3.51)	1.26 (0.52, 3.08)	0.38 (0.08, 1.93)	7.03 (0.63, 213.20)		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	1.96 (1.13, 3.50)	0.73 (0.30, 1.79)	0.33 (0.05, 1.79)	1.98 (0.54, 6.93)	0.72 (0.31, 1.63)	0.26 (0.01, 2.82)	1.00 (0.44, 2.31)	0.31 (0.06, 1.50)	5.60 (0.53, 171.40)	0.80 (0.34, 1.90)		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	4.75 (1.41, 20.80)	1.79 (0.44, 9.12)	0.81 (0.08, 7.13)	4.83 (0.89, 30.29)	1.74 (0.44, 8.55)	0.61 (0.02, 10.51)	2.45 (0.63, 11.93)	0.76 (0.11, 5.96)	14.20 (0.96, 544.50)	1.97 (0.48, 9.68)	2.45 (0.62, 11.47)		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 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)	11.20 (0.42, 6387)	4.20 (0.14, 2510)	1.87 (0.04, 1175)	11.56 (0.34, 7750)	4.17 (0.14, 2340)	1.51 (0.01, 1179)	5.80 (0.20, 3415)	1.83 (0.05, 1080)	38.03 (0.54, 45860)	4.56 (0.16, 2783)	5.78 (0.21, 3450)	2.36 (0.06, 1552)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	7.38 (0.87, 100.10)	2.77 (0.31, 38.16)	1.26 (0.07, 24.57)	7.55 (0.67, 121.20)	2.69 (0.29, 38.87)	0.94 (0.02, 33.32)	3.80 (0.41, 54.61)	1.18 (0.08, 21.98)	22.85 (0.88, 1426.00)	3.04 (0.32, 42.85)	3.78 (0.41, 54.90)	1.52 (0.11, 28.00)	0.60 (0.00, 45.39)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	2.57 (0.28, 26.75)	0.96 (0.11, 9.81)	0.43 (0.02, 7.03)	2.61 (0.22, 32.40)	0.93 (0.10, 10.23)	0.32 (0.01, 9.62)	1.31 (0.14, 14.48)	0.41 (0.03, 6.00)	7.63 (0.31, 454.30)	1.05 (0.11, 12.01)	1.30 (0.13, 14.93)	0.52 (0.04, 7.64)	0.21 (0.00, 13.04)	0.34 (0.04, 2.21)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	5.69 (0.61, 78.87)	2.12 (0.21, 30.50)	0.96 (0.05, 20.00)	5.80 (0.48, 95.15)	2.06 (0.20, 30.59)	0.73 (0.01, 25.69)	2.91 (0.29, 42.91)	0.91 (0.06, 17.33)	17.78 (0.63, 1054.00)	2.34 (0.22, 35.56)	2.90 (0.28, 43.01)	1.17 (0.08, 22.33)	0.47 (0.00, 35.45)	0.77 (0.13, 4.49)	2.27 (0.30, 18.16)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	4.11 (1.61, 10.85)	1.53 (0.47, 4.96)	0.69 (0.08, 4.39)	4.17 (0.91, 17.84)	1.50 (0.50, 4.65)	0.53 (0.01, 6.73)	2.10 (0.68, 6.61)	0.64 (0.11, 3.76)	11.90 (0.98, 382.80)	1.67 (0.53, 5.33)	2.10 (0.69, 6.47)	0.86 (0.15, 4.07)	0.36 (0.00, 11.65)	0.55 (0.03, 6.04)	1.62 (0.13, 17.54)	0.72 (0.04, 8.47)		N/A	N/A	N/A	N/A	N/A	N/A
Oxycodone	1.73 (0.33, 10.28)	0.65 (0.11, 4.25)	0.29 (0.02, 3.08)	1.76 (0.23, 13.82)	0.63 (0.11, 4.09)	0.22 (0.01, 4.29)	0.89 (0.15, 5.82)	0.27 (0.03, 2.65)	5.15 (0.28, 211.00)	0.71 (0.12, 4.68)	0.89 (0.15, 5.73)	0.36 (0.04, 3.09)	0.15 (0.00, 6.54)	0.23 (0.01, 3.62)	0.68 (0.04, 11.19)	0.30 (0.01, 5.23)	0.42 (0.06, 3.09)		N/A	N/A	N/A	N/A	N/A
Pregabalin	2.08 (1.46, 2.96)	0.78 (0.37, 1.61)	0.35 (0.05, 1.81)	2.11 (0.62, 6.70)	0.76 (0.37, 1.52)	0.27 (0.01, 2.77)	1.07 (0.53, 2.14)	0.32 (0.07, 1.48)	5.90 (0.57, 175.50)	0.85 (0.40, 1.76)	1.06 (0.54, 2.05)	0.44 (0.10, 1.56)	0.18 (0.00, 5.01)	0.28 (0.02, 2.47)	0.82 (0.08, 7.59)	0.37 (0.03, 3.54)	0.51 (0.18, 1.38)	1.20 (0.20, 6.72)		N/A	N/A	N/A	N/A
Valproate	3.56 (0.53, 49.86)	1.35 (0.18, 19.39)	0.60 (0.04, 12.40)	3.69 (0.38, 59.56)	1.31 (0.18, 18.47)	0.47 (0.01, 14.88)	1.85 (0.25, 26.62)	0.57 (0.05, 10.34)	11.01 (0.50, 703.40)	1.47 (0.19, 21.08)	1.83 (0.25, 26.86)	0.73 (0.07, 13.89)	0.31 (0.00, 21.45)	0.50 (0.02, 13.83)	1.44 (0.07, 38.79)	0.65 (0.02, 18.29)	0.87 (0.10, 13.86)	2.11 (0.15, 43.74)	1.72 (0.25, 24.35)		N/A	N/A	N/A
Topiramate	3.76 (1.84, 7.82)	1.40 (0.52, 3.83)	0.64 (0.08, 3.67)	3.80 (0.97, 14.28)	1.37 (0.53, 3.54)	0.49 (0.01, 5.65)	1.92 (0.76, 4.97)	0.59 (0.11, 3.05)	10.61 (0.96, 331.60)	1.52 (0.58, 4.17)	1.92 (0.77, 4.79)	0.78 (0.15, 3.27)	0.33 (0.00, 9.74)	0.51 (0.03, 5.07)	1.48 (0.13, 14.90)	0.66 (0.04, 7.13)	0.91 (0.28, 3.01)	2.16 (0.32, 13.61)	1.80 (0.81, 4.11)	1.04 (0.07, 8.30)		N/A	N/A
Tramadol	5.57 (2.00, 19.50)	2.09 (0.60, 8.79)	0.95 (0.11, 6.91)	5.72 (1.15, 29.86)	2.04 (0.62, 8.22)	0.74 (0.02, 10.31)	2.87 (0.86, 11.39)	0.89 (0.14, 5.90)	16.38 (1.29, 581.40)	2.31 (0.66, 9.17)	2.86 (0.87, 11.37)	1.17 (0.20, 6.59)	0.50 (0.00, 16.23)	0.76 (0.05, 9.23)	2.21 (0.17, 27.87)	0.98 (0.06, 13.73)	1.37 (0.33, 6.47)	3.25 (0.41, 25.71)	2.69 (0.90, 9.73)	1.55 (0.10, 15.33)	1.51 (0.42, 6.13)		N/A
Venlafaxine	2.56 (0.93, 7.73)	0.96 (0.29, 3.45)	0.43 (0.05, 3.08)	2.59 (0.54, 12.44)	0.93 (0.28, 3.31)	0.34 (0.01, 4.68)	1.31 (0.40, 4.63)	0.41 (0.07, 2.52)	7.32 (0.80, 220.30)	1.04 (0.31, 3.82)	1.31 (0.40, 4.53)	0.53 (0.09, 2.85)	0.23 (0.00, 7.40)	0.35 (0.02, 3.83)	1.00 (0.08, 11.45)	0.45 (0.03, 5.35)	0.62 (0.15, 2.71)	1.49 (0.19, 10.54)	1.23 (0.42, 3.93)	0.71 (0.05, 6.77)	0.68 (0.20, 2.55)	0.46 (0.09, 2.05)	
Capsaicin Cream	6.18 (2.48, 16.36)	2.30 (0.75, 7.70)	1.05 (0.13, 6.56)	6.26 (1.41, 27.60)	2.26 (0.75, 7.02)	0.82 (0.02, 9.94)	3.17 (1.06, 10.08)	0.97 (0.17, 5.75)	17.86 (1.54, 571.90)	2.50 (0.83, 8.10)	3.15 (1.07, 9.60)	1.28 (0.23, 6.26)	0.54 (0.00, 16.60)	0.83 (0.05, 8.97)	2.41 (0.19, 26.96)	1.09 (0.06, 12.60)	1.50 (0.39, 5.76)	3.57 (0.50, 24.50)	2.96 (1.13, 8.39)	1.72 (0.11, 15.05)	1.64 (0.52, 5.52)	1.09 (0.24, 4.58)	2.41 (0.58, 9.72)

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 z-scores from a frequentist analysis of direct data only, the segment above and to the right of the shaded cells is left blank.



Dose-adjusted estimates are fitted at the typical maintenance values provided by the GDG, or at the mean value in the evidence base where the GDG did not provide an estimate (see Table 4 for details).

Figure 14 withdrawal due to adverse effects - relative effect of all options compared with placebo

(values less than 1 favour the treatment; values greater than 1 favour placebo; error bars are 95% credible intervals)

Table 23 withdrawal due to adverse effects - rankings for each comparator

	No dose adjustment		Dose-adjusted	
	Probability best	**Median rank (95%CrI)**	**Probability best**	**Median rank (95%CrI)**
Placebo	0.041	3 (1, 6)	0.043	3 (1, 5)
Amitriptyline	0.000	11 (5, 19)	0.000	11 (5, 18)
Cannabis Sativa Extract	0.002	19 (4, 24)	0.000	19 (5, 24)
Capsaicin Cream	0.124	3 (1, 13)	0.114	3 (1, 12)
Capsaicin Patch	0.000	12 (5, 19)	0.000	12 (6, 18)
Duloxetine	0.009	20 (2, 24)	0.005	21 (3, 24)
Escitalopram	0.001	8 (3, 15)	0.000	7 (4, 14)
Gabapentin	0.001	19 (6, 24)	0.000	20 (9, 24)
Gabapentin+Oxycodone	0.659	1 (1, 14)	0.697	1 (1, 12)
Imipramine	0.000	10 (4, 18)	0.000	10 (5, 17)
Lacosamide	0.000	8 (3, 15)	0.000	7 (4, 14)
Lamotrigine	0.000	17 (5, 24)	0.000	18 (6, 24)
Levetiracetam	0.022	22 (2, 24)	0.022	21 (2, 24)
Lidocaine (Topical)	0.003	20 (3, 24)	0.002	20 (4, 24)
Morphine	0.050	11 (1, 22)	0.052	10 (1, 22)
Nortriptyline	0.009	18 (2, 24)	0.008	18 (2, 24)
Nortriptyline+Morphine	0.000	16 (6, 22)	0.000	15 (7, 21)
Oxcarbazepine	0.060	7 (1, 21)	0.039	6 (1, 20)
Oxycodone	0.000	8 (4, 14)	0.000	8 (4, 13)
Pregabalin	0.018	15 (2, 24)	0.016	15 (2, 24)
Valproate	0.000	15 (7, 21)	0.000	15 (10, 20)
Topiramate	0.000	18 (8, 23)	0.000	19 (9, 23)
Tramadol	0.001	11 (3, 21)	0.000	11 (3, 20)
Venlafaxine	0.000	19 (11, 23)	0.000	19 (12, 23)

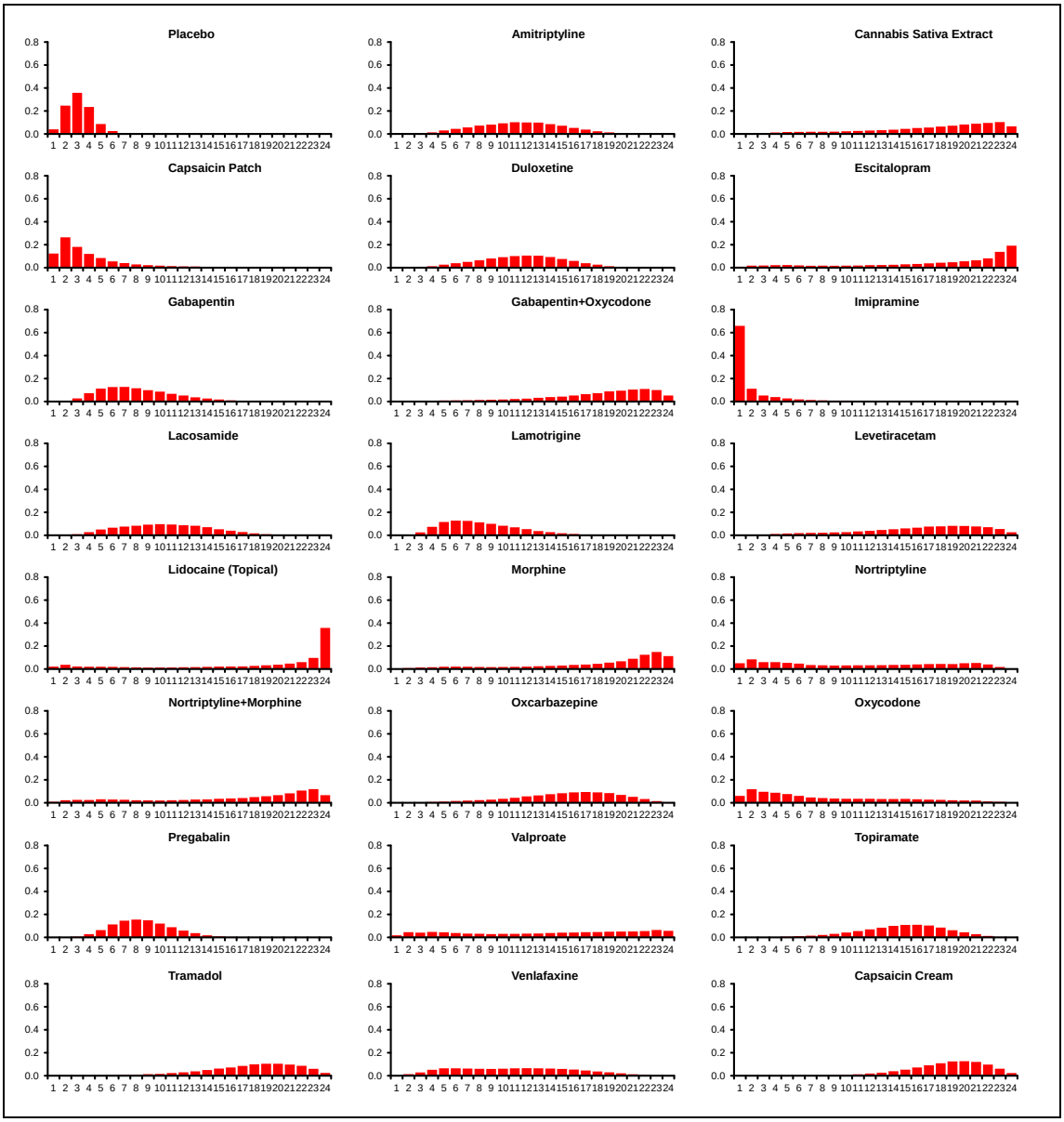


Figure 15 withdrawal due to adverse effects - rank probability histograms (no adjustment for dose)

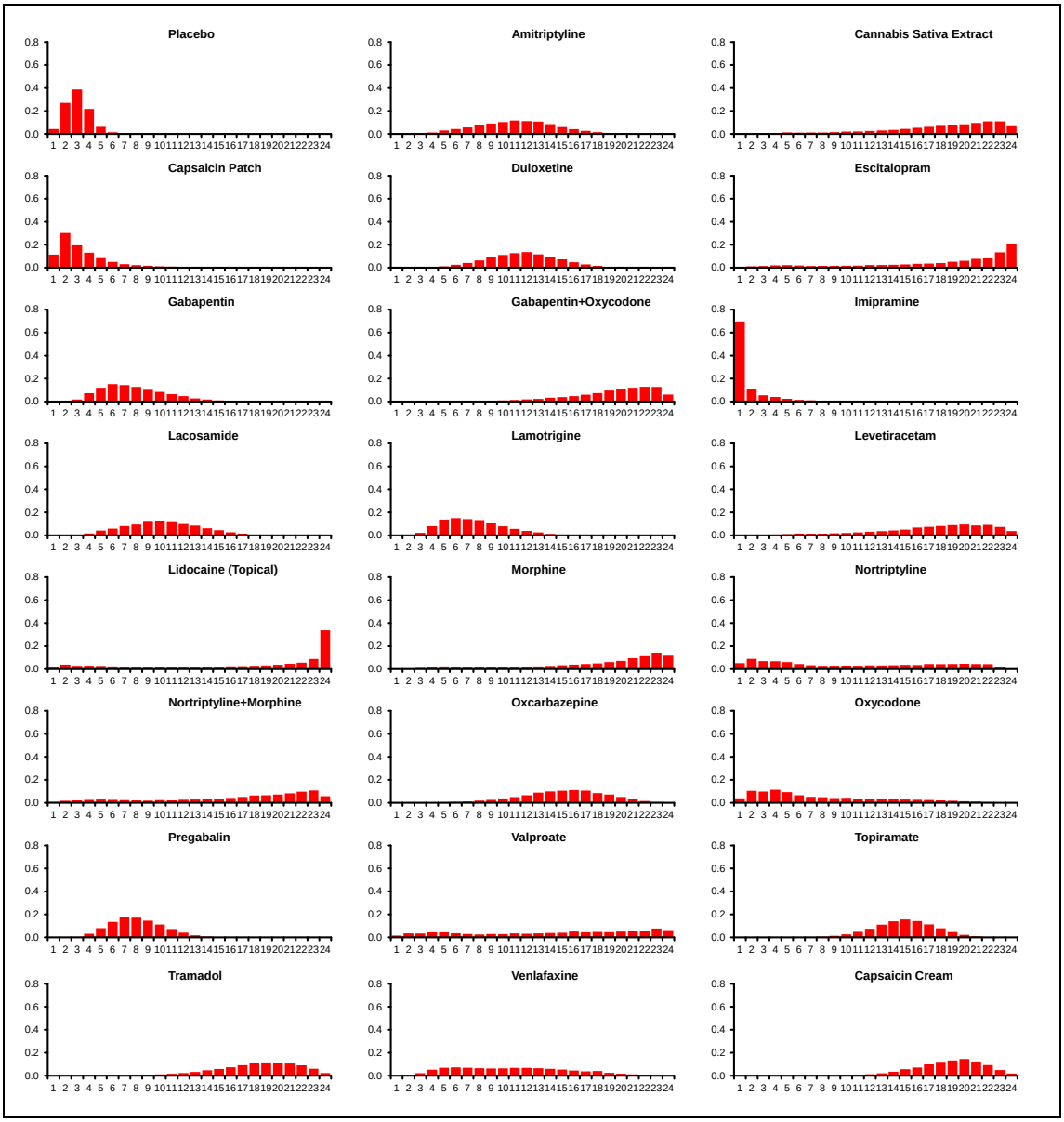


Figure 16 Withdrawal due to adverse effect(s) – rank probability histograms (dose-adjusted)

Table 24 withdrawal due to adverse effects - model fit statistics

	Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
Unadjusted	202.8 (cf. 199 datapoints)	910.3	755.7	154.6	1064.9	0.299 (95%CrI: 0.181, 0.518)
Dose-adjusted	213.7 (cf. 199 datapoints)	921.3	793.3	128.0	1049.4	0.000 (95%CrI: 0.000, 0.146)

Table 25 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.
- 50,000 burn-ins and 10,000 iterations thinned from 100,000

- Model convergence: there was poor autocorrelation for lidocaine since there was one study with small event rates and for nortriptyline, morphine and nortriptyline+morphine because the data for these interventions came mostly from one 3-armed trial with low event rates.
- Leijon and Bovie (1989) and one of the Webster et al. (2010) studies were not included in this network as they had zero events in all study arms.
- As with efficacy data (see Table 57, below), it is not straightforward to choose between these models. On the one hand, overall model fit is apparently improved in the dose-adjusted version: DIC is reduced, and the random-effects term is relied upon to explain far less of the observed heterogeneity. On the other, residual deviance rises, suggesting some data-points are poorly modelled in the dose-adjusted approach (this is particularly conspicuous for Stacey et al., 2008, a placebo-controlled control of pregabalin which has the unusual feature of a much higher dropout rate in an arm with a lower dosage of the active agent).

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)	7 RCTs[a] n=1087	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear if groups were comparable in 6 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 5 of the 6 studies

[2] I^2 was 0% for placebo vs pregabalin 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

gabapentin (n=240): Gordh et al. (2008); no concomitant drugs permitted levetiracetam (n=72): Finnerup et al. (2009); concomitant drugs apart from anti-depressants 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.

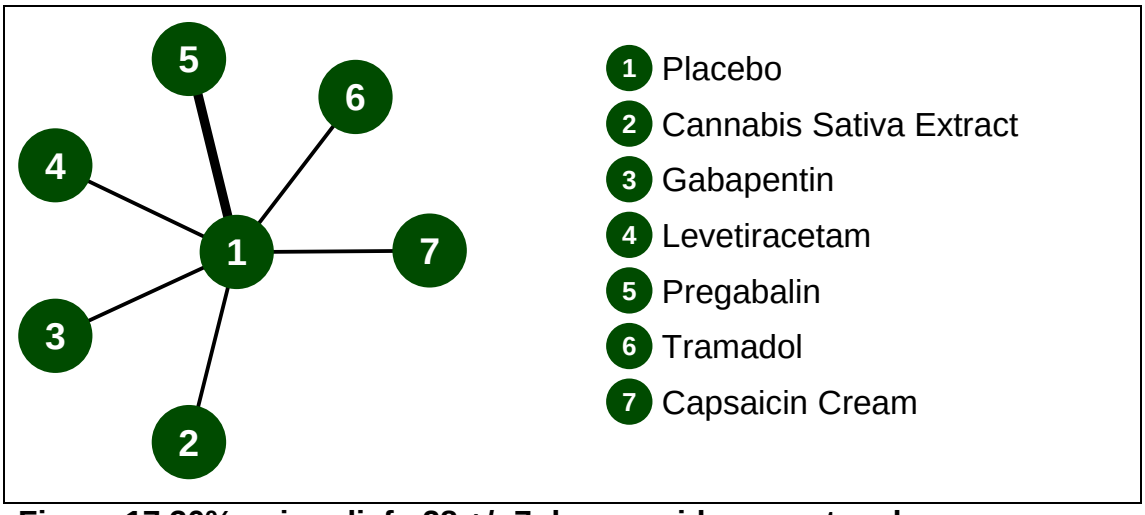


Figure 17 30% pain relief - 28 +/- 7 days - evidence network

Table 26 30% pain relief - 28 +/- 7 days - trials included in analysis

	Placebo	Cannabis Sativa Extract	Gabapentin	Levetiracetam	Pregabalin	Tramadol
Cannabis Sativa Extract	1 RCT[5] total n=125					
Gabapentin	1 RCT[3] total n=240	-				
Levetiracetam	1 RCT[2] total n=72	-	-			
Pregabalin	2 RCTs[4,7] total n=528	-	-	-		
Tramadol	1 RCT[6] total n=90	-	-	-	-	
Capsaicin Cream	1 RCT[1] total n=32	-	-	-	-	-

(1) Bernstein et al. (1989); (2) Finnerup et al. (2009); (3) Gordh et al. (2008); (4) Lesser et al. (2004); (5) Nurmikko et al. (2007); (6) Sindrup et al. (1999); (7) Stacey et al. (2008)

Table 27 30% pain relief - 28 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Gabapentin	Levetiracetam	Pregabalin	Tramadol	Capsaicin Cream
Placebo		2.00 (0.81, 4.96)	2.64 (1.32, 5.26)	0.73 (0.15, 3.51)	3.75 (2.57, 5.48)	3.59 (1.25, 10.29)	5.57 (1.13, 27.52)
Cannabis Sativa Extract	2.03 (0.40, 10.49)		-	-	-	-	-
Gabapentin	2.65 (0.58, 12.52)	1.30 (0.14, 12.50)		-	-	-	-
Levetiracetam	0.70 (0.07, 5.82)	0.35 (0.02, 5.17)	0.26 (0.02, 3.50)		-	-	-
Pregabalin	3.81 (1.51, 9.63)	1.88 (0.29, 12.36)	1.44 (0.23, 8.37)	5.46 (0.55, 60.63)		-	-
Tramadol	3.77 (0.70, 22.14)	1.86 (0.18, 20.01)	1.43 (0.15, 14.23)	5.45 (0.36, 91.59)	0.99 (0.15, 7.12)		-
Capsaicin Cream	6.18 (0.80, 62.37)	3.04 (0.23, 50.84)	2.34 (0.18, 35.96)	9.02 (0.44, 221.60)	1.62 (0.18, 19.26)	1.64 (0.11, 27.74)	

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.

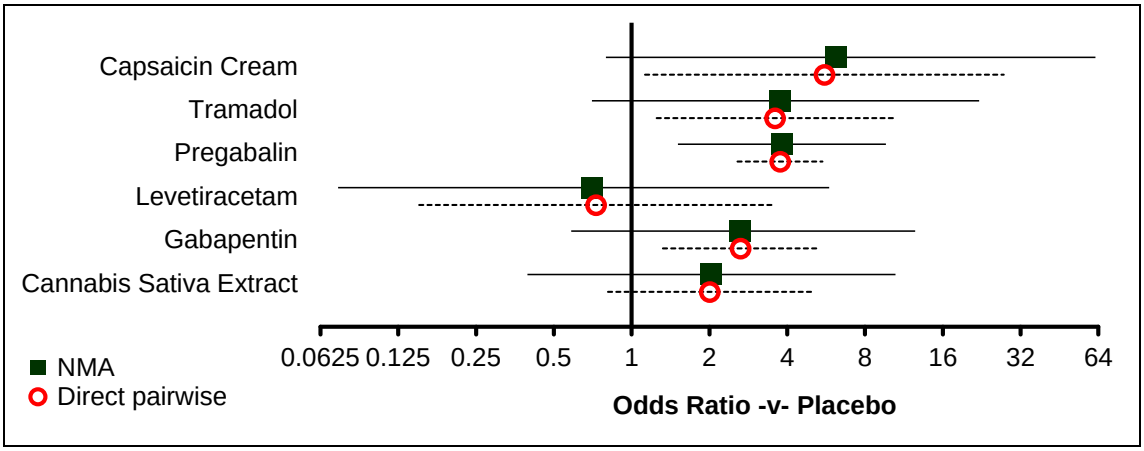


Figure 18 30% pain relief - 28 +/- 7 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 28 30% pain relief - 28 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	6 (4, 7)
Cannabis Sativa Extract	0.049	5 (1, 7)
Gabapentin	0.068	4 (1, 7)
Levetiracetam	0.013	7 (2, 7)
Pregabalin	0.129	3 (1, 5)
Tramadol	0.218	3 (1, 6)
Capsaicin Cream	0.523	1 (1, 6)

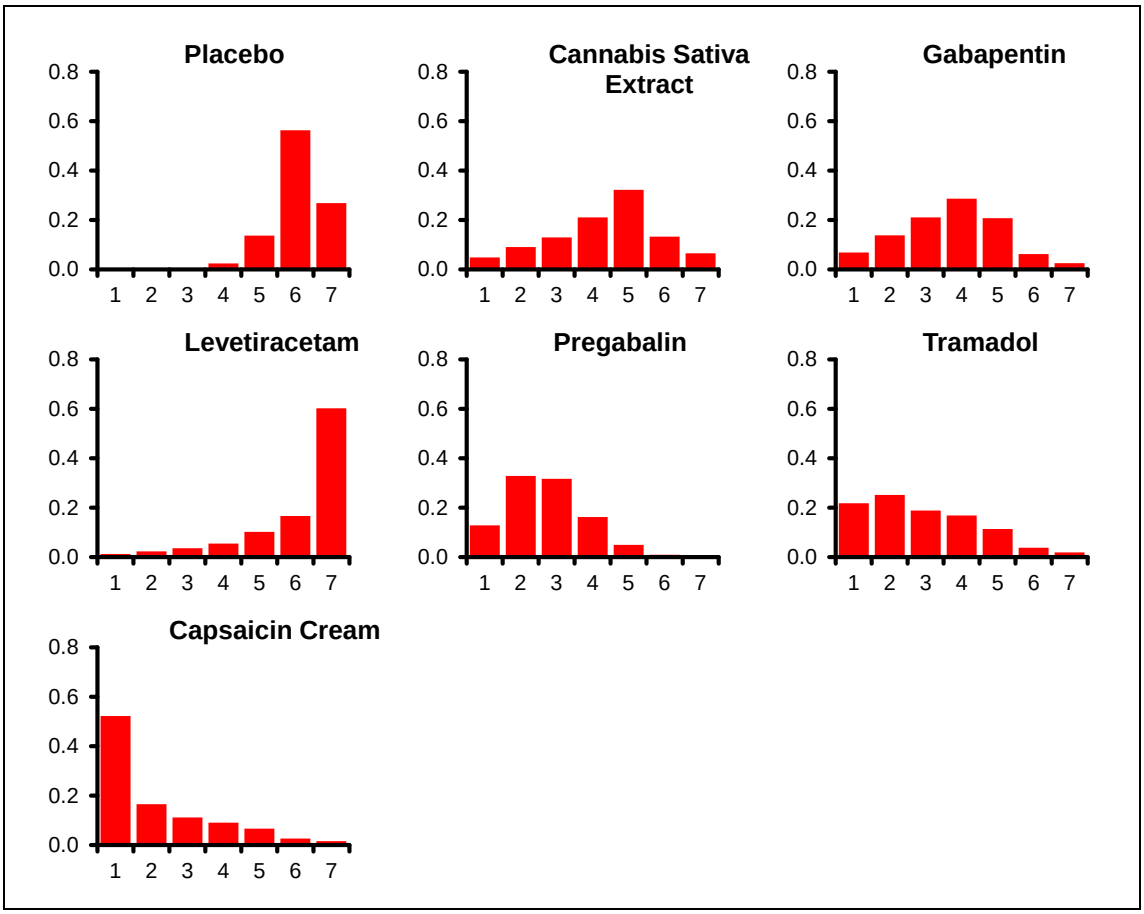


Figure 19 30% pain relief - 28 +/- 7 days - rank probability histograms

Table 29 30% pain relief - 28 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
15.97 (compared to 16 data-points)	82.278	67.363	14.916	97.194	0.000 (95%CI: 0.000, 4.252)

Table 30 30% pain relief - 28 +/- 7 days - 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=1234	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] three studies do not report about allocation concealment; treatment groups were not comparable at baseline in two studies and it was unclear if groups were comparable in two; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 80% for pregabalin vs placebo which may indicate considerable heterogeneity between the studies that make this comparison and 0% for capsaicin patch vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons with only one trial); 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] 3 of 5 links in the network are connected with only one trial (same trial with 3 links) which also provides the only head-to-head comparison; wide confidence intervals for the effect estimates of all interventions compared to placebo and for overall rankings within the network (most interventions could have any ranking)

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

amitriptyline (n=76): 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)

capsaicin patch (n=402): Backonja et al. (2008); concomitant drugs were permitted apart from topical medications

gabapentin (n=76): 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)

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

Head-to-head comparisons:

amitriptyline vs gabapentin (n=76): 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.

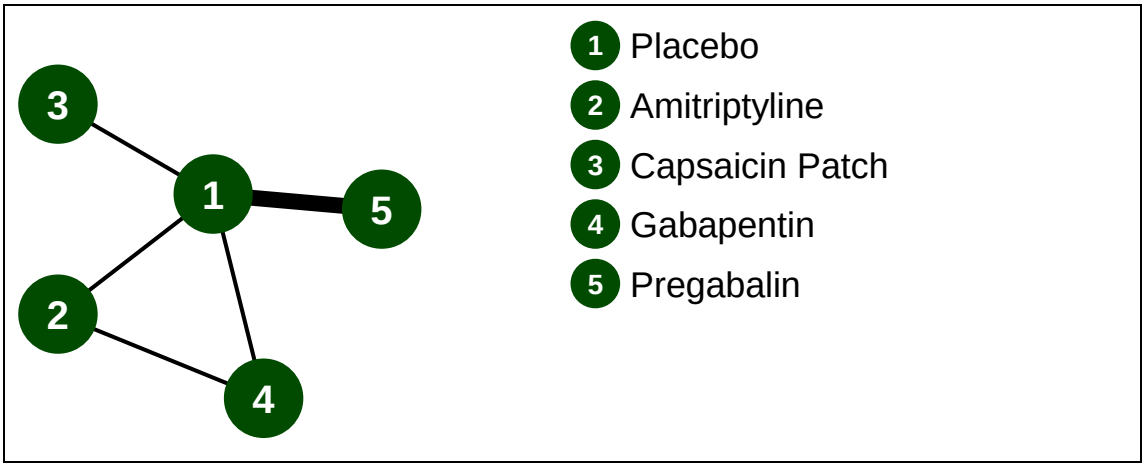


Figure 20 30% pain relief - 56 +/- 7 days - evidence network

Table 31 30% pain relief - 56 +/- 7 days - trials included in analysis

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin
Amitriptyline	1 RCT[5] total n=76			
Capsaicin Patch	1 RCT[1] total n=402	-		
Gabapentin	1 RCT[5] total n=76	1 RCT[5] total n=76	-	
Pregabalin	3 RCTs[2,3,4] total n=718	-	-	-

(1) Backonja et al. (2008); (2) Dworkin et al. (2003); (3) Guan et al. (2011); (4) Moon et al. (2010); (5) Rintala et al. (2007)

Table 32 30% pain relief - 56 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Pregabalin
Placebo		2.04 (0.70, 5.95)	1.57 (1.04, 2.36)	1.00 (0.31, 3.19)	2.20 (1.06, 4.59)
Amitriptyline	2.09 (0.04, 124.80)		-	0.49 (0.17, 1.42)	-
Capsaicin Patch	1.57 (0.03, 84.68)	0.75 (0.00, 231.80)		-	-
Gabapentin	0.99 (0.02, 62.12)	0.47 (0.01, 28.56)	0.62 (0.00, 192.60)		-
Pregabalin	2.21 (0.22, 22.89)	1.06 (0.01, 113.40)	1.41 (0.01, 139.90)	2.24 (0.02, 235.70)	

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.

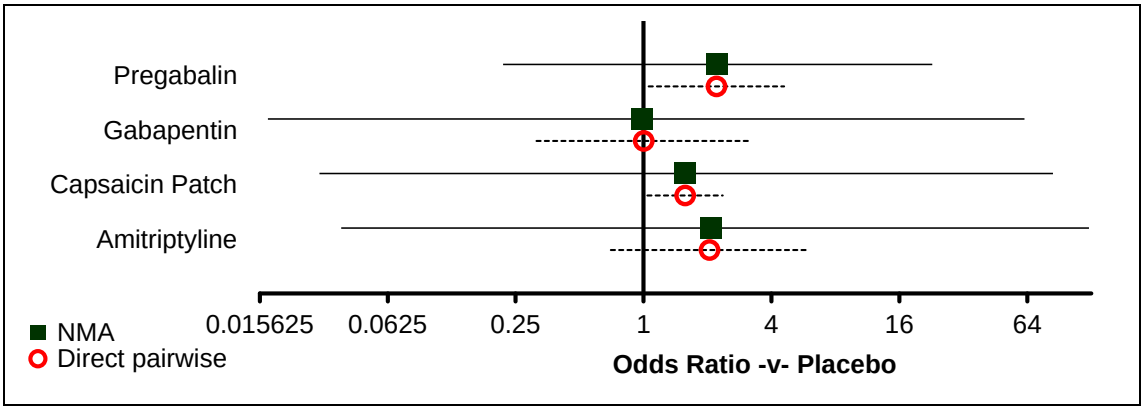


Figure 21 30% pain relief - 56 +/- 7 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 33 30% pain relief - 56 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.015	4 (2, 5)
Amitriptyline	0.331	2 (1, 5)
Capsaicin Patch	0.231	3 (1, 5)
Gabapentin	0.109	4 (1, 5)
Pregabalin	0.315	2 (1, 5)

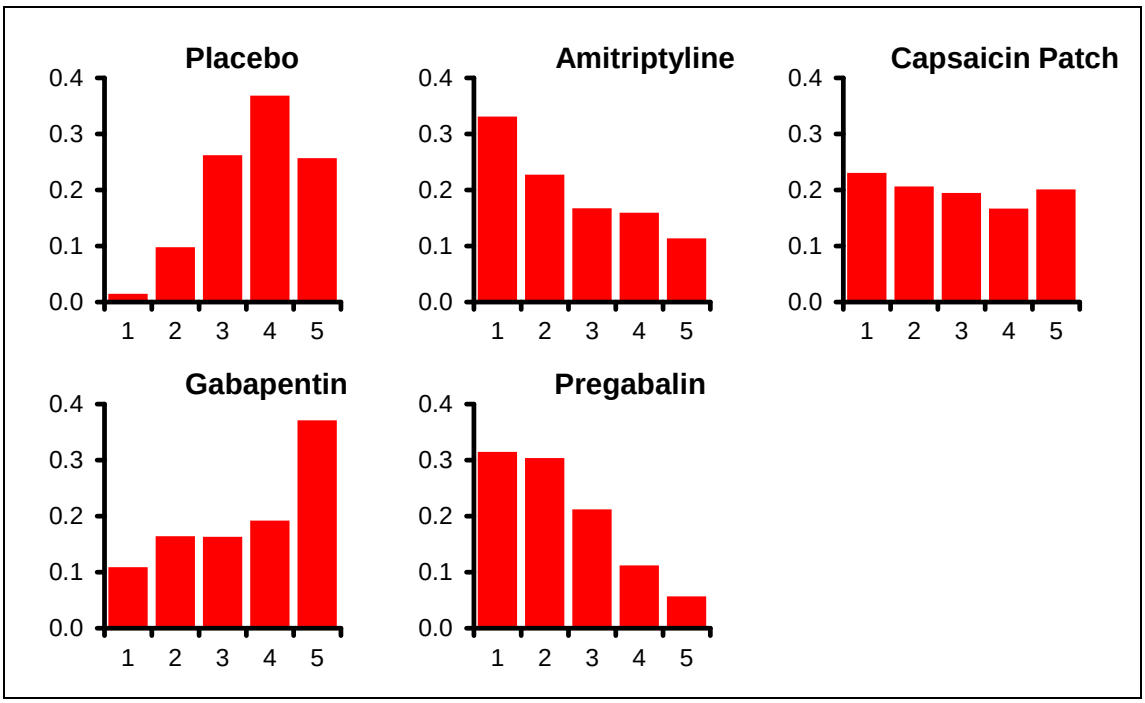


Figure 22 30% pain relief - 56 +/- 7 days - rank probability histograms

Table 34 30% pain relief - 56 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
11.32 (compared to 11 data-points)	64.318	53.208	11.11	75.428	0.016 (95%CI: 0.058, 18.947)

Table 35 30% pain relief - 56 +/- 7 days - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
- The GDG noted that gabapentin came out poorly in this synthesis but also noted that it was based on a poor quality study (Rintala et al. [2007]).

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)	18 RCTs[a] n=4840	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 four studies and it was unclear if groups were comparable in nine; 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; 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=2073): Backonja et al. (2008), Clifford et al. (2012),, Irving et al. (2011), Webster et al. (2010), Webster et al. (2010), Simpson et al (2008); 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=263): Breuer et al. (2007), Simpson et al. (2003); concomitant drugs permitted in both but with the exception of anti-convulsants in one

pregabalin (n=1145): Freynhagen et al. (2005), Siddall et al. (2006), 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.

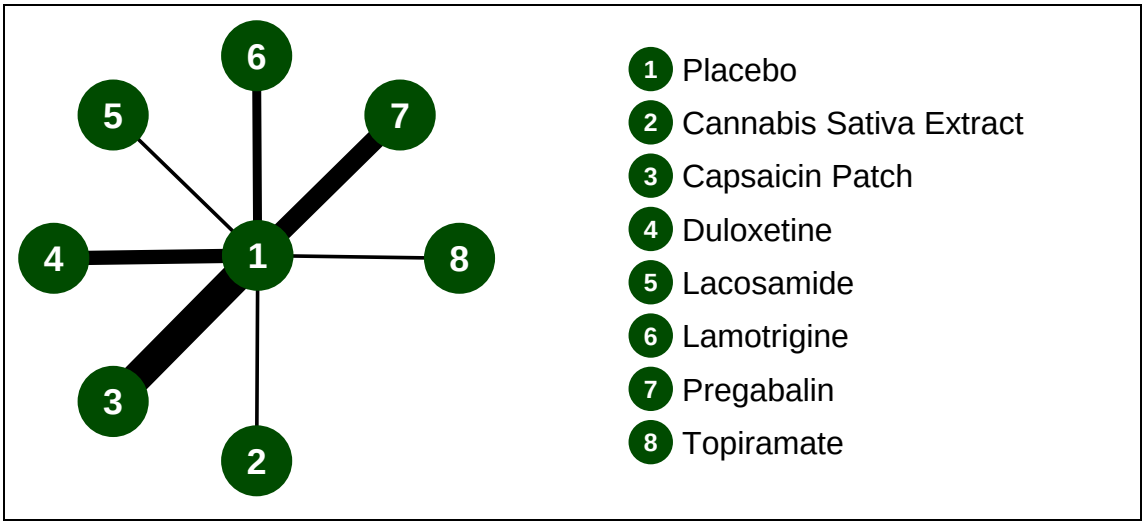


Figure 23 30% pain relief - 84 +/- 14 days - evidence network

Table 36 30% pain relief - 84 +/- 14 days - 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[1,3,6,12,15,16] total n=2073	-					
Duloxetine	3 RCTs[5,17,18] total n=887	-	-				
Lacosamide	1 RCT[8] total n=119	-	-	-			
Lamotrigine	2 RCTs[2,11] total n=263	-	-	-	-		
Pregabalin	4 RCTs[4,10,13,14] total n=1145	-	-	-	-	-	
Topiramate	1 RCT[7] total n=323	-	-	-	-	-	-

(1) Backonja et al. (2008); (2) Breuer et al. (2007); (3) Clifford et al. (2012); (4) Freynhagen et al. (2005); (5) Gao et al. (2010); (6) Irving et al. (2011); (7) Raskin et al. (2004); (8) Rauck et al. (2007); (9) Selvarajah et al. (2010); (10) Siddall et al. (2006); (11) Simpson et al. (2003); (12) Simpson et al. (2008); (13) Simpson et al. (2010); (14) van Seventer et al. (2006); (15) Webster et al. (2010); (16) Webster et al. (2010); (17) Wernicke et al. (2006); (18) Yasuda et al. (2011)

Table 37 30% pain relief - 84 +/- 14 days - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Lacosamide	Lamotrigine	Pregabalin	Topiramate
Placebo		0.76 (0.18, 3.24)	1.50 (1.24, 1.82)	2.17 (1.56, 3.01)	1.45 (0.70, 3.00)	2.15 (1.21, 3.81)	2.35 (1.21, 4.57)	1.81 (1.12, 2.91)
Cannabis Sativa Extract	0.75 (0.14, 3.75)		-	-	-	-	-	-
Capsaicin Patch	1.52 (1.12, 2.06)	2.02 (0.40, 10.92)		-	-	-	-	-
Duloxetine	2.19 (1.42, 3.37)	2.92 (0.55, 16.27)	1.44 (0.85, 2.45)		-	-	-	-
Lacosamide	1.45 (0.55, 3.80)	1.94 (0.29, 13.12)	0.96 (0.35, 2.62)	0.66 (0.23, 1.90)		-	-	-
Lamotrigine	2.24 (1.03, 5.09)	2.98 (0.51, 19.25)	1.48 (0.64, 3.53)	1.02 (0.42, 2.61)	1.55 (0.45, 5.45)		-	-
Pregabalin	2.27 (1.53, 3.57)	3.04 (0.59, 17.13)	1.50 (0.91, 2.58)	1.04 (0.58, 1.96)	1.57 (0.56, 4.60)	1.01 (0.42, 2.52)		-
Topiramate	1.81 (0.82, 4.01)	2.42 (0.40, 15.15)	1.20 (0.51, 2.80)	0.83 (0.34, 2.05)	1.25 (0.36, 4.39)	0.81 (0.26, 2.46)	0.80 (0.32, 1.93)	

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.

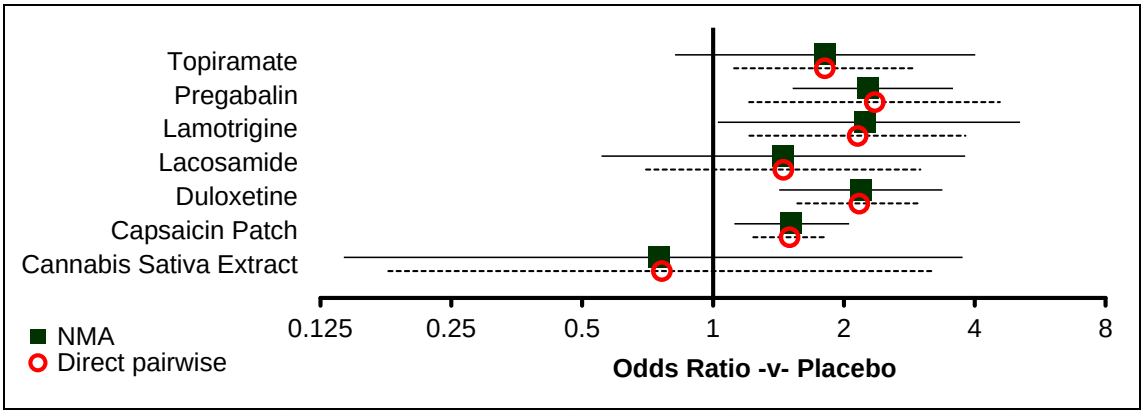


Figure 24 30% pain relief - 84 +/- 14 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 38 30% pain relief - 84 +/- 14 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	7 (6, 8)
Cannabis Sativa Extract	0.050	8 (1, 8)
Capsaicin Patch	0.002	5 (3, 7)
Duloxetine	0.184	3 (1, 6)
Lacosamide	0.086	5 (1, 8)
Lamotrigine	0.315	3 (1, 7)
Pregabalin	0.225	2 (1, 5)
Topiramate	0.138	4 (1, 7)

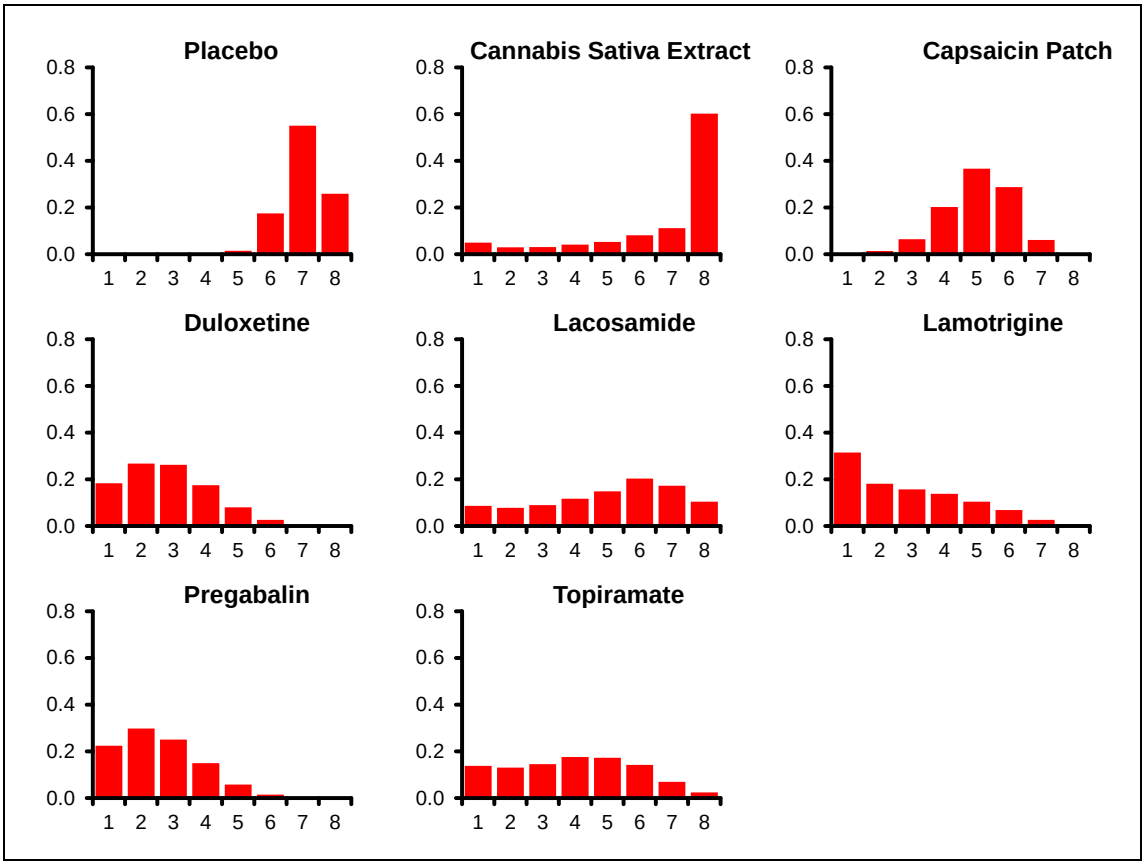


Figure 25 30% pain relief - 84 +/- 14 days - rank probability histograms

Table 39 30% pain relief - 84 +/- 14 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
47.49 (compared to 47 data-points)	273.018	236.704	36.314	309.332	0.005 (95%CI: 0.008, 0.268)

Table 40 30% pain relief - 84 +/- 14 days - 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)	8 RCTs[a] n=1181	very serious[1]	not serious[2]	not serious[3]	very serious[4]	very low	Important

[1] more than half of studies were crossover studies; it was unclear if treatment groups were comparable at baseline in all studies, particularly for concomitant drug use; baseline pain severity and concomitant drugs permitted varies across the studies in the network; insufficient follow-up in all but one study

[2] I^2 was 0% for pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity no 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 (particularly for morphine, levetiracetam, tramadol, cannabis sativa extract which is likely due to small studies) and for overall rankings within the network

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

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

gabapentin (n=240): Gordh et al. (2008); no concomitant drugs permitted levetiracetam (n=72): Finnerup et al. (2009); concomitant drugs permitted with the exception of anti-depressants

morphine (n=24): Huse et al. (2001); unclear if 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.

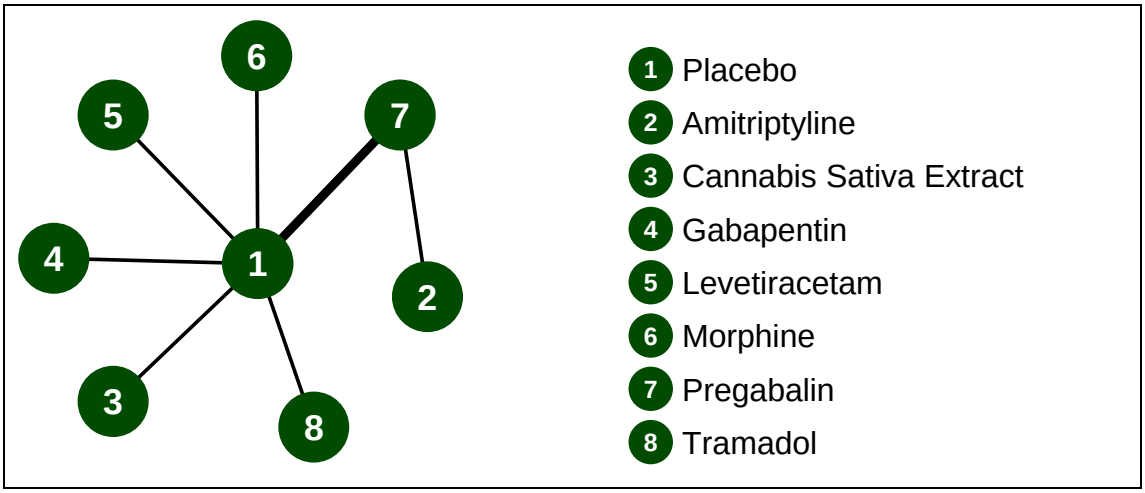


Figure 26 50% pain relief - 28 +/- 7 days - evidence network

Table 41 50% pain relief - 28 +/- 7 days - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Gabapentin	Levetiracetam	Morphine	Pregabalin
Amitriptyline	-						
Cannabis Sativa Extract	1 RCT[6] total n=125	-					
Gabapentin	1 RCT[3] total n=240		-				
Levetiracetam	1 RCT[2] total n=72	-	-	-			
Morphine	1 RCT[4] total n=24	-	-	-	-		
Pregabalin	2 RCTs[5,8] total n=528	1 RCT[1] total n=102	-	-	-	-	
Tramadol	1 RCT[7] total n=90	-					

(1) Bansal et al. (2009); (2) Finnerup et al. (2009); (3) Gordh et al. (2008); (4) Huse et al. (2001); (5) Lesser et al. (2004); (6) Nurmikko et al. (2007); (7) Sindrup et al. (1999); (8) Stacey et al. (2008)

Table 42 50% pain relief - 28 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Gabapentin	Levetiracetam	Morphine	Pregabalin	Tramadol
Placebo		-	2.96 (0.99, 8.90)	3.14 (1.34, 7.38)	1.00 (0.06, 16.63)	7.86 (0.75, 82.13)	3.67 (2.39, 5.63)	4.53 (1.17, 17.55)
Amitriptyline	2.21 (0.50, 10.16)		-	-	-	-	1.68 (0.74, 3.82)	-
Cannabis Sativa Extract	3.12 (0.68, 15.30)	1.42 (0.17, 12.49)		-	-	-	-	-2288
Gabapentin	3.23 (0.89, 12.79)	1.47 (0.20, 11.15)	1.04 (0.13, 7.91)		-	-	-	-
Levetiracetam	0.96 (0.02, 52.61)	0.44 (0.01, 33.44)	0.31 (0.00, 22.83)	0.30 (0.00, 20.07)		-	-	-
Morphine	11.64 (0.96, 429.90)	5.37 (0.28, 265.70)	3.82 (0.19, 192.10)	3.69 (0.20, 168.20)	12.72 (0.12, 2226.00)		-	-
Pregabalin	3.73 (1.78, 8.11)	1.70 (0.46, 6.20)	1.20 (0.21, 6.46)	1.16 (0.24, 5.12)	3.89 (0.06, 226.00)	0.32 (0.01, 4.44)		-
Tramadol	4.82 (0.97, 33.09)	2.24 (0.24, 24.97)	1.56 (0.16, 17.85)	1.49 (0.18, 15.03)	5.11 (0.07, 416.80)	0.41 (0.01, 9.91)	1.31 (0.22, 10.07)	

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.

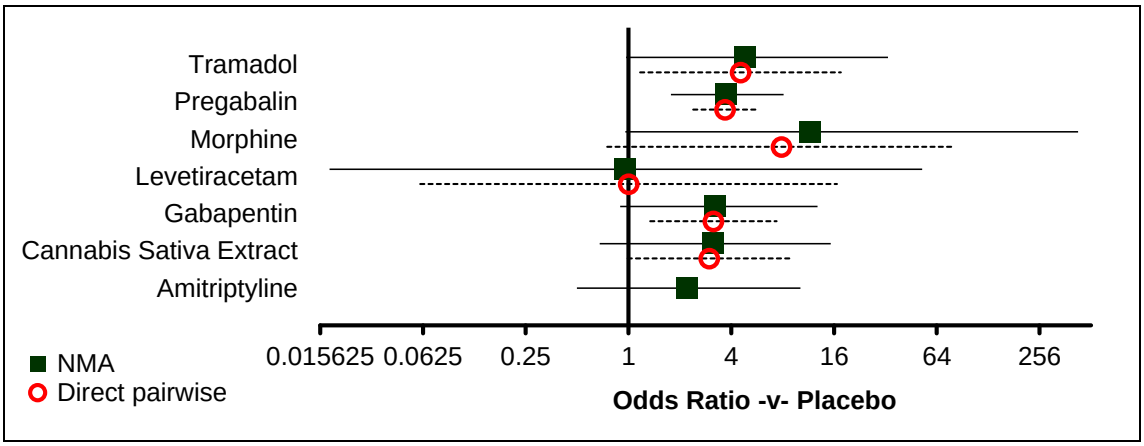


Figure 27 50% pain relief - 28 +/- 7 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 43 50% pain relief - 28 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	7 (6, 8)
Amitriptyline	0.020	6 (2, 8)
Cannabis Sativa Extract	0.063	4 (1, 8)
Gabapentin	0.050	4 (1, 7)
Levetiracetam	0.078	7 (1, 8)
Morphine	0.579	1 (1, 7)
Pregabalin	0.030	4 (1, 6)
Tramadol	0.181	3 (1, 7)

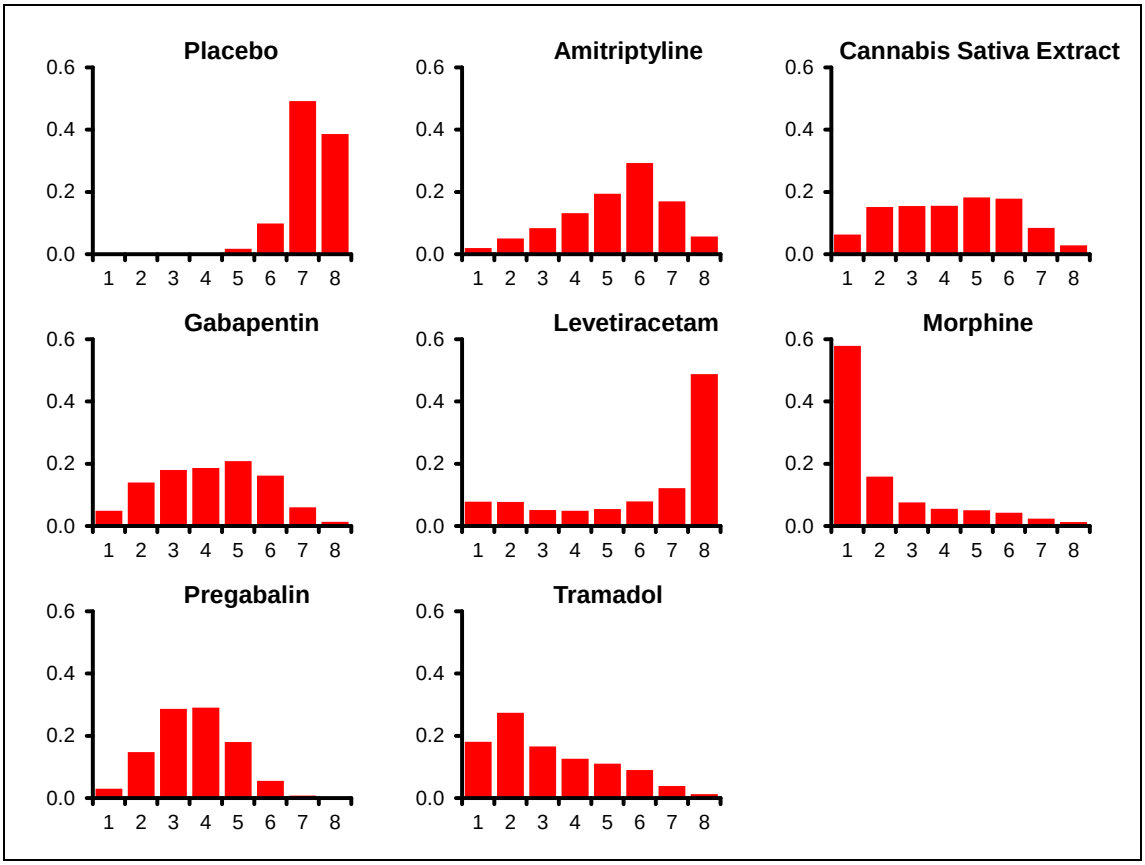


Figure 28 50% pain relief - 28 +/- 7 days - rank probability histograms

Table 44 50% pain relief - 28 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
17.4 (compared to 18 data-points)	86.376	70.353	16.023	102.399	0.000 (95%CI: 0.000, 2.732)

Table 45 50% pain relief - 28 +/- 7 days - notes

- Random-effects model was used.
- 30000 burn-ins and 50000 iterations.
- Model convergence: autocorrelation relatively poor for levetiracetam and morphine because of low event rates in the studies (1 in placebo arm in both).

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

Please see Appendix H (peripheral pain) for this outcome (only studies with peripheral pain reported this outcome at this time point).

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)	16 RCTs[a] n=5866	serious[1]	serious[2]	not serious[3]	serious[4]	Very low	Important

[1] group were not comparable at baseline in 3 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=1854): Freynhagen et al. (2005), Satoh et al. (2011), Siddall et al. (2006), 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.

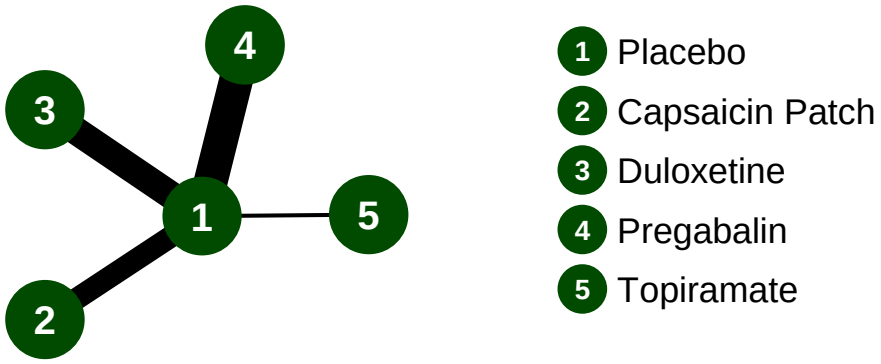


Figure 29 50% pain relief - 84 +/- 14 days - evidence network

Table 46 50% pain relief - 84 +/- 14 days - trials included in analysis

	Placebo	Capsaicin Patch	Duloxetine	Pregabalin
Capsaicin Patch	4 RCTs[4,5,13,14] total n=1997			
Duloxetine	5 RCTs[2,3,7,15,16] total n=1692	-		
Pregabalin	6 RCTs[1,8,9,10,11,12] total n=1854	-	-	
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) Siddall et al. (2006); (10) Simpson et al. (2010); (11) Tolle et al. (2008); (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 47 50% pain relief - 84 +/- 14 days - 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)	1.93 (1.16, 3.21)	1.98 (1.15, 3.39)
Capsaicin Patch	1.66 (1.14, 2.47)		-	-	-
Duloxetine	2.33 (1.70, 3.22)	1.41 (0.85, 2.30)		-	-
Pregabalin	1.84 (1.34, 2.65)	1.11 (0.68, 1.88)	0.79 (0.51, 1.29)		-
Topiramate	2.00 (0.90, 4.51)	1.21 (0.49, 2.93)	0.86 (0.36, 2.05)	1.09 (0.44, 2.56)	

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.

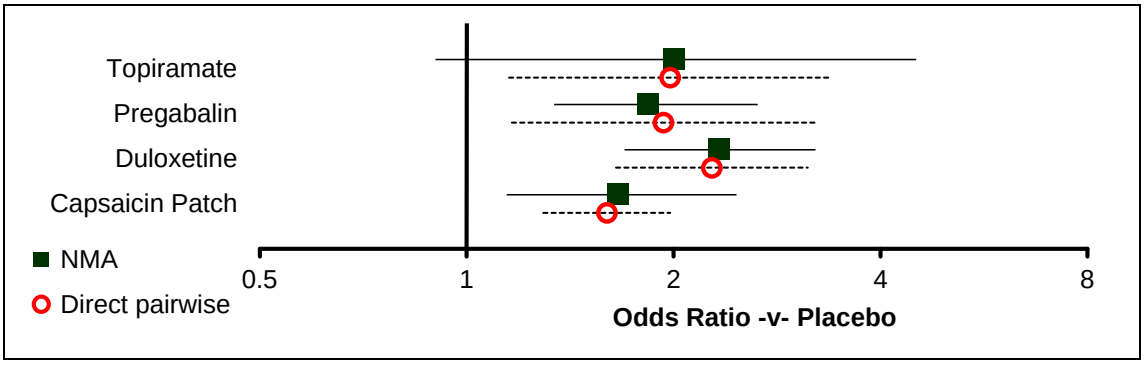


Figure 30 50% pain relief - 84 +/- 14 days - relative effect of all options compared with placebo

(values less than 1 favour placebo; values greater than 1 favour the treatment; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 48 50% pain relief - 84 +/- 14 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	5 (4, 5)
Capsaicin Patch	0.041	3 (1, 4)
Duloxetine	0.539	1 (1, 3)
Pregabalin	0.087	3 (1, 4)
Topiramate	0.333	2 (1, 5)

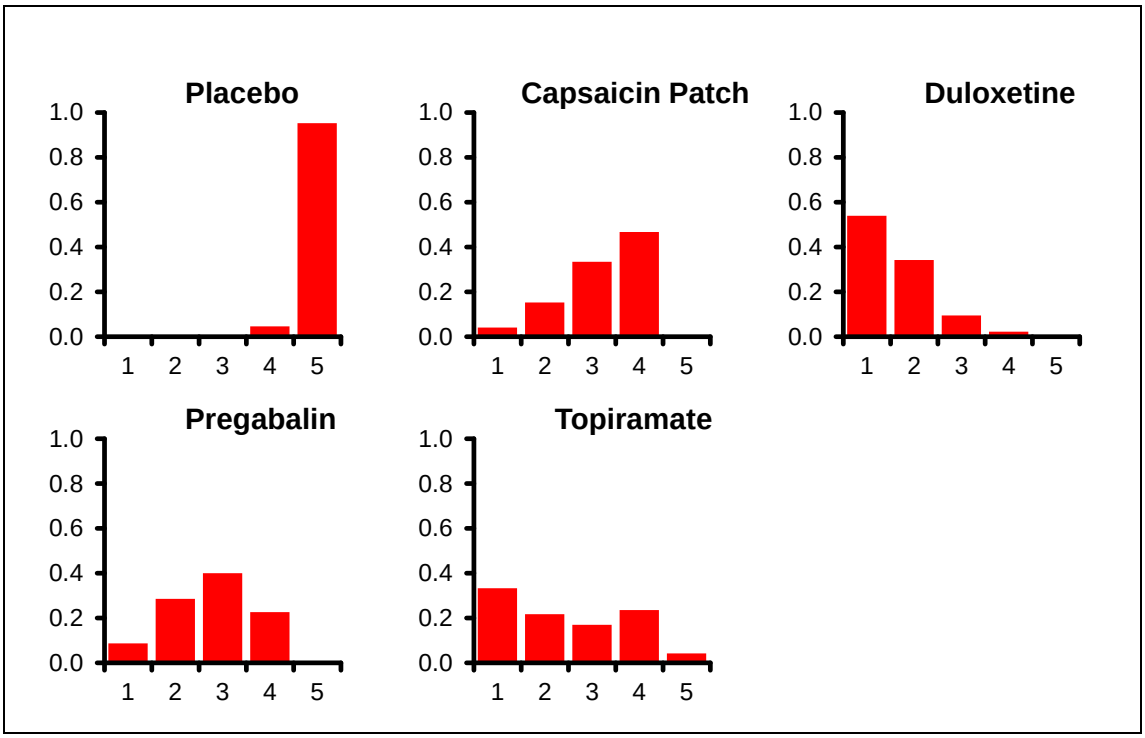


Figure 31 50% pain relief - 84 +/- 14 days - rank probability histograms

Table 49 50% pain relief - 84 +/- 14 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
47.46 (compared to 45 data-points)	268.615	236.758	31.857	300.473	0.009 (95%CrI: 0.004, 0.244)

Table 50 50% pain relief - 84 +/- 14 days - 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 6: Network meta-analysis for 30% and 50% pain relief at all time-points

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
≥ 30 and ≥ 50% pain relief on any scale at all time-points	49 RCTs[a] n=20115	serious[1]	not serious[2]	not serious[3]	serious[4]	low	Important

[1] 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 (the 'loops' in the network)

[3] all aspects of PICO conform to review protocol

[4] there are few head-to-head trials; wide confidence intervals for the overall ranking within the network

[a] Placebo-controlled trials:

amitriptyline (n= 76): Rintala et al. (2007)

cannabis sativa extract (n= 250): Nurmikko et al. (2007)

capsaicin patch (n=4890): Backonja et al. (2008), Clifford et al. (2012), Irving et al. (2011), Webster et al. (2010), Webster et al. (2010)

duloxetine (n= 2579): Gao et al. (2010), Goldstein et al. (2005), Raskin et al. (2005); Wernicke et al. (2006), Yasuda et al. (2011)

gabapentin (n= 890): Gordh et al. (2008), Rauck et al. (2007), Rintala et al. (2007)

lacosamide (n=1753): Rauck et al. (2007), Shaibani et al. (2009), Ziegler et al. (2010)

lamotrigine (n=1790): Eisenberg et al. (2001), Luria et al. (2000), Vinik et al. (2007), Simpson et al. (2003), Vinik et al. (2007), Breuer et al. (2007)

levetiracetam (n=144): Finnerup et al. (2009)

morphine (n=248): Huse et al. (2001), Wu et al. (2008)

oxycarbazepine (n=292): Dogra et al. (2005)

pregabalin (n=5816): 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), Siddall et al. (2006), Stacey et al. (2008), Tolle et al. (2008), Simpson et al. (2010), van Seventer et al. (2006)

topiramate (n=646): Raskin et al. (2004)

tramadol (n=305): Boureau et al. (2003), Sindrup et al. (1999)

venlafaxine (n=245): Rowbotham et al. (2004)

capsaicin cream (n=57): Bernstein et al. (1989), Watson & Evans (1992)

Head-to-head trials:

Gabapentin vs amitriptyline (n=76): Rintala et al. (2007)

Nortriptyline vs gabapentin (n=70): Chandra et al. (2006)

Pregabalin vs amitriptyline (n=102): Bansal et al. (2009)

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

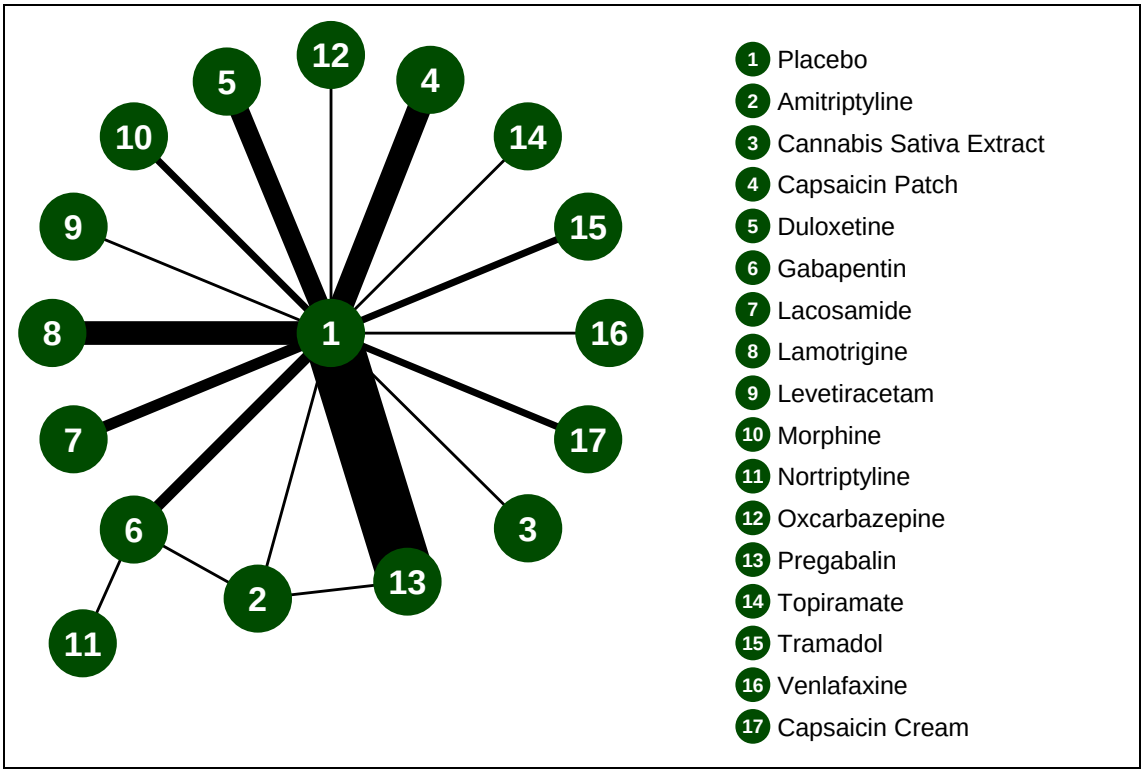


Figure 32 30% and 50% pain relief at all time-points – evidence network

Table 51 30% and 50% pain relief at all time-points – trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine
Amitriptyline	1 RCT[47] total n=76															
Cannabis Extract	1 RCT[20] total n=250	-														
Capsaicin Patch	6 RCTs[1,5,8,16,33,50] total n=2943	-	-													
Duloxetine	5 RCTs[13,14,21,30,39] total n=2579	-	-	-												
Gabapentin	3 RCTs[3,24,47] total n=890	1 RCT[47] total n=76	-	-	-											
Lacosamide	3 RCTs[23,36,37] total n=1753	-	-	-	-	-										
Lamotrigine	6 RCTs[11,18,32,35,42,44] total n=1790	-	-	-	-	-	-									
Levetiracetam	1 RCT[45] total n=144	-	-	-	-	-	-	-								
Morphine	2 RCTs[46,49] total n=248	-	-	-	-	-	-	-	-							
Nortriptyline	-	-	-	-	-	1 RCT[6] total n=70	-	-	-	-						

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine
Oxcarbazepine	1 RCT[9] total n=292	-	-	-	-	-	-	-	-	-	-					
Pregabalin	14 RCTs[7,10,12,15,17,19,25,26,28,29,31,34,40,41] total n=5816	1 RCT[43] total n=102	-	-	-	-	-	-	-	-	-	-				
Topiramate	1 RCT[22] total n=646	-	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	2 RCTs[4,48] total n=305	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	1 RCT[27] total n=245	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Capsaicin Cream	2 RCTs[2,38] total n=57	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(1) Backonja et al. (2008); (2) Bernstein et al. (1989); (3) Gordh et al. (2008); (4) Boureau et al. (2003); (5) Webster et al. (2010); (6) Chandra et al. (2006); (7) Stacey et al. (2008); (8) Clifford et al. (2012); (9) Dogra et al. (2005); (10) Dworkin et al. (2003); (11) Eisenberg et al. (2001); (12) Freynhagen et al. (2005); (13) Gao et al. (2010); (14) Goldstein et al. (2005); (15) Guan et al. (2011); (16) Irving et al. (2011); (17) Lesser et al. (2004); (18) Luria et al. (2000); (19) Moon et al. (2010); (20) Nurmikko et al. (2007); (21) Raskin et al. (2005); (22) Raskin et al. (2004); (23) Rauck et al. (2007); (24) Rice & Maton (2001); (25) Richter et al. (2005); (26) Rosenstock et al. (2004); (27) Rowbotham et al. (2004); (28) Sabatowski et al. (2004); (29) Satoh et al. (2011); (30) Wernicke et al. (2006); (31) Simpson et al. (2010); (32) Vinik et al. (2007); (33) Webster et al. (2010); (34) van Seventer et al. (2006); (35) Simpson et al. (2003); (36) Shaibani et al. (2009); (37) Ziegler et al. (2010); (38) Watson & Evans (1992); (39) Yasuda et al. (2011); (40) Tolle et al. (2008); (41) Siddall et al. (2006); (42) Vinik et al. (2007); (43) Bansal et al. (2009); (44) Breuer et al. (2007); (45) Finnerup et al. (2009); (46) Huse et al. (2001); (47) Rintala et al. (2007); (48) Sindrup et al. (1999); (49) Wu et al. (2008); (50) Simpson et al. (2008)

Table 52 30% and 50% pain relief at all time-points – relative effectiveness of all pairwise combinations (z-scores)

	Placebo	Amitriptyline	Cannabis Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine
Amitriptyline	-0.43 (-0.87,0.02)		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 Extract	-0.47 (-1.08,0.15)	-0.04 (-0.81,0.72)		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	-0.27 (-0.44,-0.10)	0.16 (-0.32,0.64)	0.20 (-0.44,0.83)		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	-0.53 (-0.71,-0.34)	-0.10 (-0.58,0.38)	-0.06 (-0.70,0.58)	-0.26 (-0.51,0.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin	-0.44 (-0.75,-0.13)	-0.01 (-0.51,0.48)	0.02 (-0.66,0.71)	-0.17 (-0.53,0.19)	0.08 (-0.27,0.45)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lacosamide	-0.23 (-0.50,0.04)	0.19 (-0.32,0.71)	0.23 (-0.44,0.91)	0.04 (-0.28,0.36)	0.29 (-0.03,0.62)	0.21 (-0.20,0.62)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lamotrigine	-0.24 (-0.47,-0.01)	0.19 (-0.32,0.69)	0.23 (-0.43,0.89)	0.03 (-0.26,0.32)	0.29 (-0.01,0.58)	0.20 (-0.19,0.58)	-0.01 (-0.36,0.34)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Levetiracetam	0.16 (-0.72,1.06)	0.58 (-0.40,1.59)	0.62 (-0.45,1.72)	0.43 (-0.47,1.34)	0.69 (-0.22,1.61)	0.60 (-0.34,1.56)	0.39 (-0.53,1.33)	0.40 (-0.51,1.32)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	-0.70 (-1.22,-0.19)	-0.27 (-0.96,0.40)	-0.23 (-1.04,0.58)	-0.43 (-0.98,0.11)	-0.17 (-0.73,0.37)	-0.26 (-0.87,0.34)	-0.46 (-1.06,0.12)	-0.46 (-1.03,0.10)	-0.86 (-1.89,0.16)		N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	-0.59 (-1.40,0.21)	-0.17 (-1.06,0.73)	-0.12 (-1.15,0.90)	-0.32 (-1.14,0.50)	-0.07 (-0.90,0.76)	-0.15 (-0.90,0.59)	-0.36 (-1.21,0.49)	-0.36 (-1.19,0.48)	-0.75 (-1.95,0.44)	0.10 (-0.85,1.08)		N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	-0.48 (-1.02,0.06)	-0.05 (-0.76,0.65)	-0.01 (-0.83,0.80)	-0.21 (-0.78,0.36)	0.05 (-0.53,0.62)	-0.04 (-0.67,0.59)	-0.25 (-0.85,0.36)	-0.24 (-0.82,0.35)	-0.64 (-1.68,0.40)	0.22 (-0.52,0.97)	0.11 (-0.87,1.09)		N/A	N/A	N/A	N/A
Pregabalin	-0.53 (-0.66,-0.41)	-0.11 (-0.55,0.34)	-0.07 (-0.69,0.56)	-0.27 (-0.48,-0.05)	-0.01 (-0.24,0.22)	-0.09 (-0.43,0.23)	-0.30 (-0.60,-0.01)	-0.30 (-0.56,-0.04)	-0.69 (-1.60,0.20)	0.16 (-0.37,0.70)	0.06 (-0.76,0.87)	-0.06 (-0.61,0.50)		N/A	N/A	N/A
Topiramate	-0.39 (-0.85,0.08)	0.04 (-0.60,0.67)	0.08 (-0.69,0.86)	-0.12 (-0.60,0.37)	0.14 (-0.36,0.63)	0.05 (-0.51,0.60)	-0.16 (-0.68,0.37)	-0.15 (-0.66,0.37)	-0.55 (-1.55,0.45)	0.31 (-0.37,1.01)	0.21 (-0.73,1.13)	0.09 (-0.63,0.80)	0.15 (-0.32,0.63)		N/A	N/A
Tramadol	-0.55 (-0.99,-0.11)	-0.12 (-0.74,0.50)	-0.08 (-0.83,0.67)	-0.28 (-0.76,0.19)	-0.02 (-0.50,0.45)	-0.11 (-0.65,0.43)	-0.32 (-0.83,0.19)	-0.31 (-0.81,0.18)	-0.71 (-1.71,0.28)	0.15 (-0.53,0.83)	0.04 (-0.88,0.96)	-0.07 (-0.78,0.63)	-0.01 (-0.48,0.44)	-0.16 (-0.80,0.47)		N/A
Venlafaxine	-0.35 (-0.81,0.10)	0.07 (-0.57,0.71)	0.11 (-0.64,0.88)	-0.09 (-0.58,0.41)	0.17 (-0.32,0.67)	0.09 (-0.48,0.64)	-0.12 (-0.66,0.42)	-0.12 (-0.63,0.40)	-0.51 (-1.51,0.48)	0.34 (-0.34,1.04)	0.23 (-0.69,1.17)	0.12 (-0.59,0.84)	0.18 (-0.29,0.66)	0.03 (-0.62,0.68)	0.19 (-0.43,0.84)	
Capsaicin Cream	-1.26 (-2.09,-0.48)	-0.84 (-1.77,0.07)	-0.80 (-1.82,0.20)	-0.99 (-1.84,-0.19)	-0.73 (-1.58,0.07)	-0.82 (-1.70,0.02)	-1.03 (-1.89,-0.21)	-1.02 (-1.87,-0.21)	-1.42 (-2.63,-0.25)	-0.56 (-1.54,0.37)	-0.67 (-1.82,0.44)	-0.78 (-1.76,0.17)	-0.73 (-1.56,0.06)	-0.87 (-1.82,0.03)	-0.71 (-1.66,0.19)	-0.91 (-1.84,0.00)

Values given are z-scores.
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 z-scores from a frequentist analysis of direct data only, the segment above and to the right of the shaded cells is left blank.

Table 53 30% and 50% pain relief at all time-points – probability of pain relief over time

	placebo	amitriptyline	cannabis extract	capsaicin cream	capsaicin patch	duloxetine	gabapentin	lacosamide	lamotrigine	levetiracetam	morphine	nortriptyline	oxcarbazepine	pregabalin	topiramate	tramadol	venlafaxine
4 weeks																	
<30%	0.82 (0.70,0.90)	0.68 (0.46,0.86)	0.66 (0.39,0.88)	0.37 (0.10,0.70)	0.74 (0.59,0.86)	0.65 (0.48,0.79)	0.68 (0.49,0.84)	0.75 (0.59,0.88)	0.75 (0.59,0.87)	0.83 (0.55,0.98)	0.58 (0.33,0.81)	0.62 (0.29,0.89)	0.66 (0.40,0.87)	0.65 (0.49,0.79)	0.69 (0.48,0.87)	0.64 (0.41,0.83)	0.70 (0.49,0.88)
30–49%	0.09 (0.05,0.12)	0.12 (0.07,0.16)	0.12 (0.06,0.16)	0.14 (0.09,0.16)	0.11 (0.07,0.15)	0.13 (0.09,0.16)	0.12 (0.08,0.16)	0.11 (0.06,0.15)	0.11 (0.07,0.14)	0.07 (0.01,0.15)	0.14 (0.09,0.16)	0.13 (0.06,0.16)	0.13 (0.07,0.16)	0.13 (0.10,0.16)	0.12 (0.07,0.16)	0.13 (0.08,0.16)	0.12 (0.06,0.16)
≥50%	0.10 (0.04,0.18)	0.20 (0.07,0.38)	0.21 (0.06,0.45)	0.48 (0.18,0.81)	0.15 (0.07,0.27)	0.22 (0.11,0.36)	0.20 (0.08,0.35)	0.15 (0.06,0.27)	0.15 (0.06,0.26)	0.09 (0.01,0.30)	0.28 (0.10,0.51)	0.25 (0.05,0.56)	0.22 (0.06,0.44)	0.22 (0.12,0.35)	0.19 (0.06,0.37)	0.23 (0.09,0.43)	0.18 (0.06,0.36)
8 weeks																	
<30%	0.69 (0.60,0.77)	0.53 (0.33,0.72)	0.51 (0.26,0.75)	0.24 (0.05,0.52)	0.59 (0.47,0.70)	0.49 (0.36,0.61)	0.52 (0.37,0.67)	0.60 (0.46,0.74)	0.60 (0.47,0.72)	0.73 (0.40,0.94)	0.43 (0.22,0.64)	0.47 (0.18,0.77)	0.51 (0.28,0.73)	0.49 (0.38,0.60)	0.54 (0.35,0.74)	0.48 (0.29,0.67)	0.55 (0.35,0.75)
30–49%	0.12 (0.10,0.14)	0.15 (0.12,0.16)	0.15 (0.11,0.16)	0.13 (0.06,0.16)	0.14 (0.12,0.16)	0.15 (0.14,0.17)	0.15 (0.13,0.16)	0.14 (0.11,0.16)	0.14 (0.11,0.16)	0.11 (0.03,0.16)	0.15 (0.13,0.17)	0.14 (0.10,0.16)	0.15 (0.11,0.16)	0.15 (0.14,0.17)	0.15 (0.11,0.16)	0.15 (0.13,0.17)	0.15 (0.11,0.16)
≥50%	0.19 (0.13,0.26)	0.32 (0.16,0.52)	0.34 (0.14,0.59)	0.63 (0.32,0.89)	0.27 (0.18,0.37)	0.36 (0.25,0.48)	0.33 (0.20,0.48)	0.26 (0.15,0.39)	0.26 (0.16,0.37)	0.17 (0.02,0.44)	0.42 (0.22,0.65)	0.39 (0.13,0.70)	0.35 (0.15,0.57)	0.36 (0.26,0.47)	0.31 (0.15,0.50)	0.37 (0.20,0.56)	0.30 (0.14,0.49)
12 weeks																	
<30%	0.66 (0.58,0.73)	0.49 (0.30,0.68)	0.48 (0.24,0.72)	0.21 (0.04,0.48)	0.55 (0.45,0.66)	0.45 (0.35,0.56)	0.49 (0.35,0.63)	0.57 (0.44,0.70)	0.57 (0.45,0.68)	0.70 (0.38,0.93)	0.39 (0.20,0.60)	0.43 (0.16,0.74)	0.47 (0.25,0.70)	0.45 (0.36,0.55)	0.51 (0.32,0.69)	0.45 (0.27,0.63)	0.52 (0.33,0.71)
30–49%	0.13 (0.11,0.15)	0.15 (0.13,0.17)	0.15 (0.11,0.17)	0.12 (0.05,0.16)	0.15 (0.13,0.16)	0.16 (0.15,0.17)	0.15 (0.14,0.17)	0.15 (0.12,0.16)	0.15 (0.13,0.16)	0.11 (0.04,0.16)	0.15 (0.13,0.17)	0.15 (0.10,0.16)	0.15 (0.12,0.17)	0.16 (0.15,0.17)	0.15 (0.12,0.16)	0.15 (0.13,0.17)	0.15 (0.12,0.16)
≥50%	0.21 (0.16,0.27)	0.36 (0.19,0.55)	0.37 (0.16,0.62)	0.67 (0.36,0.91)	0.30 (0.21,0.40)	0.39 (0.29,0.50)	0.36 (0.23,0.50)	0.29 (0.18,0.40)	0.29 (0.19,0.40)	0.19 (0.03,0.47)	0.46 (0.25,0.67)	0.42 (0.15,0.73)	0.38 (0.18,0.61)	0.39 (0.30,0.49)	0.34 (0.18,0.53)	0.40 (0.23,0.59)	0.33 (0.17,0.52)
16 weeks																	
<30%	0.58 (0.08,0.97)	0.45 (0.03,0.94)	0.44 (0.03,0.94)	0.23 (0.00,0.78)	0.50 (0.05,0.95)	0.42 (0.03,0.91)	0.45 (0.03,0.93)	0.51 (0.05,0.95)	0.51 (0.05,0.95)	0.62 (0.08,0.99)	0.37 (0.02,0.90)	0.41 (0.01,0.93)	0.43 (0.03,0.93)	0.42 (0.03,0.91)	0.46 (0.03,0.94)	0.42 (0.02,0.92)	0.47 (0.04,0.94)
30–49%	0.11 (0.02,0.16)	0.12 (0.02,0.16)	0.12 (0.02,0.16)	0.10 (0.01,0.16)	0.12 (0.03,0.16)	0.12 (0.03,0.16)	0.12 (0.03,0.16)	0.12 (0.02,0.16)	0.12 (0.03,0.16)	0.10 (0.01,0.16)	0.12 (0.02,0.16)	0.12 (0.02,0.16)	0.12 (0.02,0.16)	0.12 (0.03,0.16)	0.12 (0.02,0.16)	0.12 (0.03,0.16)	0.12 (0.02,0.16)
≥50%	0.30 (0.01,0.84)	0.43 (0.03,0.93)	0.44 (0.03,0.94)	0.67 (0.12,0.99)	0.38 (0.02,0.90)	0.46 (0.04,0.93)	0.43 (0.03,0.93)	0.37 (0.02,0.89)	0.37 (0.02,0.89)	0.27 (0.00,0.85)	0.51 (0.05,0.96)	0.48 (0.03,0.96)	0.45 (0.03,0.94)	0.46 (0.04,0.93)	0.42 (0.03,0.93)	0.46 (0.04,0.94)	0.41 (0.02,0.92)
20 weeks																	
<30%	0.64 (0.49,0.77)	0.47 (0.25,0.70)	0.46 (0.20,0.73)	0.20 (0.03,0.48)	0.53 (0.37,0.70)	0.43 (0.27,0.60)	0.47 (0.28,0.66)	0.55 (0.36,0.72)	0.55 (0.37,0.72)	0.68 (0.34,0.93)	0.38 (0.16,0.62)	0.42 (0.13,0.74)	0.45 (0.22,0.71)	0.43 (0.28,0.59)	0.49 (0.27,0.72)	0.43 (0.22,0.65)	0.50 (0.27,0.73)
30–49%	0.13 (0.10,0.16)	0.15 (0.12,0.17)	0.15 (0.11,0.17)	0.12 (0.04,0.16)	0.15 (0.12,0.16)	0.15 (0.14,0.17)	0.15 (0.13,0.17)	0.15 (0.12,0.16)	0.15 (0.12,0.16)	0.12 (0.04,0.16)	0.15 (0.12,0.17)	0.14 (0.09,0.16)	0.15 (0.12,0.17)	0.16 (0.14,0.17)	0.15 (0.12,0.17)	0.15 (0.13,0.17)	0.15 (0.11,0.17)
≥50%	0.23 (0.13,0.36)	0.38 (0.18,0.60)	0.39 (0.16,0.66)	0.68 (0.36,0.92)	0.32 (0.18,0.48)	0.41 (0.26,0.58)	0.38 (0.21,0.57)	0.31 (0.16,0.48)	0.31 (0.17,0.47)	0.20 (0.03,0.50)	0.48 (0.24,0.72)	0.44 (0.15,0.77)	0.40 (0.17,0.65)	0.41 (0.26,0.58)	0.36 (0.17,0.59)	0.42 (0.21,0.64)	0.35 (0.16,0.58)

NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credible intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

Table 54 30% and 50% pain relief at all time-points – probability of pain relief over time (dose-adjusted estimates)

	placebo	amitriptyl-ine	cannabis sativa extract	capsaicin patch	duloxetine	gabapentin	lacosamide	lamotrigine	levetirace-tam	morphine	nortriptyline	oxcarbaze-pine	pregabalin	topiramate	tramadol	venlafaxine	capsaicin cream
Assumed dose	**-**	**50mg/d[a]**	**4 spray/d[a]**	**1×60-min[a]**	**60mg/d[a]**	**1800mg/d[a]**	**400mg/d[a]**	**400mg/d[a]**	**3000mg/d[b]**	**120mg/d[a]**	**50mg/d[a]**	**1800mg/d[b]**	**300mg/d[a]**	**100mg/d[a]**	**400mg/d[a]**	**75mg/d[a]**	**4apps/d[a]**
4 weeks																	
<30%	0.82 (0.70,0.90)	0.74 (0.52,0.90)	0.66 (0.35,0.91)	0.37 (0.10,0.70)	0.74 (0.59,0.86)	0.65 (0.49,0.80)	0.60 (0.38,0.80)	0.75 (0.59,0.88)	0.74 (0.59,0.87)	0.83 (0.55,0.98)	0.60 (0.35,0.82)	0.64 (0.28,0.92)	0.66 (0.41,0.86)	0.68 (0.53,0.82)	0.67 (0.22,0.97)	0.64 (0.41,0.83)	0.75 (0.53,0.90)
30–49%	0.09 (0.05,0.12)	0.11 (0.05,0.15)	0.12 (0.05,0.16)	0.14 (0.09,0.16)	0.11 (0.07,0.15)	0.13 (0.09,0.16)	0.14 (0.09,0.16)	0.11 (0.06,0.15)	0.11 (0.07,0.15)	0.07 (0.01,0.15)	0.14 (0.09,0.16)	0.12 (0.05,0.16)	0.13 (0.07,0.16)	0.12 (0.09,0.15)	0.11 (0.02,0.16)	0.13 (0.08,0.16)	0.11 (0.05,0.15)
≥50%	0.10 (0.04,0.18)	0.15 (0.04,0.32)	0.22 (0.04,0.50)	0.49 (0.17,0.81)	0.15 (0.07,0.27)	0.22 (0.11,0.36)	0.26 (0.11,0.46)	0.14 (0.06,0.26)	0.15 (0.06,0.27)	0.09 (0.01,0.30)	0.26 (0.09,0.50)	0.24 (0.04,0.58)	0.21 (0.07,0.43)	0.19 (0.10,0.32)	0.22 (0.01,0.65)	0.23 (0.09,0.43)	0.15 (0.04,0.32)
8 weeks																	
<30%	0.69 (0.60,0.77)	0.60 (0.39,0.79)	0.51 (0.22,0.80)	0.23 (0.05,0.52)	0.59 (0.47,0.70)	0.49 (0.37,0.61)	0.44 (0.26,0.64)	0.61 (0.46,0.74)	0.60 (0.46,0.73)	0.72 (0.40,0.94)	0.44 (0.23,0.67)	0.49 (0.17,0.82)	0.51 (0.29,0.72)	0.53 (0.41,0.64)	0.54 (0.13,0.92)	0.48 (0.29,0.67)	0.61 (0.39,0.79)
30–49%	0.12 (0.10,0.14)	0.14 (0.10,0.16)	0.14 (0.09,0.16)	0.13 (0.05,0.16)	0.14 (0.12,0.16)	0.15 (0.14,0.17)	0.15 (0.13,0.17)	0.14 (0.11,0.16)	0.14 (0.11,0.16)	0.11 (0.03,0.16)	0.15 (0.12,0.17)	0.14 (0.08,0.16)	0.15 (0.12,0.17)	0.15 (0.13,0.16)	0.13 (0.04,0.16)	0.15 (0.13,0.17)	0.14 (0.09,0.16)
≥50%	0.19 (0.13,0.26)	0.26 (0.12,0.46)	0.34 (0.11,0.64)	0.64 (0.33,0.90)	0.27 (0.17,0.37)	0.35 (0.24,0.47)	0.40 (0.23,0.59)	0.25 (0.15,0.38)	0.26 (0.16,0.38)	0.17 (0.03,0.44)	0.41 (0.20,0.64)	0.37 (0.09,0.71)	0.34 (0.16,0.56)	0.32 (0.22,0.43)	0.34 (0.04,0.77)	0.37 (0.20,0.57)	0.26 (0.11,0.45)
12 weeks																	
<30%	0.66 (0.58,0.73)	0.56 (0.35,0.75)	0.48 (0.20,0.77)	0.21 (0.04,0.47)	0.55 (0.45,0.66)	0.46 (0.35,0.57)	0.41 (0.24,0.59)	0.57 (0.44,0.70)	0.56 (0.44,0.68)	0.69 (0.37,0.93)	0.41 (0.21,0.63)	0.46 (0.15,0.79)	0.47 (0.26,0.68)	0.49 (0.39,0.59)	0.50 (0.11,0.90)	0.45 (0.26,0.63)	0.57 (0.37,0.76)
30–49%	0.13 (0.11,0.15)	0.14 (0.11,0.16)	0.15 (0.10,0.16)	0.12 (0.05,0.16)	0.15 (0.13,0.16)	0.16 (0.14,0.17)	0.15 (0.13,0.17)	0.15 (0.12,0.16)	0.15 (0.13,0.16)	0.11 (0.04,0.16)	0.15 (0.13,0.17)	0.14 (0.09,0.16)	0.15 (0.12,0.17)	0.15 (0.14,0.17)	0.13 (0.05,0.16)	0.15 (0.13,0.17)	0.14 (0.11,0.16)
≥50%	0.21 (0.15,0.27)	0.29 (0.14,0.49)	0.38 (0.13,0.67)	0.67 (0.37,0.91)	0.30 (0.21,0.40)	0.39 (0.28,0.50)	0.44 (0.26,0.62)	0.28 (0.18,0.40)	0.29 (0.19,0.40)	0.19 (0.03,0.47)	0.44 (0.23,0.66)	0.40 (0.11,0.74)	0.38 (0.19,0.60)	0.35 (0.26,0.45)	0.36 (0.05,0.80)	0.40 (0.23,0.59)	0.29 (0.14,0.48)
16 weeks																	
<30%	0.58 (0.09,0.97)	0.51 (0.05,0.95)	0.44 (0.02,0.94)	0.23 (0.00,0.78)	0.50 (0.05,0.94)	0.42 (0.03,0.92)	0.39 (0.02,0.90)	0.51 (0.06,0.95)	0.51 (0.06,0.95)	0.62 (0.08,0.99)	0.39 (0.02,0.90)	0.43 (0.02,0.95)	0.44 (0.03,0.93)	0.45 (0.04,0.93)	0.46 (0.02,0.97)	0.41 (0.03,0.92)	0.51 (0.05,0.96)
30–49%	0.11 (0.02,0.16)	0.12 (0.02,0.16)	0.12 (0.02,0.16)	0.10 (0.01,0.16)	0.12 (0.03,0.16)	0.12 (0.03,0.16)	0.12 (0.02,0.16)	0.12 (0.02,0.16)	0.12 (0.03,0.16)	0.11 (0.01,0.16)	0.12 (0.02,0.16)	0.12 (0.02,0.16)	0.12 (0.03,0.16)	0.12 (0.03,0.16)	0.11 (0.01,0.16)	0.12 (0.03,0.16)	0.12 (0.02,0.16)
≥50%	0.30 (0.01,0.83)	0.37 (0.02,0.90)	0.44 (0.02,0.94)	0.68 (0.12,0.99)	0.38 (0.02,0.89)	0.45 (0.04,0.93)	0.49 (0.05,0.95)	0.37 (0.02,0.88)	0.37 (0.02,0.88)	0.27 (0.00,0.84)	0.49 (0.05,0.95)	0.46 (0.02,0.96)	0.44 (0.03,0.94)	0.43 (0.03,0.91)	0.43 (0.01,0.96)	0.46 (0.04,0.94)	0.37 (0.02,0.89)
20 weeks																	
<30%	0.64 (0.49,0.78)	0.54 (0.30,0.77)	0.46 (0.17,0.78)	0.20 (0.03,0.48)	0.53 (0.36,0.70)	0.44 (0.28,0.61)	0.39 (0.19,0.62)	0.55 (0.37,0.73)	0.54 (0.37,0.72)	0.68 (0.34,0.93)	0.39 (0.17,0.65)	0.44 (0.13,0.79)	0.46 (0.22,0.70)	0.47 (0.31,0.64)	0.49 (0.09,0.90)	0.43 (0.22,0.66)	0.55 (0.31,0.77)
30–49%	0.13 (0.10,0.16)	0.14 (0.10,0.16)	0.14 (0.10,0.16)	0.12 (0.04,0.16)	0.15 (0.12,0.16)	0.15 (0.14,0.17)	0.15 (0.12,0.17)	0.15 (0.11,0.16)	0.15 (0.12,0.16)	0.12 (0.04,0.16)	0.15 (0.11,0.17)	0.14 (0.08,0.16)	0.15 (0.12,0.17)	0.15 (0.13,0.17)	0.13 (0.05,0.16)	0.15 (0.13,0.17)	0.14 (0.10,0.16)
≥50%	0.23 (0.12,0.36)	0.31 (0.13,0.54)	0.39 (0.12,0.71)	0.68 (0.36,0.93)	0.32 (0.18,0.48)	0.41 (0.25,0.58)	0.46 (0.24,0.68)	0.30 (0.16,0.47)	0.31 (0.17,0.48)	0.21 (0.03,0.51)	0.46 (0.22,0.72)	0.42 (0.11,0.77)	0.39 (0.18,0.65)	0.37 (0.22,0.54)	0.38 (0.05,0.83)	0.42 (0.21,0.65)	0.30 (0.13,0.53)

[a] estimate provided by GDG; rounded up to nearest dose achievable using whole tablets

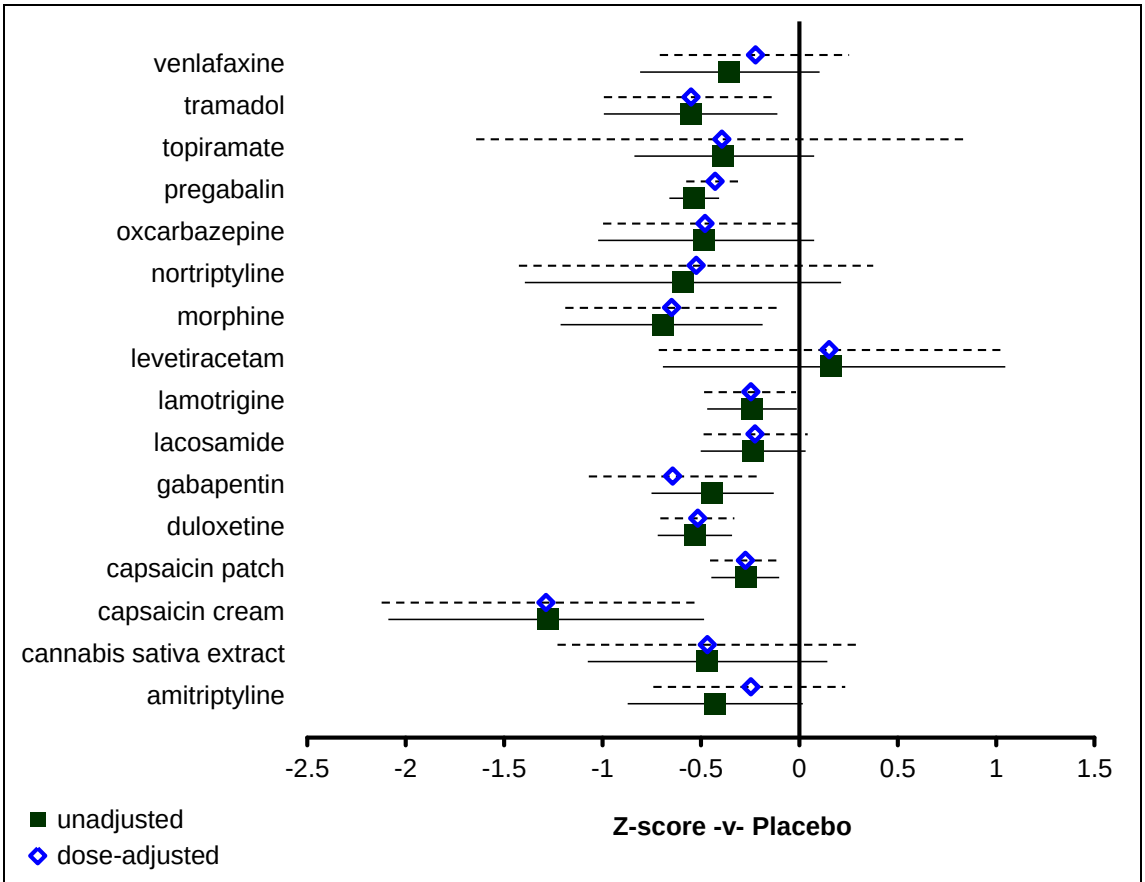
[b] GDG feel unable to comment based on own experience; weighted mean of dosages in trials contributing to evidence-base used instead

NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credible intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

Table 55 30% and 50% pain relief at all time-points – raw outputs of synthesis models

	Unadjusted	Dose−adjusted	
	Z−score −v− placebo	Z−score −v− placebo	Coefficient for dose[a]
Amitriptyline	−0.427 (−0.872,0.017)	−0.286 (−0.758,0.174)	−0.783 (−4.259,2.602)
Cannabis extract	−0.467 (−1.075,0.143)	−0.467 (−1.073,0.132)	−0.004 (−3.928,3.893)
Capsaicin cream	−1.274 (−2.088,−0.484)	−1.287 (−2.122,−0.511)	0.035 (−3.884,3.891)
Capsaicin patch	−0.271 (−0.447,−0.102)	−0.269 (−0.438,−0.103)	−0.275 (−3.475,2.908)
Duloxetine	−0.528 (−0.719,−0.342)	−0.526 (−0.712,−0.345)	−0.560 (−2.986,1.936)
Gabapentin	−0.441 (−0.750,−0.130)	−0.411 (−0.712,−0.098)	0.291 (−0.149,0.733)
Lacosamide	−0.234 (−0.502,0.033)	−0.234 (−0.495,0.033)	−0.261 (−1.174,0.669)
Lamotrigine	−0.238 (−0.468,−0.013)	−0.234 (−0.459,−0.015)	−0.303 (−1.844,1.223)
Levetiracetam	0.164 (−0.693,1.046)	0.151 (−0.714,1.021)	−0.015 (−3.924,3.905)
Morphine	−0.693 (−1.213,−0.186)	−0.738 (−1.282,−0.199)	−0.749 (−4.136,2.619)
Nortriptyline	−0.587 (−1.394,0.212)	−0.522 (−1.330,0.297)	0.019 (−3.945,3.963)
Oxcarbazepine	−0.483 (−1.022,0.075)	−0.479 (−0.997,0.034)	0.003 (−3.944,3.965)
Pregabalin	−0.534 (−0.660,−0.407)	−0.512 (−0.636,−0.396)	−0.589 (−1.055,−0.108)
Topiramate	−0.384 (−0.838,0.076)	−0.387 (−0.817,0.048)	0.022 (−3.900,3.905)
Tramadol	−0.548 (−0.993,−0.111)	−0.550 (−0.993,−0.110)	−0.741 (−4.163,2.704)
Venlafaxine	−0.356 (−0.809,0.104)	−0.355 (−0.800,0.084)	−1.772 (−4.278,0.785)

[a] units for dose covariate are arbitrary, as each is estimated independently. For all oral medications, dose was measured in g per day; for cannabis extract, the unit was g of THC per day; for capsaicin cream, it was number of applications per day; for capsaicin patch, it was duration of application in minutes.



Dose-adjusted estimates are fitted at the typical maintenance values provided by the GDG, or at the mean value in the evidence base where the GDG did not provide an estimate (see Table 54 for details)

Figure 33 30% and 50% pain relief at all time-points – relative effect of all options compared with placebo

(values less than 0 favour the treatment; values greater than 0 favour placebo; error bars are 95% credible intervals)

Table 56 30% and 50% pain relief at all time-points – rankings for each comparator

	No dose adjustment		Dose-adjusted	
	Probability best	**Median rank (95%CrI)**	**Probability best**	**Median rank (95%CrI)**
Placebo	0.000	16 (14, 17)	0.000	16 (13, 17)
Amitriptyline	0.006	9 (2, 16)	0.001	12 (4, 17)
Cannabis Extract	0.026	8 (1, 17)	0.014	7 (2, 16)
Capsaicin Cream	0.759	1 (1, 7)	0.682	1 (1, 6)
Capsaicin Patch	0.000	12 (8, 15)	0.000	11 (7, 15)
Duloxetine	0.001	6 (3, 11)	0.000	6 (3, 11)
Gabapentin	0.001	8 (3, 14)	0.019	5 (2, 12)
Lacosamide	0.000	13 (7, 16)	0.000	13 (7, 16)
Lamotrigine	0.000	13 (7, 16)	0.000	12 (6, 15)
Levetiracetam	0.003	17 (3, 17)	0.003	16 (3, 17)
Morphine	0.071	3 (1, 14)	0.041	4 (1, 13)
Nortriptyline	0.086	5 (1, 17)	0.059	6 (1, 17)
Oxcarbazepine	0.019	8 (2, 16)	0.148	7 (1, 17)
Pregabalin	0.001	6 (3, 10)	0.000	8 (4, 11)
Topiramate	0.005	10 (2, 16)	0.004	9 (2, 16)
Tramadol	0.019	6 (2, 15)	0.026	5 (1, 14)
Venlafaxine	0.003	10 (2, 16)	0.001	12 (4, 17)

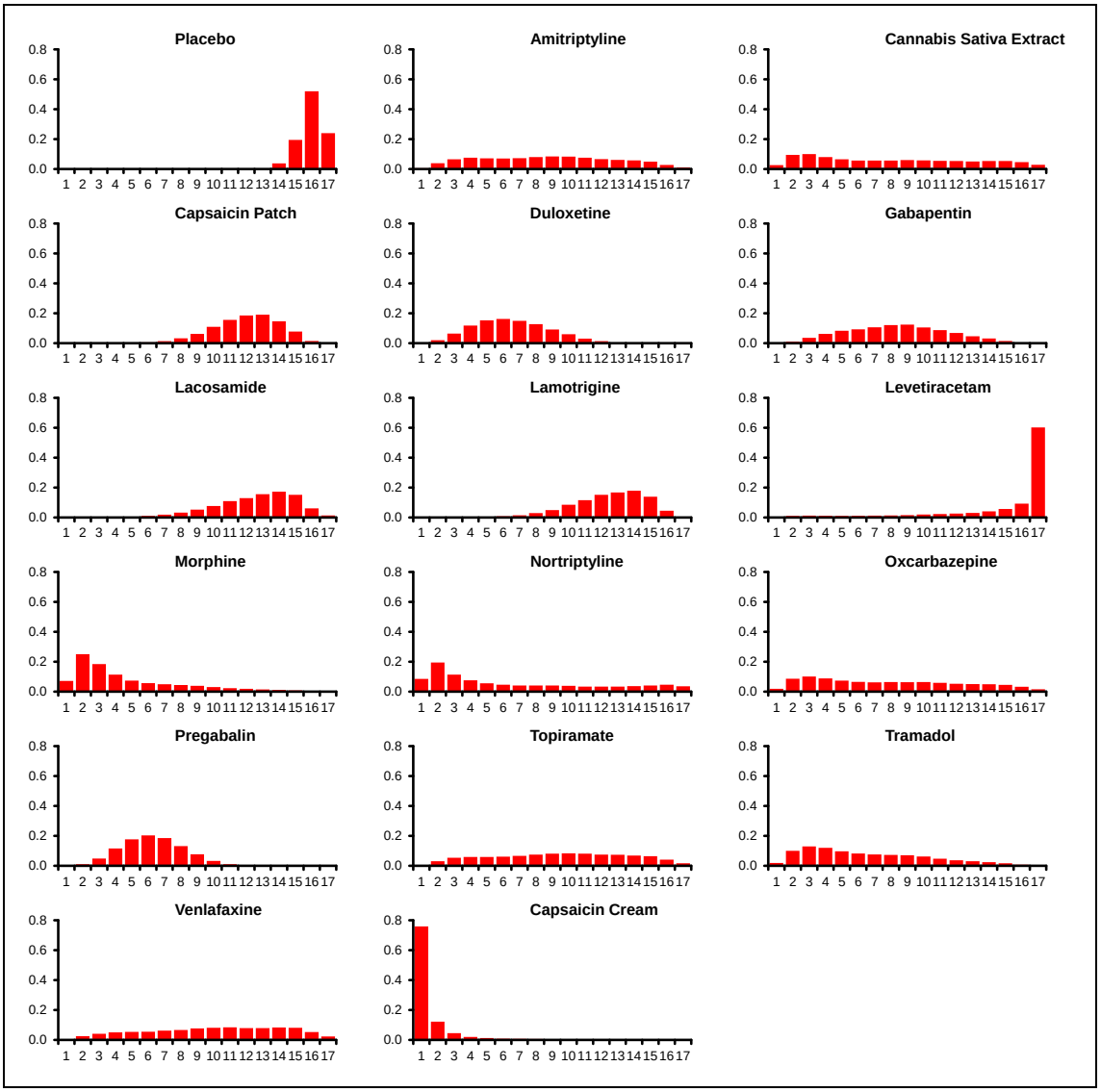


Figure 34 30% and 50% pain relief at all time-points – rank probability histograms; no adjustment for dose

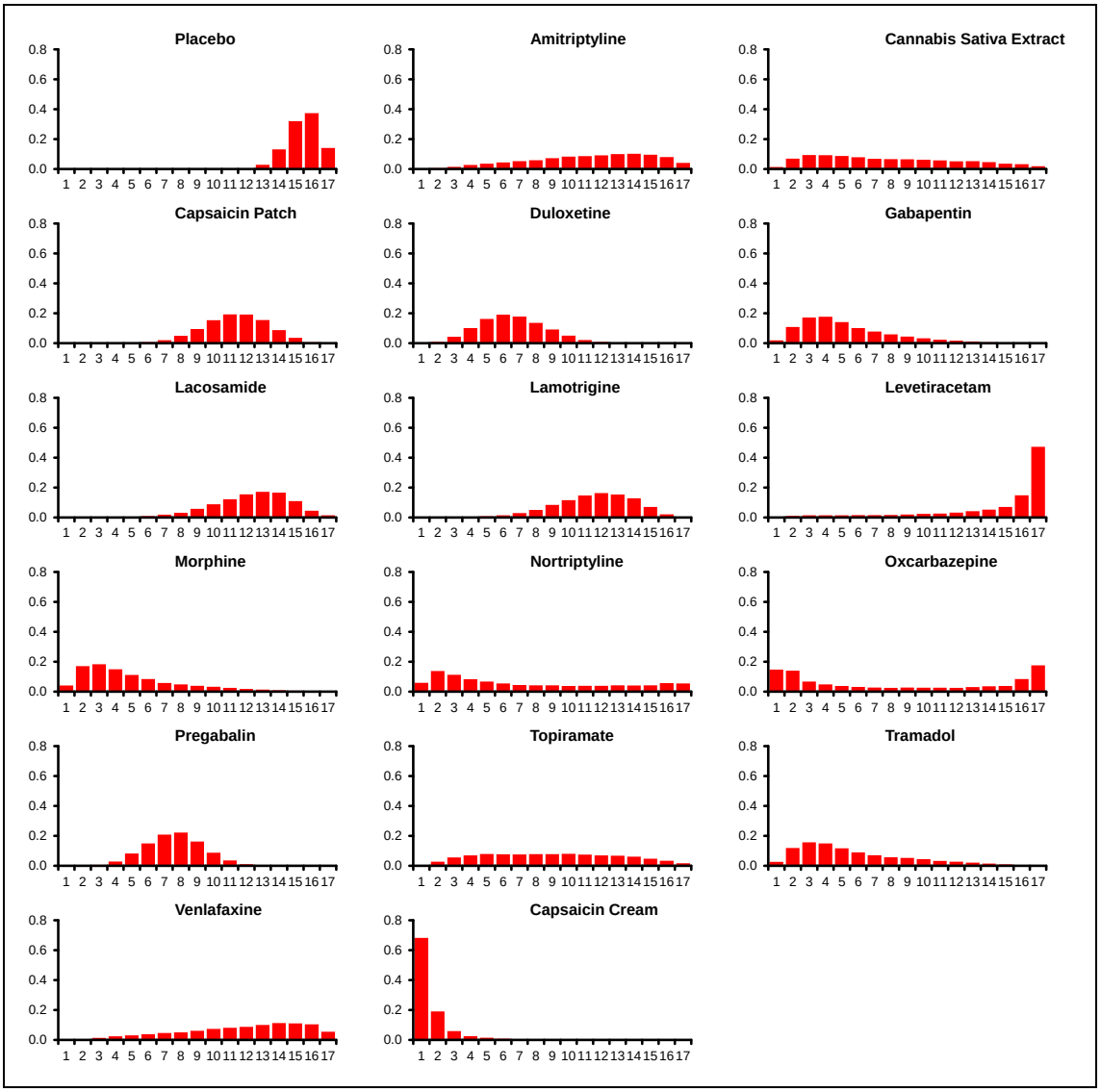


Figure 35 30% and 50% pain relief at all time-points – rank probability histograms; dose-adjusted

Table 57 30% and 50% pain relief at all time-points – model fit statistics

	Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
Unadjusted	233.3 (cf. 197 data-points)	1086.1	989.1	97.0	1183.1	0.028 (95%CrI: 0.013, 0.062)
Dose-adjusted	232.1 (cf. 197 data-points)	1084.9	987.1	97.9	1182.8	0.022 (95%CrI: 0.009, 0.056)

Table 58 30% and 50% pain relief at all time-points - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 50,000 burn-ins and 10,000 iterations thinned from 100,000

- It is difficult to distinguish between the 2 models on the basis of these statistics. This is largely because the random-effects term in the model is broad enough to absorb much of the heterogeneity that may be explained by dose–response effects. However, as would be expected, the width of the estimated random-effects distribution is reduced a small amount in the dose-adjusted model. Moreover, when the covariate was included in fixed-effect exploration of the same dataset, it demonstrably improved model fit (DIC fell from 1187.9 to 1178.7), though it certainly did not explain all the heterogeneity in the modelled data: total residual deviance fell but, without the flexibility afforded by the random-effects term, remained high (263.1 compared with 197 data-points).

Summary GRADE profile 7a: 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)	30 RCTs[a] n=3546	very serious[1]	very 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 24 others; over half of the studies had inadequate follow-up; concomitant drugs permitted varies across the studies in the network; one study was single-blind

[2] I^2 was 90, 97, 90 and 33% for amitriptyline, gabapentin, pregabalin, tramadol vs placebo, respectively which may indicate considerable heterogeneity in the first 3 comparisons and moderate in the last; there appears to be some inconsistency between direct and indirect comparisons, but they appear to be small and not larger than a minimally important difference

[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 for effectiveness estimates of most interventions compared to placebo and in the overall ranking in the network

[a] **Placebo-controlled trials**

amitriptyline (n=148): Kalso et al. (1995), Mishra et al. (2012), Vrethem et al. (1997) (both with and without diabetes); concomitant drugs allowed in one and unclear in two

cannabis sativa extract (n=190): Nurmikko et al. (2007), Rog et al. (2005); concomitant drugs permitted

duloxetine (n=48): Vranken et al. (2011); concomitant drugs permitted if stable except anti-depressants

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

gabapentin (n=758): Backonja et al. (1998), Bone et al. (2002), Gordh et al. (2008), Levendoglu et al. (2004), Mishra et al. (2012), Rao et al. (2007), Rice & Maton (2001); concomitant drug not permitted in two, unclear if permitted in 1, 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

levetiracetam (n=19): Rossi et al. (2009); concomitant drugs not permitted

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

morphine (n=24): Huse et al. (2001); unclear if concomitant drugs permitted

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

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

pregabalin (n=725): Guan et al. (2011), Lesser et al. (2004), Mishra et al. (2012), Vranken et al. (2008); concomitant drugs permitted in 3 (but only SSRIs in two), unclear if concomitants permitted in the other

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 vs amitriptyline vs pregabalin (n=60): Mishra et al. (2012); unclear if concomitant drugs permitted

gabapentin+nortriptyline vs gabapentin vs nortriptyline (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

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.

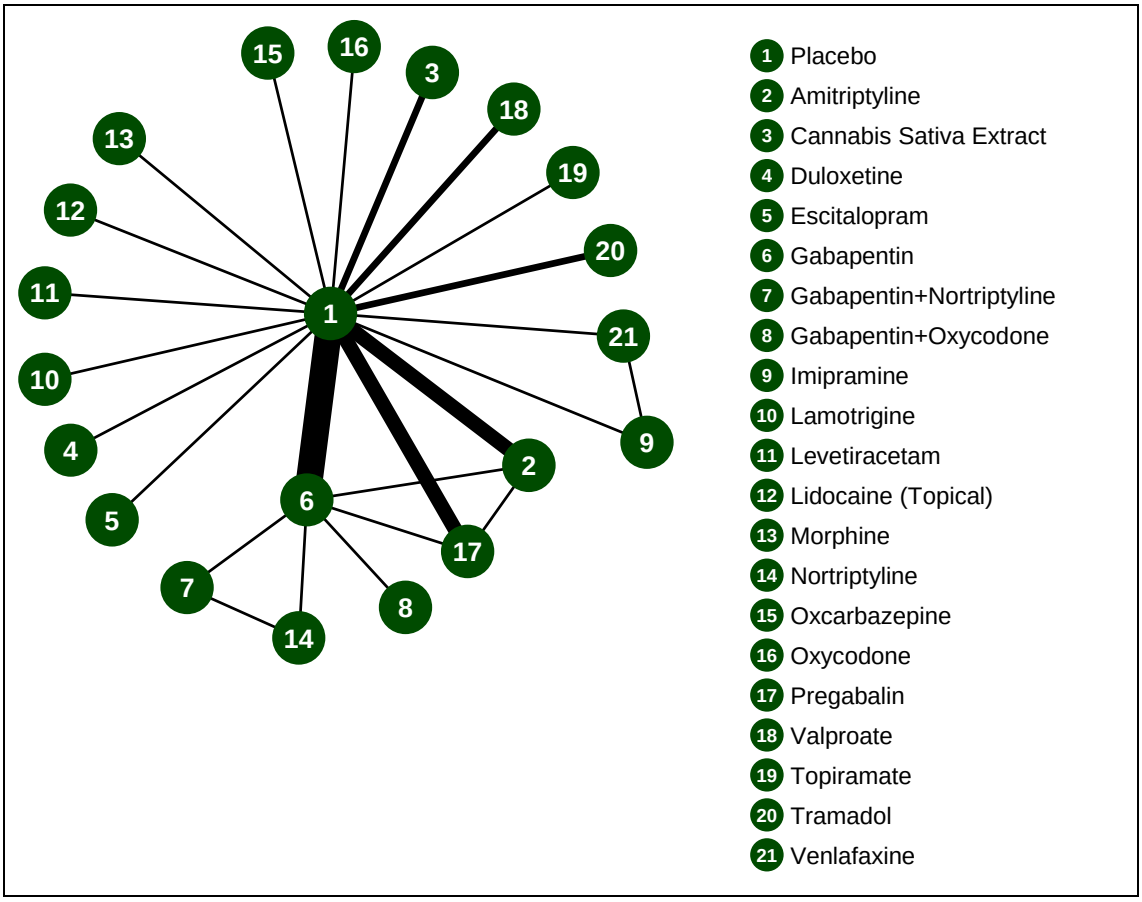


Figure 36 pain (continuous) - 28 +/- 7 days - evidence network

Table 59 pain (continuous) - 28 +/- 7 days - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol
Amitriptyline	4 RCTs[12,17,30,30] total n=148																			
Cannabis Sativa Extract	2 RCTs[18,24] total n=190	-																		
Duloxetine	1 RCT[29] total n=48	-	-																	
Escitalopram	1 RCT[19] total n=82	-	-	-																
Gabapentin	7 RCTs[1,2,8,16,17,20,23] total n=758	1 RCT[17] total n=60	-	-	-															
Gabapentin +Nortriptyline	-	-	-	-	-	1 RCT[6] total n=96														
Gabapentin +Oxycodone	-	-	-	-	-	1 RCT[10] total n=328	-													
Imipramine	1 RCT[27] total n=64	-	-	-	-	-	-	-												
Lamotrigine	1 RCT[21] total n=125	-	-	-	-	-	-	-	-											
Levetiracetam	1 RCT[25] total n=19	-	-	-	-	-	-	-	-	-										
Lidocaine	1 RCT[4]	-	-	-	-	-	-	-	-	-	-									

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol
(Topical)	total n=28																			
Morphine	1 RCT[11] total n=24	-	-	-	-	-	-	-	-	-	-	-								
Nortriptyline	-	-	-	-	-	1 RCT[6] total n=96	1 RCT[6] total n=100	-	-	-	-	-	-							
Oxcarbazepine	1 RCT[5] total n=146	-	-	-	-	-	-	-	-	-	-	-	-	-						
Oxycodone	1 RCT[7] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Pregabalin	4 RCTs[9,15,17,28] total n=725	1 RCT[17] total n=60	-	-	-	1 RCT[17] total n=60	-	-	-	-	-	-	-	-	-	-				
Valproate	2 RCTs[13,14] total n=91	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Topiramate	1 RCT[22] total n=317	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Tramadol	2 RCTs[3,26] total n=176	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Venlafaxine	1 RCT[27] total n=64	-	-	-	-	-	-	-	1 RCT[27] total n=64	-	-	-	-	-	-	-	-	-	-	-

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

(22) Raskin et al. (2004); (23) Rice & Maton (2001); (24) Rog et al. (2005); (25) Rossi et al. (2009); (26) Sindrup et al. (1999); (27) Sindrup et al. (2003); (28) Vranken et al. (2008); (29) Vranken et al. (2011); (30) Vrethem et al. (1997)

Table 60 pain (continuous) - 28 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Placebo		-1.22 (-2.18, -0.26)	-1.21 (-1.64, -0.77)	-0.50 (-1.34, 0.34)	-1.00 (-1.57, -0.43)	-0.84 (-1.72, 0.05)	-	-	-1.30 (-2.04, -0.56)	0.35 (-0.32, 1.02)	-1.51 (-2.63, -0.39)	0.10 (-0.78, 0.98)	-0.73 (-1.41, -0.05)	-	-0.72 (-1.18, -0.26)	-0.70 (-1.14, -0.26)	-0.96 (-1.51, -0.41)	-1.34 (-1.98, -0.69)	-0.18 (-0.50, 0.15)	-1.19 (-1.85, -0.53)	-1.00 (-1.74, -0.26)
Amitriptyline	-1.19 (-2.13, -0.25)		-	-	-	0.11 (-0.21, 0.43)	-	-	-	-	-	-	-	-	-	-	-0.73 (-1.00, -0.46)	-	-	-	-
Cannabis Sativa Extract	-1.21 (-2.61, 0.18)	-0.02 (-1.71, 1.66)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duloxetine	-0.50 (-2.56, 1.56)	0.69 (-1.58, 2.95)	0.72 (-1.79, 3.20)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	-1.00 (-2.97, 0.97)	0.18 (-2.00, 2.38)	0.21 (-2.20, 2.62)	-0.50 (-3.34, 2.35)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	-0.88 (-1.57, -0.18)	0.31 (-0.80, 1.43)	0.34 (-1.22, 1.90)	-0.38 (-2.55, 1.80)	0.12 (-1.96, 2.21)		-0.90 (-1.42, -0.38)	-0.80 (-1.22, -0.38)	-	-	-	-	-	-0.30 (-0.82, 0.22)	-	-	-0.84 (-1.13, -0.55)	-	-	-	-
Gabapentin +Nortriptyline	-1.77 (-3.84, 0.31)	-0.58 (-2.82, 1.68)	-0.56 (-3.06, 1.94)	-1.27 (-4.18, 1.65)	-0.77 (-3.64, 2.09)	-0.89 (-2.85, 1.06)		-	-	-	-	-	-	0.60 (0.19, 1.01)	-	-	-	-	-	-	-
Gabapentin +Oxycodone	-1.68 (-3.72, 0.38)	-0.49 (-2.71, 1.74)	-0.46 (-2.94, 2.01)	-1.18 (-4.07, 1.74)	-0.68 (-3.52, 2.16)	-0.80 (-2.73, 1.12)	0.09 (-2.66, 2.83)		-	-	-	-	-	-	-	-	-	-	-	-	-
Imipramine	-1.29 (-3.31, 0.72)	-0.10 (-2.34, 2.12)	-0.08 (-2.54, 2.36)	-0.80 (-3.67, 2.09)	-0.30 (-3.11, 2.52)	-0.41 (-2.55, 1.71)	0.48 (-2.42, 3.38)	0.39 (-2.50, 3.25)		-	-	-	-	-	-	-	-	-	-	-	0.30 (-0.54, 1.14)

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Lamotrigine	0.35 (-1.63, 2.36)	1.54 (-0.67, 3.76)	1.56 (-0.87, 4.00)	0.85 (-1.99, 3.74)	1.35 (-1.43, 4.17)	1.23 (-0.88, 3.35)	2.13 (-0.76, 5.01)	2.03 (-0.83, 4.89)	1.65 (-1.18, 4.48)		-	-	-	-	-	-	-	-	-	-	-
Levetiracetam	-1.52 (-3.69, 0.66)	-0.33 (-2.69, 2.06)	-0.31 (-2.89, 2.29)	-1.02 (-4.01, 1.99)	-0.52 (-3.46, 2.43)	-0.64 (-2.93, 1.64)	0.25 (-2.77, 3.25)	0.16 (-2.83, 3.16)	-0.23 (-3.21, 2.75)	-1.88 (-4.83, 1.09)		-	-	-	-	-	-	-	-	-	-
Lidocaine (Topical)	0.10 (-1.98, 2.17)	1.29 (-0.98, 3.57)	1.31 (-1.19, 3.82)	0.60 (-2.34, 3.52)	1.10 (-1.76, 3.95)	0.98 (-1.22, 3.16)	1.87 (-1.07, 4.78)	1.78 (-1.15, 4.70)	1.39 (-1.49, 4.29)	-0.25 (-3.13, 2.64)	1.62 (-1.37, 4.61)		-	-	-	-	-	-	-	-	-
Morphine	-0.73 (-2.72, 1.27)	0.46 (-1.74, 2.67)	0.49 (-1.94, 2.93)	-0.23 (-3.10, 2.66)	0.27 (-2.53, 3.06)	0.15 (-1.97, 2.26)	1.05 (-1.84, 3.92)	0.95 (-1.90, 3.81)	0.57 (-2.26, 3.39)	-1.08 (-3.91, 1.74)	0.80 (-2.16, 3.76)	-0.83 (-3.70, 2.05)		-	-	-	-	-	-	-	-
Nortriptyline	-1.17 (-3.25, 0.91)	0.01 (-2.22, 2.27)	0.04 (-2.46, 2.54)	-0.67 (-3.59, 2.26)	-0.17 (-3.03, 2.68)	-0.29 (-2.25, 1.66)	0.60 (-1.32, 2.51)	0.51 (-2.23, 3.25)	0.12 (-2.77, 3.01)	-1.52 (-4.41, 1.36)	0.34 (-2.65, 3.35)	-1.27 (-4.20, 1.66)	-0.44 (-3.34, 2.44)		-	-	-	-	-	-	-
Oxcarbazepine	-0.71 (-2.64, 1.21)	0.47 (-1.69, 2.62)	0.50 (-1.88, 2.88)	-0.22 (-3.03, 2.62)	0.28 (-2.46, 3.04)	0.17 (-1.90, 2.20)	1.06 (-1.79, 3.87)	0.96 (-1.85, 3.77)	0.58 (-2.22, 3.39)	-1.07 (-3.84, 1.71)	0.80 (-2.11, 3.70)	-0.82 (-3.66, 2.00)	0.01 (-2.78, 2.77)	0.45 (-2.37, 3.28)		-	-	-	-	-	-
Oxycodone	-0.70 (-2.65, 1.23)	0.48 (-1.68, 2.63)	0.51 (-1.87, 2.88)	-0.20 (-3.03, 2.62)	0.29 (-2.47, 3.03)	0.18 (-1.88, 2.22)	1.07 (-1.78, 3.89)	0.98 (-1.84, 3.79)	0.59 (-2.20, 3.39)	-1.05 (-3.84, 1.74)	0.81 (-2.11, 3.73)	-0.80 (-3.63, 2.03)	0.02 (-2.75, 2.79)	0.47 (-2.36, 3.30)	0.01 (-2.72, 2.74)		-	-	-	-	-
Pregabalin	-1.17 (-2.07, -0.29)	0.02 (-1.20, 1.23)	0.05 (-1.63, 1.68)	-0.67 (-2.91, 1.56)	-0.17 (-2.33, 1.98)	-0.29 (-1.39, 0.77)	0.60 (-1.65, 2.82)	0.51 (-1.71, 2.69)	0.13 (-2.09, 2.32)	-1.52 (-3.72, 0.66)	0.35 (-2.03, 2.69)	-1.27 (-3.53, 0.98)	-0.44 (-2.64, 1.72)	0.01 (-2.23, 2.22)	-0.45 (-2.59, 1.66)	-0.46 (-2.60, 1.65)		-	-	-	-
Valproate	-1.52 (-3.27, 0.20)	-0.33 (-2.32, 1.63)	-0.31 (-2.57, 1.89)	-1.02 (-3.73, 1.66)	-0.52 (-3.16, 2.07)	-0.64 (-2.53, 1.20)	0.25 (-2.47, 2.93)	0.16 (-2.55, 2.82)	-0.23 (-2.91, 2.41)	-1.87 (-4.55, 0.75)	0.00 (-2.79, 2.75)	-1.62 (-4.34, 1.07)	-0.79 (-3.46, 1.83)	-0.34 (-3.08, 2.33)	-0.80 (-3.39, 1.77)	-0.82 (-3.44, 1.76)	-0.35 (-2.30, 1.58)		-	-	-
Topiramate	-0.18 (-2.08,	1.01 (-1.11,	1.04 (-1.32,	0.32 (-2.47,	0.82 (-1.91,	0.70 (-1.33,	1.60 (-1.24,	1.50 (-1.30,	1.12 (-1.64,	-0.53 (-3.30,	1.34 (-1.55,	-0.27 (-3.09,	0.55 (-2.20,	1.00 (-1.84,	0.54 (-2.16,	0.53 (-2.19,	0.99 (-1.10,	1.34 (-1.22,		-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
	1.73)	3.13)	3.39)	3.13)	3.56)	2.72)	4.43)	4.29)	3.90)	2.25)	4.24)	2.53)	3.30)	3.83)	3.23)	3.24)	3.10)	3.94)			
Tramadol	-1.30 (-2.76, 0.14)	-0.12 (-1.85, 1.61)	-0.09 (-2.11, 1.91)	-0.80 (-3.33, 1.70)	-0.31 (-2.77, 2.13)	-0.43 (-2.05, 1.18)	0.47 (-2.08, 2.98)	0.38 (-2.15, 2.88)	-0.01 (-2.50, 2.47)	-1.66 (-4.13, 0.80)	0.21 (-2.43, 2.84)	-1.41 (-3.93, 1.12)	-0.58 (-3.07, 1.88)	-0.13 (-2.67, 2.39)	-0.58 (-3.02, 1.82)	-0.60 (-3.03, 1.81)	-0.14 (-1.83, 1.57)	0.22 (-2.03, 2.49)	-1.12 (-3.52, 1.25)		-
Venlafaxine	-1.00 (-3.02, 1.02)	0.19 (-2.03, 2.43)	0.22 (-2.25, 2.67)	-0.49 (-3.38, 2.39)	0.00 (-2.82, 2.82)	-0.12 (-2.26, 2.01)	0.77 (-2.12, 3.69)	0.68 (-2.21, 3.55)	0.30 (-1.75, 2.35)	-1.35 (-4.18, 1.49)	0.52 (-2.45, 3.49)	-1.10 (-4.01, 1.80)	-0.27 (-3.12, 2.56)	0.17 (-2.73, 3.08)	-0.29 (-3.07, 2.51)	-0.29 (-3.09, 2.49)	0.17 (-2.03, 2.39)	0.52 (-2.11, 3.22)	-0.82 (-3.58, 1.95)	0.30 (-2.18, 2.80)	

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.

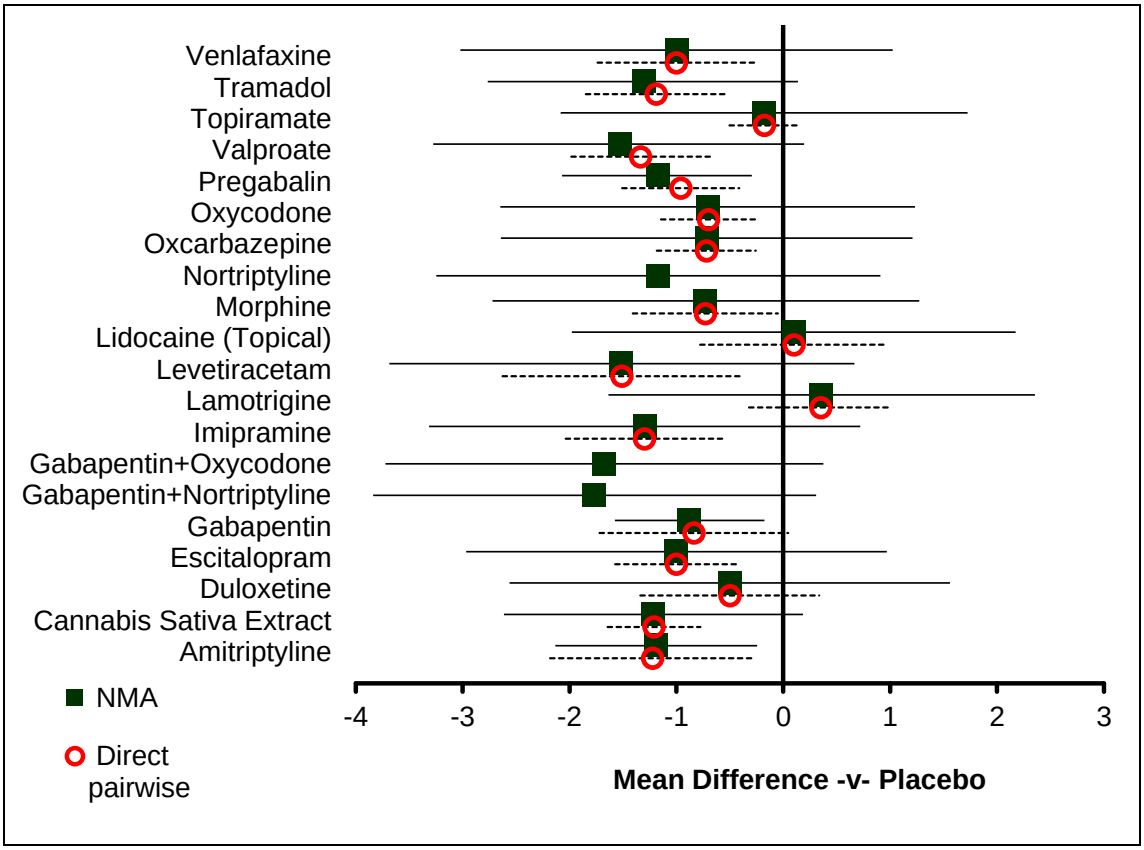


Figure 37 pain (continuous) - 28 +/- 7 days - relative effect of all options compared with placebo

(values less than 0 favour the treatment; values greater than 0 favour placebo; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 61 pain (continuous) - 28 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	18 (14, 20)
Amitriptyline	0.007	9 (2, 16)
Cannabis Sativa Extract	0.029	9 (1, 18)
Duloxetine	0.019	15 (2, 21)
Escitalopram	0.047	10 (1, 21)
Gabapentin	0.000	12 (6, 17)
Gabapentin+Nortriptyline	0.183	4 (1, 18)
Gabapentin+Oxycodone	0.164	5 (1, 19)
Imipramine	0.081	8 (1, 20)
Lamotrigine	0.002	19 (6, 21)
Levetiracetam	0.150	6 (1, 20)
Lidocaine (Topical)	0.005	18 (4, 21)
Morphine	0.028	13 (1, 21)
Nortriptyline	0.046	9 (1, 20)
Oxcarbazepine	0.023	13 (2, 21)
Oxycodone	0.023	13 (2, 21)
Pregabalin	0.005	9 (3, 16)
Valproate	0.100	6 (1, 18)
Topiramate	0.006	17 (3, 21)
Tramadol	0.042	8 (1, 18)
Venlafaxine	0.042	11 (1, 21)

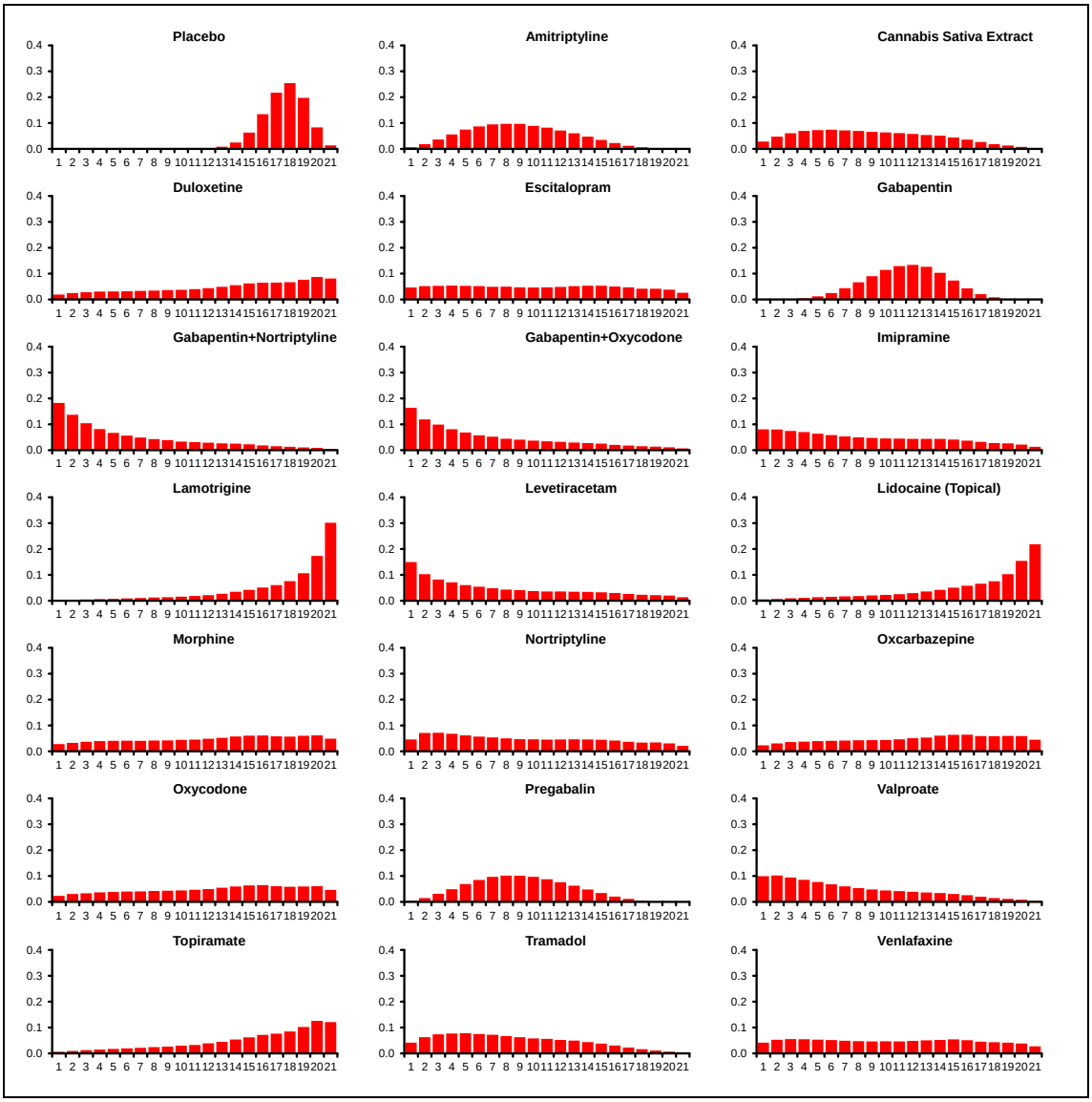


Figure 38 pain (continuous) - 28 +/- 7 days - rank probability histograms

Table 62 pain (continuous) - 28 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
68.66 (compared to 69 data-points)	-21.183	-88.062	66.879	45.697	0.765 (95%CrI: 0.398, 1.878)

Table 63 pain (continuous) - 28 +/- 7 days - 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 7b: 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)	21 RCTs[a] n=2923	very serious[1]	very 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 4 studies and it was unclear if they were comparable in 10 others; concomitant drugs permitted varies across the studies in the network; one study was single-blind

[2] I^2 was 96 and 90 for gabapentin and pregabalin vs placebo, respectively, which may indicate considerable heterogeneity; I^2 was 47% for the two arms of Rintala comparing amitriptyline vs gabapentin (with and without depression) which may indicate moderate inconsistency; there did not appear to be differences between indirect and direct comparisons for most, however, the direct comparison for amitriptyline and gabapentin was slightly different than that for the indirect comparison but this is not likely to be considered clinical different.

[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 for effectiveness estimates of most interventions compared to placebo and in the overall ranking in the network

[a] **Placebo-controlled trials**

amitriptyline (n=68): Graff-Radford et al. (2000), Rintala et al. (2007); unclear if concomitant drugs were permitted in one, but as oxycodone was used as a rescue medication in the other (this is in the scope of the guideline for the use in NP so considered a concomitant medication)

duloxetine (n=48): Vranken et al. (2011); concomitant drugs permitted if stable except anti-depressants

gabapentin (n=758): Backonja et al. (1998), Levendoglu et al. (2004), Rice & Maton (2001), Rintala et al. (2007), Rowbotham et al. (1998); concomitant drugs not permitted in one, unclear in one, but permitted in the others (but only SSRIs in one, and one only allowed oxycodone as rescue medication so is considered concomitant medication)

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

levetiracetam (n=19): Rossi et al. (2009); 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.

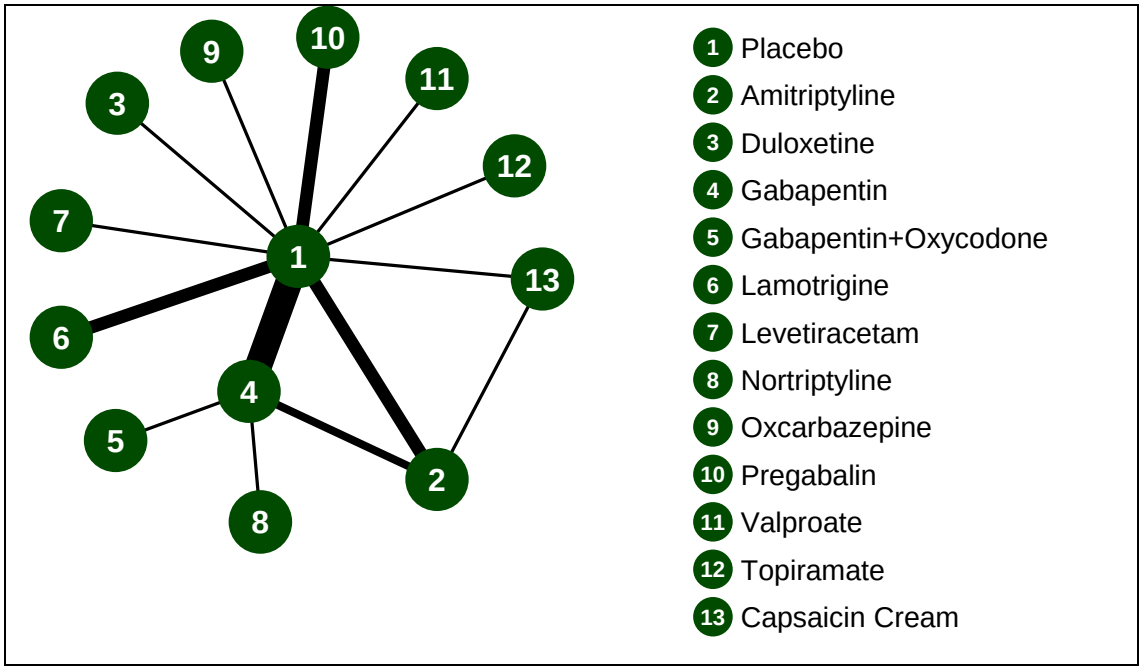


Figure 39 pain (continuous) - 56 +/- 7 days - evidence network

Table 64 pain (continuous) - 56 +/- 7 days - trials included in analysis

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lamotrigine	Levetiracetam	Nortriptyline	Oxcarbazepine	Pregabalin	Valproate	Topiramate
Amitriptyline	3 RCTs[6,16,16] total n=68											
Duloxetine	1 RCT[21] total n=48	-										
Gabapentin	6 RCTs[1,10,15,16,16,18] total n=716	2 RCTs[16,16] total n=44	-									
Gabapentin +Oxycodone	-	-	-	1 RCT[8] total n=328								
Lamotrigine	3 RCTs[5,11,13] total n=212	-	-	-	-							
Levetiracetam	1 RCT[17] total n=19	-	-	-	-	-						
Nortriptyline	-	-	-	1 RCT[3] total n=70	-	-	-					
Oxcarbazepine	1 RCT[4] total n=146	-	-	-	-	-	-	-				
Pregabalin	3 RCTs[7,12,19] total n=749	-	-	-	-	-	-	-	-			
Valproate	1 RCT[9] total n=40	-	-	-	-	-	-	-	-	-		
Topiramate	1 RCT[14] total n=317	-	-	-	-	-	-	-	-	-	-	
Capsaicin Cream	1 RCT[20] 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) Levendoglu et al. (2004); (11) Luria et al. (2000); (12) Moon et al. (2010); (13) Rao et al. (2008); (14) Raskin et al. (2004); (15) Rice & Maton (2001); (16) Rintala et al. (2007); (17) Rossi et al. (2009); (18) Rowbotham et al. (1998); (19) Sabatowski et al. (2004); (20) Tandan et al. (1992); (21) Vranken et al. (2011)

Table 65 pain (continuous) - 56 +/- 7 days - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lamotrigine	Levetiracetam	Nortriptyline	Oxcarbazepine	Pregabalin	Valproate	Topiramate	Capsaicin Cream
Placebo		-1.99 (-2.89, -1.09)	-1.00 (-1.85, -0.15)	-1.51 (-2.80, -0.21)	-	-0.97 (-1.20, -0.74)	-2.71 (-4.27, -1.15)	-	-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	-2.29 (-3.62, -0.96)		-	1.55 (-0.09, 3.20)	-	-	-	-	-	-	-	-	0.30 (0.22, 0.38)
Duloxetine	-1.00 (-3.33, 1.33)	1.29 (-1.40, 3.99)		-	-	-	-	-	-	-	-	-	-
Gabapentin	-1.57 (-2.46, -0.59)	0.73 (-0.69, 2.21)	-0.57 (-3.05, 2.00)		-0.80 (-1.31, -0.29)	-	-	-0.21 (-1.05, 0.63)	-	-	-	-	-
Gabapentin +Oxycodone	-2.37 (-4.76, 0.13)	-0.08 (-2.73, 2.65)	-1.37 (-4.70, 2.05)	-0.80 (-3.06, 1.46)		-	-	-	-	-	-	-	-
Lamotrigine	-0.89 (-2.26, 0.48)	1.40 (-0.50, 3.31)	0.11 (-2.61, 2.81)	0.68 (-1.02, 2.29)	1.48 (-1.37, 4.23)		-	-	-	-	-	-	-
Levetiracetam	-2.71 (-5.40, -0.04)	-0.42 (-3.42, 2.54)	-1.72 (-5.28, 1.83)	-1.15 (-4.01, 1.64)	-0.35 (-4.03, 3.23)	-1.83 (-4.85, 1.19)		-	-	-	-	-	-
Nortriptyline	-1.78 (-4.25, 0.79)	0.51 (-2.20, 3.31)	-0.78 (-4.17, 2.71)	-0.22 (-2.56, 2.14)	0.58 (-2.67, 3.85)	-0.89 (-3.73, 2.03)	0.94 (-2.69, 4.66)		-	-	-	-	-
Oxcarbazepine	-0.92 (-3.21, 1.38)	1.37 (-1.28, 4.03)	0.08 (-3.20, 3.35)	0.65 (-1.87, 3.09)	1.44 (-1.94, 4.77)	-0.04 (-2.69, 2.63)	1.79 (-1.73, 5.33)	0.85 (-2.59, 4.23)		-	-	-	-

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lamotrigine	Levetiracetam	Nortriptyline	Oxcarbazepine	Pregabalin	Valproate	Topiramate	Capsaicin Cream
Pregabalin	-0.99 (-2.22, 0.24)	1.30 (-0.50, 3.11)	0.01 (-2.64, 2.65)	0.57 (-1.01, 2.07)	1.37 (-1.40, 4.05)	-0.11 (-1.94, 1.73)	1.72 (-1.22, 4.67)	0.79 (-2.07, 3.54)	-0.07 (-2.67, 2.52)		-	-	-
Valproate	-2.54 (-4.95, -0.11)	-0.25 (-2.99, 2.51)	-1.53 (-4.91, 1.82)	-0.97 (-3.60, 1.60)	-0.17 (-3.65, 3.23)	-1.65 (-4.42, 1.13)	0.18 (-3.44, 3.79)	-0.75 (-4.30, 2.68)	-1.62 (-4.95, 1.73)	-1.54 (-4.25, 1.18)		-	-
Topiramate	-0.65 (-2.91, 1.60)	1.63 (-0.96, 4.25)	0.35 (-2.90, 3.60)	0.91 (-1.57, 3.31)	1.71 (-1.67, 4.99)	0.23 (-2.40, 2.87)	2.06 (-1.40, 5.56)	1.13 (-2.32, 4.45)	0.27 (-2.93, 3.48)	0.34 (-2.24, 2.91)	1.87 (-1.43, 5.18)		-
Capsaicin Cream	-1.68 (-3.51, 0.18)	0.61 (-1.12, 2.39)	-0.67 (-3.65, 2.32)	-0.11 (-2.13, 1.85)	0.69 (-2.35, 3.67)	-0.79 (-3.06, 1.52)	1.04 (-2.20, 4.31)	0.10 (-3.00, 3.16)	-0.75 (-3.68, 2.20)	-0.68 (-2.87, 1.54)	0.86 (-2.16, 3.92)	-1.02 (-3.89, 1.89)	

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.

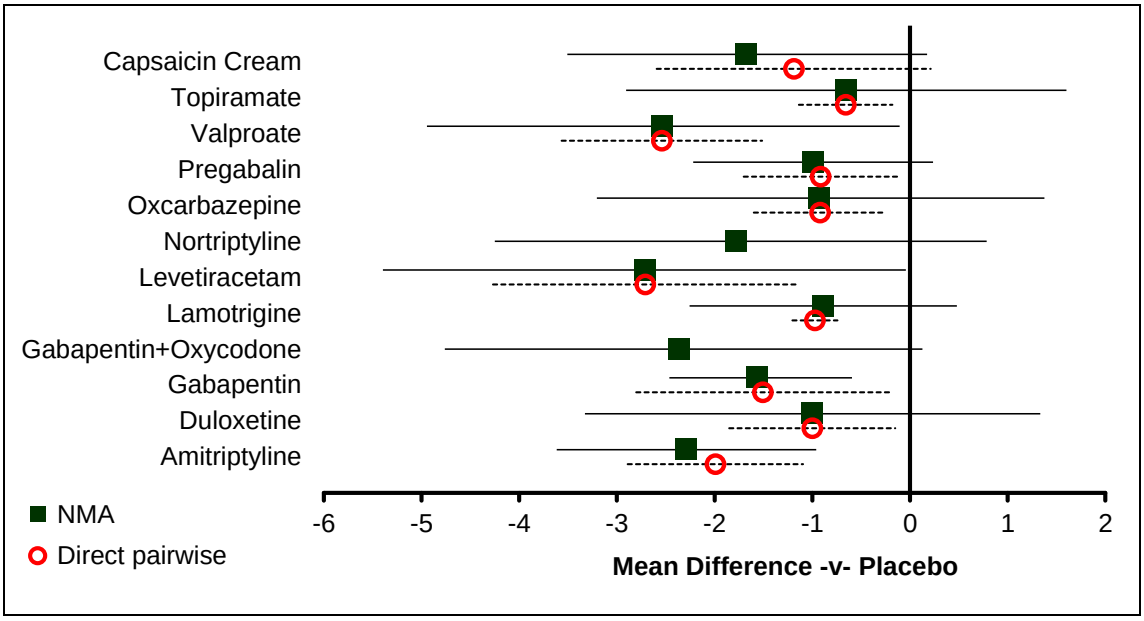


Figure 40 pain (continuous) - 56 +/- 7 days - relative effect of all options compared with placebo

(values less than 0 favour the treatment; values greater than 0 favour placebo; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 66 pain (continuous) - 56 +/- 7 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	12 (10, 13)
Amitriptyline	0.073	4 (1, 9)
Duloxetine	0.023	9 (2, 13)
Gabapentin	0.001	7 (3, 10)
Gabapentin+Oxycodone	0.187	3 (1, 12)
Lamotrigine	0.002	9 (4, 13)
Levetiracetam	0.322	3 (1, 12)
Nortriptyline	0.087	6 (1, 13)
Oxcarbazepine	0.019	9 (2, 13)
Pregabalin	0.001	9 (4, 12)
Valproate	0.243	3 (1, 11)
Topiramate	0.011	10 (2, 13)
Capsaicin Cream	0.033	6 (1, 12)

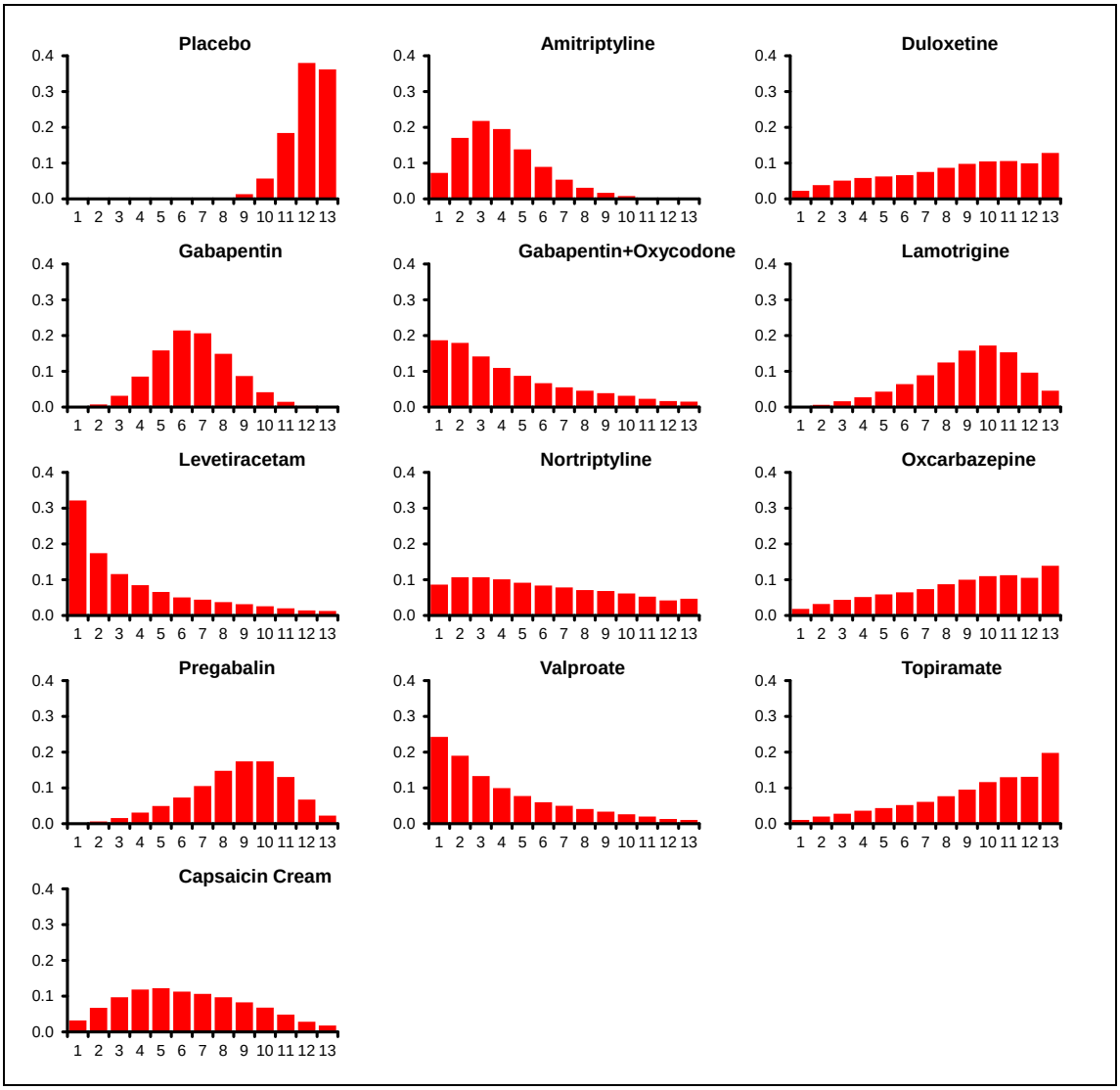


Figure 41 pain (continuous) - 56 +/- 7 days - rank probability histograms

Table 67 pain (continuous) - 56 +/- 7 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
47.61 (compared to 48 data-points)	1.522	-44.108	45.63	47.151	0.965 (95%CrI: 0.448, 2.870)

Table 68 pain (continuous) - 56 +/- 7 days - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
- Rintala (2007) reported this outcome separately in those with and without depression – both arms are included here since the study did not report this outcome for both of these groups separately.

Summary GRADE profile 7c: 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)	15 RCTs[a] n=2987	very serious[1]	serious[2]	not serious[3]	serious[4]	low	Important

[1] over half of the studies were unclear about allocation concealment; groups were not comparable at baseline in 3 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; one study was single-blind

[2] I^2 was 90% 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 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

levetiracetam (n=19): Rossi et al. (2009); concomitant drugs not permitted

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

pregabalin (n=801): Siddall et al. (2006), Simpson et al. (2010), van Seventer et al. (2006); concomitant drugs permitted but anti-convulsants excluded in one and gabapentin excluded in another

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.

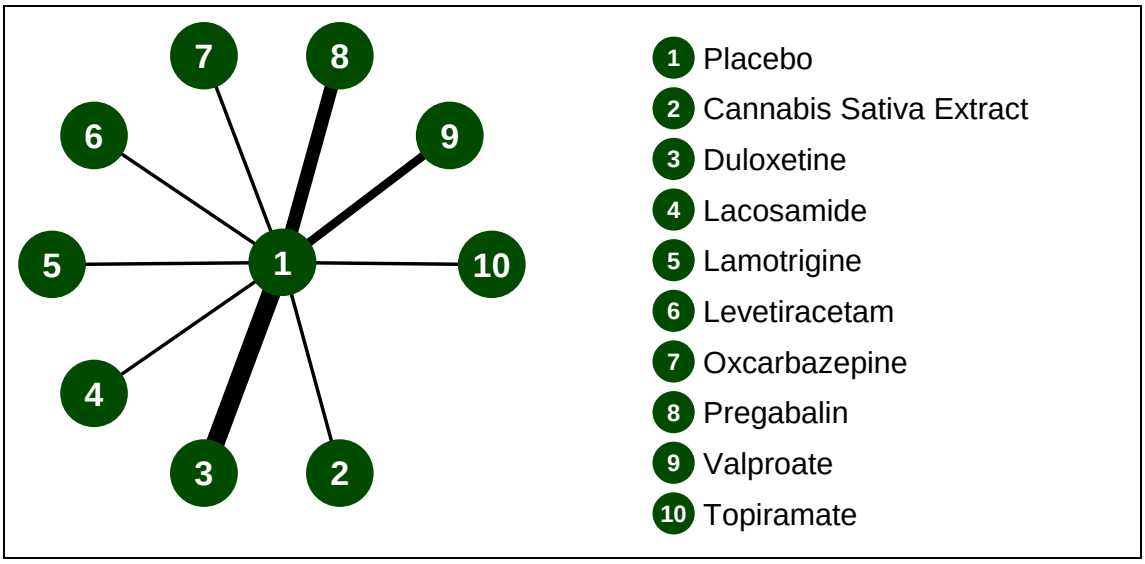


Figure 42 pain (continuous) - 84 +/- 14 days - evidence network

Table 69 pain (continuous) - 84 +/- 14 days - trials included in analysis

	Placebo	Cannabis Sativa Extract	Duloxetine	Lacosamide	Lamotrigine	Levetiracetam	Oxcarbazepine	Pregabalin	Valproate
Cannabis Sativa Extract	1 RCT[10] total n=30								
Duloxetine	4 RCTs[3,7,14,15] total n=1352	-							
Lacosamide	1 RCT[8] total n=119	-	-						
Lamotrigine	1 RCT[5] total n=125	-	-	-					
Levetiracetam	1 RCT[9] total n=18	-	-	-	-				
Oxcarbazepine	1 RCT[2] total n=146	-	-	-	-	-			
Pregabalin	3 RCTs[11,12,13] total n=801	-	-	-	-	-	-		
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) Rossi et al. (2009); (10) Selvarajah et al. (2010); (11) Siddall et al. (2006); (12) Simpson et al. (2010); (13) van Seventer et al. (2006); (14) Wernicke et al. (2006); (15) Yasuda et al. (2011)

Table 70 pain (continuous) - 84 +/- 14 days - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Duloxetine	Lacosamide	Lamotrigine	Levetiracetam	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)	-2.81 (-4.54, -1.08)	-0.82 (-1.61, -0.03)	-0.86 (-1.61, -0.11)	-0.56 (-2.77, 1.64)	-0.67 (-1.23, -0.11)
Cannabis Sativa Extract	0.41 (-1.77, 2.55)		-	-	-	-	-	-	-	-
Duloxetine	-1.01 (-1.51, -0.51)	-1.42 (-3.62, 0.82)		-	-	-	-	-	-	-
Lacosamide	-0.90 (-2.20, 0.41)	-1.30 (-3.82, 1.23)	0.11 (-1.28, 1.52)		-	-	-	-	-	-
Lamotrigine	-0.15 (-1.69, 1.40)	-0.55 (-3.19, 2.12)	0.86 (-0.75, 2.50)	0.75 (-1.29, 2.77)		-	-	-	-	-
Levetiracetam	-2.81 (-4.80, -0.80)	-3.21 (-6.16, -0.23)	-1.80 (-3.86, 0.28)	-1.91 (-4.30, 0.48)	-2.66 (-5.19, -0.12)		-	-	-	-
Oxcarbazepine	-0.82 (-2.11, 0.47)	-1.22 (-3.73, 1.31)	0.19 (-1.19, 1.58)	0.08 (-1.78, 1.92)	-0.68 (-2.69, 1.35)	1.98 (-0.40, 4.36)		-	-	-
Pregabalin	-0.84 (-1.48, -0.25)	-1.24 (-3.49, 1.01)	0.17 (-0.64, 0.94)	0.06 (-1.40, 1.48)	-0.69 (-2.37, 0.95)	1.97 (-0.15, 4.04)	-0.01 (-1.47, 1.39)		-	-
Valproate	-0.23 (-1.42, 0.88)	-0.63 (-3.10, 1.80)	0.79 (-0.52, 2.01)	0.68 (-1.12, 2.38)	-0.08 (-2.04, 1.82)	2.57 (0.23, 4.85)	0.59 (-1.18, 2.29)	0.61 (-0.71, 1.89)		-
Topiramate	-0.67 (-1.84, 0.50)	-1.07 (-3.52, 1.40)	0.34 (-0.93, 1.62)	0.23 (-1.53, 1.99)	-0.52 (-2.46, 1.43)	2.14 (-0.18, 4.46)	0.15 (-1.59, 1.90)	0.17 (-1.13, 1.52)	-0.44 (-2.05, 1.25)	

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.

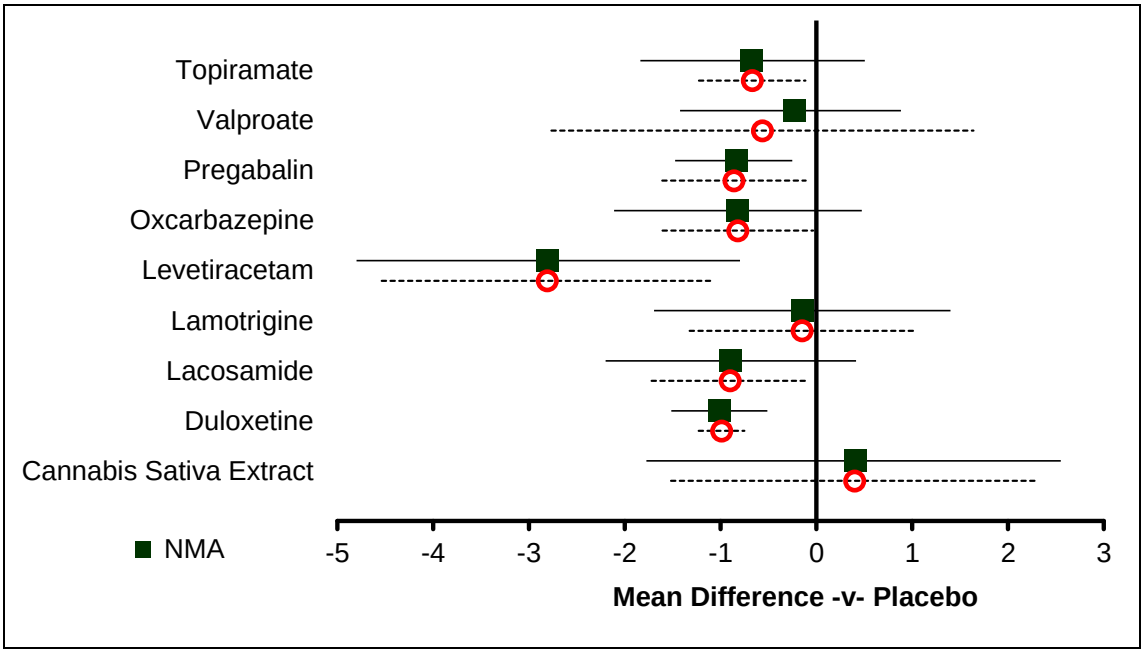


Figure 43 pain (continuous) - 84 +/- 14 days - relative effect of all options compared with placebo

(values less than 0 favour the treatment; values greater than 0 favour placebo; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 71 pain (continuous) - 84 +/- 14 days - rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	8 (6, 10)
Cannabis Sativa Extract	0.010	10 (2, 10)
Duloxetine	0.012	4 (2, 7)
Lacosamide	0.036	4 (1, 9)
Lamotrigine	0.008	8 (2, 10)
Levetiracetam	0.883	1 (1, 5)
Oxcarbazepine	0.028	5 (1, 10)
Pregabalin	0.006	5 (2, 8)
Valproate	0.004	7 (2, 10)
Topiramate	0.014	5 (2, 10)

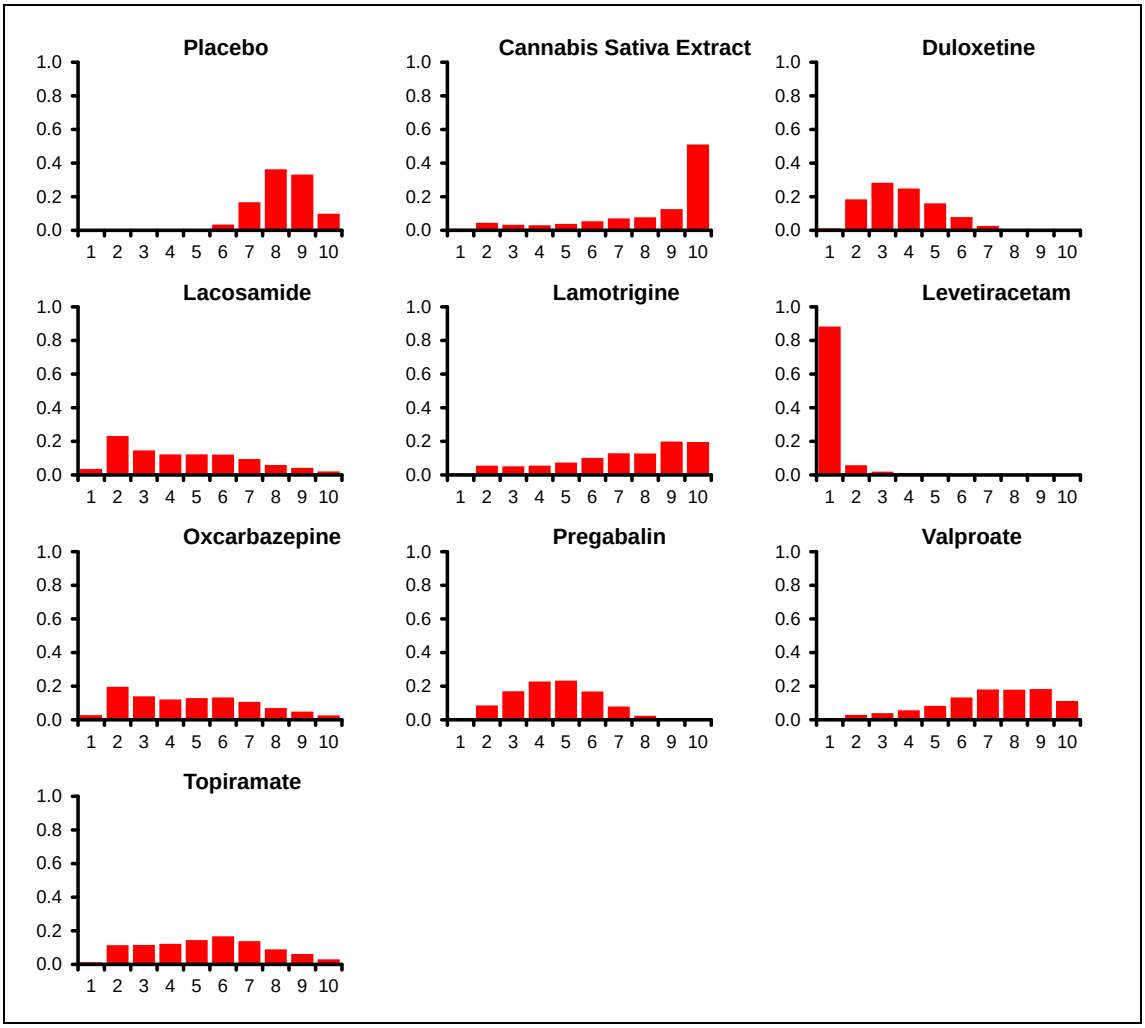


Figure 44 pain (continuous) - 84 +/- 14 days - rank probability histograms

Table 72 pain (continuous) - 84 +/- 14 days - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
37.27 (compared to 37 data-points)	7.357	-25.746	33.103	40.461	0.182 (95%CrI: 0.066, 0.727)

Table 73 pain (continuous) - 84 +/- 14 days - notes

- Random-effects model was used.
- 10000 burn-ins and 50000 iterations.
- Hanna (2008) was excluded from this analysis as it was not connected to the network
- Includes Rauck et al (2007) and Rao et al (2008) which report outcomes at 70 days.