Appendix K Evidence syntheses for health economic model

Dedicated evidence syntheses were performed to provide estimates of efficacy and safety for the health economic model. These conformed to the methods set out in appendix L, with some additional features as detailed below.

1 All neuropathic pain

1.1 Efficacy

1.1.1 30% and 50% pain relief

Basis of model

The model categorises people into those with less than 30% pain relief, those with more than 30% but less than 50% pain relief and those with 50% pain relief or greater. The probability of achieving each of these outcomes with each of the drugs is derived from a single synthesis model that incorporates reported 30% and 50% response rates from all trials reporting 1 or both (network meta-analysis for ordered categorical data using a generalised linear model with probit link function; see Dias et al., NICE DSU Technical Support Document 2 for technical details).

Relative effects are estimated as *z*-scores – standard deviations on a standard normal distribution – which can then be converted into probabilities. Please note that the use of a standard normal distribution for this transformation does not imply any assumption about the distribution of the underlying variable (in this case, pain relief): the model is not configured to recognise relief as fundamentally associated with the quantities 30% and 50%; rather, it treats these thresholds as arbitrary and estimates response probabilities from the response data alone.

More formally, the probability (p) of patients in arm k of trial i achieving category j is modelled as

$$p_{ikj} = \Phi\left(\mu_i + z_j + \delta_{t_{ik},t_{i1}} I_{\{k\neq 1\}}\right), \quad (1)$$

where Φ represents the cumulative distribution function of the standard normal distribution, μ_i is the trial-specific baseline probability of achieving the first response category with the 'control' treatment, z_j represents the differences on the standard normal scale between the response to category j and the response to category $j-1$, $\delta_{t_{ik},t_{i1}}$ is the trial-specific treatment effect of the treatment in arm k relative to the treatment in arm 1 (the 'control' treatment), and $I_{\{k\neq 1\}}$ is an indicator function taking the value 0 where treatment k is the 'control' treatment, and 1 otherwise. The choice of which treatment is designated as 'control' is arbitrary. In the syntheses reported here, placebo arms, where available, were assumed to be the 'control'; in the case of head-to-head trials, the distinction was made alphabetically. The z_js are modelled as fixed effects – that is, a single estimate of the difference between categories is shared across all trials.

Data from all follow-up times are included in the synthesis of relative effects, to provide a single estimate of **relative** probability of response for each treatment compared with a common baseline (placebo). In the few instances where a trial provided estimates of response at more than 1 timepoint, only the latest-reported was used, to avoid double-counting of trial participants.

These probabilities are then applied to a series of **absolute** probabilities of response, estimated in a separate baseline model comprising data from the placebo arms of all included trials (see Dias et al., NICE DSU Technical Support Document 5 for technical details). These juncture-specific absolute (baseline) results and the time-independent estimates of relative effect are combined to estimate probability of response over time (at 4, 8, 12, 16 and 20 weeks' follow-up).

For instance, if the probability of achieving 50% pain relief with placebo after 8 weeks' treatment is 0.185 and the z-score associated with gabapentin compared with placebo is −0.367, the probability of 50% response with gabapentin can be estimated as

$$1-\Phi\left(\Phi^{-1}\left[1-0.185\right]-0.367\right), \\ =0.299$$

where Φ again represents the cumulative distribution function of the standard normal distribution, and Φ^{-1} is the inverse function of the same.

Models presented

Two models are presented. Each relies on an identical dataset comprising response probabilities from all available trials. However, in recognition of heterogeneity of dosages investigated in the included trials, the second model (Table 4) includes an additional term for each comparator, which estimates the relationship between dose and effect in reported response rates. This term is incorporated as an additional coefficient in the linear model; in this way, estimated probability of response becomes a combination of baseline (placebo) expectation + relative effect for the drug in question + amount effect is observed to vary with dose (the covariate is centred around the mean dose for the comparator in the dataset).

Expressed algebraically, the model in equation (1) is extended such that (2)

$$p_{ikj}=\Phi\left(\mu_i+z_j+\left[\delta_{t_{ik},t_{t1}}+\left\{\beta_{t_{ik}}\left(x_{ik}-\bar{x}_{t_{ik}}\right)-\beta_{t_{i1}}\left(x_{i1}-\bar{x}_{t_{i1}}\right)\right\}\right]I_{\{k\neq 1\}}\right),$$

where $\beta_{t_{ik}}$ and $\beta_{t_{i1}}$ are dose–response coefficients for the 'treatment' and 'control' arms of each comparison, x_{ik} and x_{i1} represent the doses at which the treatments in these arms were delivered, and $\bar{x}_{t_{ik}}$ and $\bar{x}_{t_{i1}}$ are the mean doses observed for those treatments in the dataset under synthesis.

Using this model, estimates of response probability can be computed for any specified dose level. The GDG was asked to estimate typical maintenance dosages for each drug in the decision-set, and these values were used as the expected dosage with which effects were calculated. For some less commonly used drugs, the GDG was unable to provide estimates of typical practice; for these, the mean value of dosages used in the trials was used instead.

Other potential covariates of outcome – including fixed versus flexible dose regimens, baseline pain status, age, sex and diagnosis – were explored both in combination with and instead of dose–response adjustment. These did not provide informative results or improve model fit.

Models were run for 50,000 burn-ins and 10,000 captured iterations. Where there was judged to be evidence of conspicuous autocorrelation on inspection of diagnostic graphics, results were instead based on 10,000 iterations thinned from 100,000. In either event, the 10,000 lines of raw output ('CODA file') were stored and used in the health economic model.

Data and results

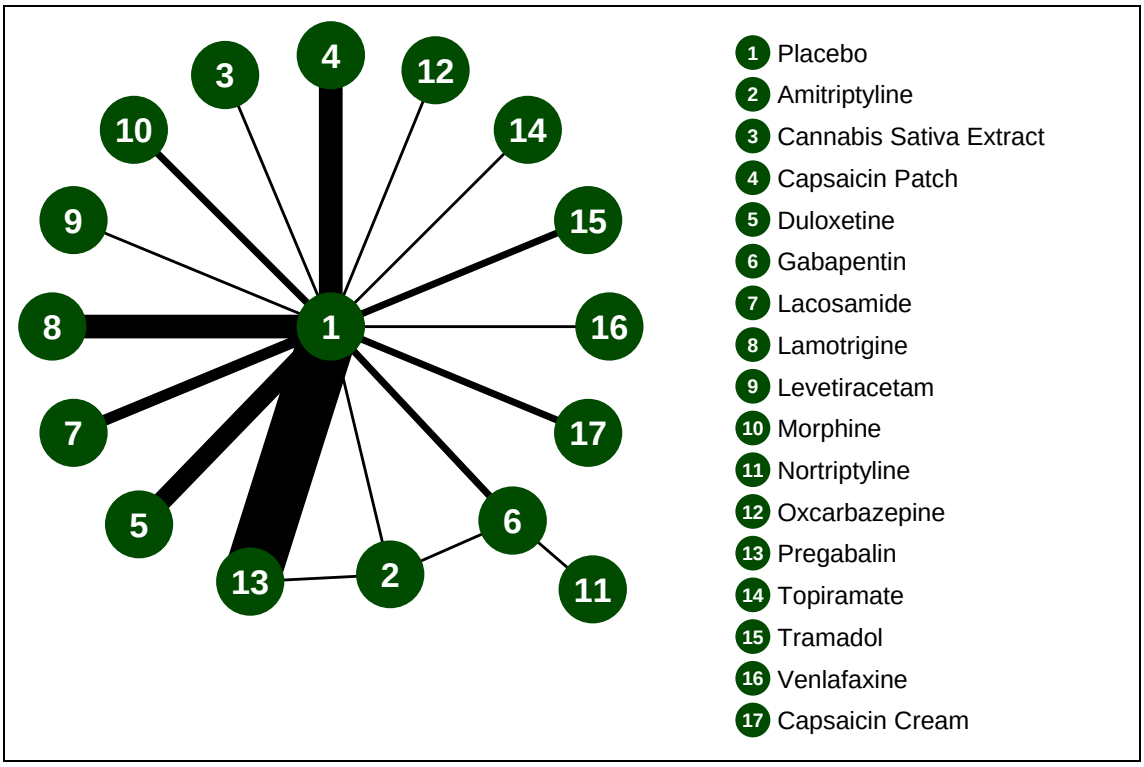


Figure 1 30% and 50% pain relief – evidence network

1 **Table 1 30% and 50% pain relief – trials included in analysis**

	Placebo	Amitriptyline	Cannabis 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[1,4,7,15,16,33] total n=4890	-	-													
Duloxetine	5 RCTs[12,13,21,30,39] total n=2579	-	-	-												
Gabapentin	2 RCTs[24,47] total n=410	1 RCT[47] total n=76	-	-	-											
Lacosamide	3 RCTs[23,36,37] total n=1753	-	-	-	-	-										
Lamotrigine	6 RCTs[10,18,32,35,42,44] total n=1790	-	-	-	-	-	-									
Levetiracetam	1 RCT[45] total n=144	-	-	-	-	-	-	-								
Morphine	2 RCTs[46,49] total n=248	-	-	-	-	-	-	-	-							
Nortriptyline	-	-	-	-	-	1 RCT[5] total n=70	-	-	-	-						
Oxcarbazepine	1 RCT[8] total n=292	-	-	-	-	-	-	-	-	-	-					
Pregabalin	14 RCTs[6,9,11,14,17,19,25,26,28,29,31,34,40,41] total n=5816	1 RCT[43] total n=102	-	-	-	-	-	-	-	-	-	-				
Topiramate	1 RCT[22] total n=646	-	-	-	-	-	-	-	-	-	-	-	-			

	Placebo	Amitriptyline	Cannabis Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine
Tramadol	2 RCTs[3,48] 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) Boureau et al. (2003); (4) Webster et al. (2010); (5) Chandra et al. (2006); (6) Stacey et al. (2008); (7) Clifford et al. (2012); (8) Dogra et al. (2005); (9) Dworkin et al. (2003); (10) Eisenberg et al. (2001); (11) Freynhagen et al. (2005); (12) Gao et al. (2010); (13) Goldstein et al. (2005); (14) Guan et al. (2011); (15) Irving et al. (2012); (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)

1 **Table 2 30% and 50% pain relief – relative effectiveness of all pairwise combinations (z-scores; no adjustment for dose)**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amitriptyline	-0.40 (-0.86,0.05)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cannabis Sativa Extract	-0.48 (-1.09,0.12)	-0.08 (-0.83,0.68)		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
Capsaicin Patch	-0.24 (-0.41,-0.07)	0.16 (-0.32,0.65)	0.24 (-0.38,0.87)		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	-0.53 (-0.71,-0.34)	-0.12 (-0.62,0.37)	-0.05 (-0.67,0.58)	-0.28 (-0.53,-0.04)		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	-0.36 (-0.73,0.02)	0.04 (-0.48,0.57)	0.12 (-0.58,0.83)	-0.12 (-0.52,0.29)	0.17 (-0.25,0.59)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lacosamide	-0.24 (-0.51,0.03)	0.16 (-0.37,0.70)	0.24 (-0.42,0.90)	0.00 (-0.32,0.31)	0.28 (-0.04,0.61)	0.12 (-0.34,0.58)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lamotrigine	-0.23 (-0.47,-0.01)	0.17 (-0.35,0.67)	0.24 (-0.40,0.90)	0.01 (-0.28,0.28)	0.29 (-0.01,0.58)	0.13 (-0.32,0.56)	0.01 (-0.35,0.35)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Levetiracetam	0.15 (-0.71,1.06)	0.56 (-0.43,1.57)	0.64 (-0.41,1.70)	0.39 (-0.49,1.32)	0.68 (-0.20,1.61)	0.51 (-0.41,1.48)	0.39 (-0.50,1.35)	0.39 (-0.50,1.32)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	-0.70 (-1.22,-0.17)	-0.30 (-0.96,0.39)	-0.22 (-0.99,0.56)	-0.46 (-1.00,0.10)	-0.17 (-0.72,0.39)	-0.34 (-0.97,0.30)	-0.45 (-1.04,0.13)	-0.47 (-1.02,0.11)	-0.85 (-1.89,0.17)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	-0.50 (-1.32,0.34)	-0.09 (-1.00,0.81)	-0.02 (-1.05,1.03)	-0.25 (-1.10,0.60)	0.03 (-0.83,0.89)	-0.13 (-0.88,0.58)	-0.25 (-1.11,0.62)	-0.26 (-1.12,0.62)	-0.66 (-1.83,0.57)	0.20 (-0.77,1.17)		N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	-0.47 (-1.01,0.05)	-0.07 (-0.78,0.62)	0.00 (-0.80,0.81)	-0.23 (-0.80,0.32)	0.05 (-0.52,0.61)	-0.11 (-0.77,0.52)	-0.23 (-0.83,0.35)	-0.24 (-0.81,0.33)	-0.63 (-1.67,0.36)	0.22 (-0.52,0.96)	0.01 (-0.95,1.01)		N/A	N/A	N/A	N/A	N/A
Pregabalin	-0.53 (-0.66,-0.42)	-0.13 (-0.59,0.32)	-0.06 (-0.66,0.56)	-0.29 (-0.50,-0.09)	-0.01 (-0.23,0.21)	-0.18 (-0.56,0.20)	-0.29 (-0.59,0.00)	-0.30 (-0.56,-0.04)	-0.68 (-1.60,0.18)	0.17 (-0.38,0.70)	-0.04 (-0.88,0.80)	-0.06 (-0.59,0.49)		N/A	N/A	N/A	N/A
Topiramate	-0.39 (-0.83,0.06)	0.02 (-0.62,0.65)	0.09 (-0.65,0.85)	-0.15 (-0.62,0.33)	0.14 (-0.35,0.62)	-0.02 (-0.61,0.55)	-0.15 (-0.66,0.37)	-0.15 (-0.65,0.36)	-0.54 (-1.54,0.43)	0.31 (-0.37,1.00)	0.11 (-0.85,1.05)	0.09 (-0.59,0.78)	0.15 (-0.32,0.61)		N/A	N/A	N/A
Tramadol	-0.55 (-0.99,-0.12)	-0.15 (-0.79,0.48)	-0.07 (-0.82,0.67)	-0.31 (-0.78,0.15)	-0.03 (-0.50,0.44)	-0.19 (-0.78,0.37)	-0.31 (-0.82,0.20)	-0.32 (-0.80,0.18)	-0.71 (-1.68,0.26)	0.14 (-0.52,0.82)	-0.06 (-1.01,0.89)	-0.08 (-0.76,0.61)	-0.02 (-0.47,0.43)	-0.16 (-0.80,0.46)		N/A	N/A
Venlafaxine	-0.35 (-0.80,0.12)	0.06 (-0.60,0.71)	0.14 (-0.63,0.90)	-0.11 (-0.60,0.39)	0.18 (-0.32,0.68)	0.01 (-0.60,0.61)	-0.11 (-0.64,0.43)	-0.11 (-0.63,0.41)	-0.50 (-1.50,0.48)	0.35 (-0.36,1.06)	0.15 (-0.83,1.09)	0.13 (-0.57,0.83)	0.19 (-0.28,0.67)	0.04 (-0.60,0.68)	0.21 (-0.43,0.84)		N/A
Capsaicin Cream	-1.27 (-2.06,-0.52)	-0.87 (-1.74,0.01)	-0.78 (-1.77,0.16)	-1.02 (-1.84,-0.26)	-0.74 (-1.55,0.03)	-0.90 (-1.77,-0.09)	-1.03 (-1.86,-0.22)	-1.03 (-1.85,-0.25)	-1.41 (-2.62,-0.26)	-0.56 (-1.50,0.31)	-0.77 (-1.87,0.30)	-0.78 (-1.73,0.12)	-0.73 (-1.52,0.03)	-0.88 (-1.78,0.00)	-0.71 (-1.61,0.16)	-0.92 (-1.82,-0.01)	

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). 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.

2

Table 3 Probability of pain relief over time as applied in the health economic model – no adjustment for dose

	placebo	amitriptyl-ine	cannabis sativa extract	capsaicin patch	duloxetine	gabapentin	lacosamide	lamotrigine	levetirace-tam	morphine	nortriptyline	oxcarbaze-pine	pregabalin	topiramate	tramadol	venlafaxine	capsaicin cream
4 weeks																	
<30%	0.80 (0.66,0.91)	0.67 (0.41,0.86)	0.64 (0.34,0.87)	0.73 (0.55,0.87)	0.63 (0.44,0.80)	0.69 (0.44,0.87)	0.73 (0.54,0.88)	0.74 (0.55,0.87)	0.85 (0.52,0.98)	0.56 (0.29,0.79)	0.64 (0.27,0.91)	0.65 (0.37,0.87)	0.63 (0.44,0.78)	0.68 (0.42,0.87)	0.62 (0.36,0.81)	0.70 (0.45,0.88)	0.33 (0.09,0.67)
30–49%	0.09 (0.05,0.13)	0.13 (0.07,0.16)	0.14 (0.07,0.16)	0.12 (0.07,0.15)	0.14 (0.10,0.16)	0.13 (0.07,0.16)	0.11 (0.06,0.15)	0.11 (0.06,0.15)	0.08 (0.01,0.15)	0.15 (0.09,0.17)	0.14 (0.05,0.16)	0.14 (0.07,0.16)	0.14 (0.10,0.16)	0.13 (0.07,0.16)	0.14 (0.09,0.16)	0.12 (0.06,0.16)	0.16 (0.08,0.17)
≥50%	0.10 (0.04,0.21)	0.20 (0.07,0.43)	0.22 (0.06,0.50)	0.15 (0.06,0.30)	0.23 (0.11,0.40)	0.19 (0.06,0.40)	0.15 (0.06,0.30)	0.15 (0.06,0.29)	0.08 (0.01,0.32)	0.29 (0.11,0.56)	0.22 (0.04,0.58)	0.22 (0.06,0.46)	0.23 (0.12,0.41)	0.19 (0.07,0.42)	0.24 (0.10,0.48)	0.18 (0.06,0.39)	0.52 (0.21,0.83)
8 weeks																	
<30%	0.69 (0.60,0.77)	0.53 (0.33,0.73)	0.50 (0.25,0.76)	0.60 (0.48,0.71)	0.49 (0.37,0.61)	0.55 (0.37,0.73)	0.60 (0.45,0.73)	0.60 (0.48,0.74)	0.75 (0.41,0.95)	0.41 (0.22,0.63)	0.50 (0.18,0.82)	0.51 (0.29,0.73)	0.48 (0.37,0.59)	0.54 (0.34,0.73)	0.47 (0.28,0.66)	0.56 (0.36,0.76)	0.21 (0.05,0.48)
30–49%	0.13 (0.10,0.15)	0.15 (0.12,0.17)	0.16 (0.11,0.17)	0.15 (0.12,0.16)	0.16 (0.14,0.17)	0.15 (0.12,0.17)	0.14 (0.11,0.16)	0.14 (0.11,0.16)	0.11 (0.03,0.16)	0.16 (0.13,0.17)	0.16 (0.09,0.17)	0.16 (0.12,0.17)	0.16 (0.14,0.17)	0.15 (0.11,0.17)	0.16 (0.13,0.17)	0.15 (0.11,0.17)	0.13 (0.06,0.16)
≥50%	0.19 (0.12,0.26)	0.31 (0.16,0.51)	0.34 (0.14,0.61)	0.26 (0.17,0.36)	0.35 (0.24,0.47)	0.30 (0.16,0.48)	0.26 (0.15,0.38)	0.25 (0.15,0.36)	0.14 (0.02,0.43)	0.43 (0.23,0.64)	0.35 (0.09,0.69)	0.34 (0.16,0.56)	0.36 (0.26,0.48)	0.31 (0.15,0.50)	0.37 (0.21,0.57)	0.29 (0.14,0.48)	0.66 (0.36,0.89)
12 weeks																	
<30%	0.65 (0.57,0.72)	0.49 (0.29,0.68)	0.45 (0.23,0.71)	0.55 (0.45,0.65)	0.44 (0.34,0.55)	0.50 (0.34,0.68)	0.56 (0.42,0.68)	0.56 (0.44,0.68)	0.71 (0.36,0.93)	0.37 (0.19,0.59)	0.45 (0.16,0.79)	0.46 (0.26,0.67)	0.44 (0.35,0.53)	0.49 (0.31,0.69)	0.43 (0.25,0.61)	0.52 (0.34,0.70)	0.18 (0.04,0.42)
30–49%	0.14 (0.12,0.15)	0.16 (0.13,0.17)	0.16 (0.12,0.17)	0.15 (0.13,0.16)	0.16 (0.15,0.17)	0.16 (0.13,0.17)	0.15 (0.13,0.16)	0.15 (0.13,0.16)	0.12 (0.04,0.16)	0.16 (0.12,0.17)	0.16 (0.09,0.17)	0.16 (0.13,0.17)	0.16 (0.15,0.17)	0.16 (0.13,0.17)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.12 (0.05,0.16)
≥50%	0.22 (0.16,0.28)	0.36 (0.19,0.56)	0.39 (0.17,0.64)	0.29 (0.21,0.39)	0.40 (0.30,0.50)	0.34 (0.19,0.50)	0.29 (0.19,0.42)	0.29 (0.19,0.40)	0.17 (0.03,0.49)	0.47 (0.27,0.68)	0.39 (0.11,0.72)	0.38 (0.20,0.60)	0.40 (0.32,0.50)	0.35 (0.18,0.54)	0.41 (0.24,0.61)	0.33 (0.17,0.50)	0.70 (0.42,0.91)
16 weeks																	
<30%	0.61 (0.08,0.96)	0.44 (0.03,0.91)	0.41 (0.02,0.91)	0.51 (0.04,0.93)	0.40 (0.02,0.89)	0.46 (0.04,0.93)	0.51 (0.05,0.95)	0.52 (0.06,0.94)	0.67 (0.07,0.99)	0.33 (0.02,0.85)	0.41 (0.01,0.93)	0.42 (0.03,0.93)	0.39 (0.03,0.89)	0.45 (0.04,0.92)	0.39 (0.02,0.92)	0.47 (0.04,0.94)	0.15 (0.00,0.69)
30–49%	0.14 (0.02,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.17)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.13 (0.01,0.16)	0.16 (0.02,0.16)	0.16 (0.02,0.16)	0.16 (0.02,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.02,0.16)	0.16 (0.03,0.16)	0.11 (0.00,0.16)
≥50%	0.25 (0.01,0.85)	0.40 (0.04,0.92)	0.43 (0.04,0.94)	0.33 (0.03,0.91)	0.44 (0.05,0.94)	0.38 (0.03,0.92)	0.33 (0.02,0.89)	0.33 (0.02,0.89)	0.20 (0.00,0.85)	0.51 (0.07,0.96)	0.43 (0.03,0.96)	0.42 (0.03,0.94)	0.45 (0.05,0.94)	0.39 (0.03,0.92)	0.45 (0.03,0.95)	0.37 (0.03,0.92)	0.73 (0.18,0.99)
20 weeks																	
<30%	0.64 (0.49,0.77)	0.48 (0.25,0.70)	0.44 (0.20,0.73)	0.54 (0.37,0.70)	0.43 (0.27,0.60)	0.49 (0.28,0.71)	0.55 (0.36,0.71)	0.55 (0.37,0.72)	0.70 (0.32,0.94)	0.36 (0.16,0.61)	0.44 (0.14,0.78)	0.45 (0.21,0.71)	0.43 (0.27,0.59)	0.48 (0.26,0.71)	0.42 (0.22,0.64)	0.51 (0.27,0.73)	0.17 (0.04,0.43)
30–49%	0.14 (0.10,0.16)	0.16 (0.12,0.17)	0.16 (0.11,0.17)	0.15 (0.12,0.16)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.15 (0.12,0.17)	0.15 (0.12,0.17)	0.12 (0.04,0.16)	0.16 (0.12,0.17)	0.16 (0.09,0.17)	0.16 (0.12,0.17)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.16 (0.13,0.17)	0.16 (0.11,0.17)	0.12 (0.05,0.16)
≥50%	0.22 (0.13,0.35)	0.37 (0.18,0.60)	0.40 (0.15,0.67)	0.30 (0.17,0.46)	0.41 (0.25,0.58)	0.35 (0.17,0.56)	0.30 (0.17,0.49)	0.30 (0.17,0.47)	0.18 (0.03,0.53)	0.48 (0.24,0.71)	0.40 (0.12,0.74)	0.39 (0.17,0.66)	0.41 (0.27,0.58)	0.36 (0.17,0.59)	0.42 (0.22,0.65)	0.34 (0.15,0.59)	0.71 (0.41,0.92)

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 4 Probability of pain relief over time as applied in the health economic model – dose-variable version

	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%	0.80 (0.65,0.91)	0.73 (0.47,0.90)	0.65 (0.32,0.89)	0.73 (0.54,0.88)	0.63 (0.44,0.80)	0.61 (0.29,0.83)	0.74 (0.54,0.88)	0.73 (0.53,0.87)	0.85 (0.55,0.98)	0.58 (0.27,0.80)	0.64 (0.26,0.91)	0.65 (0.37,0.85)	0.67 (0.52,0.85)	0.68 (0.19,0.96)	0.62 (0.38,0.84)	0.74 (0.49,0.89)	0.36 (0.10,0.69)
30–49%	0.09 (0.05,0.13)	0.12 (0.05,0.16)	0.13 (0.06,0.16)	0.12 (0.06,0.15)	0.14 (0.09,0.16)	0.14 (0.08,0.16)	0.11 (0.06,0.15)	0.12 (0.07,0.15)	0.08 (0.01,0.15)	0.15 (0.10,0.16)	0.14 (0.05,0.16)	0.14 (0.07,0.16)	0.13 (0.07,0.16)	0.13 (0.02,0.16)	0.14 (0.08,0.16)	0.11 (0.06,0.16)	0.16 (0.09,0.17)
≥50%	0.10 (0.04,0.21)	0.15 (0.04,0.37)	0.21 (0.05,0.52)	0.15 (0.05,0.31)	0.23 (0.11,0.40)	0.25 (0.09,0.56)	0.15 (0.06,0.31)	0.15 (0.06,0.32)	0.08 (0.01,0.31)	0.27 (0.11,0.58)	0.22 (0.04,0.59)	0.22 (0.07,0.47)	0.20 (0.07,0.32)	0.19 (0.01,0.68)	0.24 (0.08,0.46)	0.15 (0.05,0.35)	0.48 (0.18,0.81)
8 weeks																	
<30%	0.69 (0.60,0.77)	0.60 (0.38,0.79)	0.51 (0.23,0.78)	0.60 (0.47,0.74)	0.49 (0.37,0.62)	0.47 (0.21,0.68)	0.60 (0.46,0.73)	0.60 (0.47,0.72)	0.74 (0.41,0.94)	0.44 (0.20,0.64)	0.50 (0.18,0.84)	0.51 (0.30,0.72)	0.53 (0.44,0.68)	0.54 (0.11,0.91)	0.47 (0.30,0.70)	0.61 (0.39,0.79)	0.23 (0.06,0.52)
30–49%	0.13 (0.10,0.15)	0.15 (0.10,0.16)	0.16 (0.10,0.17)	0.15 (0.11,0.16)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.14 (0.12,0.16)	0.15 (0.12,0.16)	0.11 (0.04,0.16)	0.16 (0.13,0.17)	0.16 (0.08,0.17)	0.16 (0.12,0.17)	0.16 (0.13,0.16)	0.15 (0.05,0.17)	0.16 (0.12,0.17)	0.14 (0.10,0.16)	0.14 (0.07,0.17)
≥50%	0.18 (0.13,0.26)	0.26 (0.12,0.47)	0.33 (0.11,0.63)	0.26 (0.15,0.37)	0.35 (0.24,0.47)	0.38 (0.19,0.66)	0.25 (0.15,0.38)	0.26 (0.16,0.37)	0.14 (0.03,0.43)	0.40 (0.22,0.67)	0.34 (0.08,0.70)	0.34 (0.17,0.55)	0.32 (0.19,0.40)	0.31 (0.04,0.79)	0.37 (0.17,0.55)	0.25 (0.12,0.46)	0.63 (0.32,0.87)
12 weeks																	
<30%	0.65 (0.57,0.72)	0.55 (0.33,0.76)	0.47 (0.20,0.74)	0.56 (0.42,0.68)	0.45 (0.34,0.55)	0.42 (0.19,0.63)	0.56 (0.42,0.68)	0.55 (0.44,0.67)	0.71 (0.36,0.92)	0.39 (0.18,0.58)	0.45 (0.15,0.80)	0.46 (0.26,0.67)	0.48 (0.41,0.63)	0.49 (0.10,0.89)	0.43 (0.28,0.65)	0.56 (0.37,0.73)	0.20 (0.05,0.48)
30–49%	0.14 (0.12,0.15)	0.15 (0.11,0.17)	0.16 (0.11,0.17)	0.15 (0.13,0.16)	0.16 (0.15,0.17)	0.16 (0.12,0.17)	0.15 (0.13,0.17)	0.15 (0.13,0.16)	0.12 (0.04,0.16)	0.16 (0.12,0.17)	0.16 (0.09,0.17)	0.16 (0.13,0.17)	0.16 (0.14,0.17)	0.16 (0.05,0.17)	0.16 (0.14,0.17)	0.15 (0.11,0.17)	0.13 (0.06,0.16)
≥50%	0.22 (0.16,0.28)	0.29 (0.14,0.51)	0.37 (0.15,0.67)	0.29 (0.19,0.41)	0.39 (0.29,0.51)	0.42 (0.23,0.69)	0.29 (0.19,0.42)	0.29 (0.20,0.40)	0.17 (0.03,0.48)	0.45 (0.28,0.70)	0.39 (0.11,0.73)	0.38 (0.20,0.59)	0.36 (0.23,0.43)	0.35 (0.05,0.81)	0.41 (0.22,0.57)	0.29 (0.15,0.47)	0.67 (0.37,0.89)
16 weeks																	
<30%	0.60 (0.11,0.97)	0.51 (0.05,0.95)	0.42 (0.03,0.95)	0.51 (0.06,0.95)	0.40 (0.04,0.92)	0.38 (0.03,0.91)	0.51 (0.06,0.95)	0.51 (0.07,0.94)	0.67 (0.09,0.99)	0.35 (0.02,0.89)	0.41 (0.03,0.95)	0.42 (0.03,0.92)	0.43 (0.06,0.94)	0.45 (0.01,0.96)	0.38 (0.03,0.94)	0.51 (0.05,0.96)	0.17 (0.00,0.81)
30–49%	0.14 (0.02,0.16)	0.16 (0.03,0.17)	0.16 (0.02,0.17)	0.16 (0.03,0.17)	0.16 (0.03,0.17)	0.16 (0.03,0.16)	0.16 (0.03,0.17)	0.16 (0.03,0.17)	0.13 (0.01,0.16)	0.16 (0.02,0.16)	0.16 (0.02,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.17)	0.16 (0.01,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.12 (0.01,0.16)
≥50%	0.25 (0.01,0.80)	0.34 (0.02,0.89)	0.42 (0.02,0.93)	0.34 (0.02,0.87)	0.44 (0.04,0.92)	0.47 (0.04,0.94)	0.33 (0.02,0.88)	0.34 (0.02,0.86)	0.20 (0.00,0.82)	0.49 (0.05,0.95)	0.43 (0.02,0.93)	0.42 (0.03,0.92)	0.41 (0.03,0.88)	0.39 (0.01,0.96)	0.46 (0.03,0.92)	0.33 (0.02,0.89)	0.71 (0.10,0.99)
20 weeks																	
<30%	0.64 (0.48,0.77)	0.54 (0.31,0.78)	0.46 (0.18,0.76)	0.55 (0.37,0.74)	0.44 (0.27,0.62)	0.41 (0.15,0.66)	0.55 (0.36,0.71)	0.54 (0.36,0.72)	0.70 (0.33,0.93)	0.38 (0.15,0.60)	0.44 (0.13,0.80)	0.45 (0.23,0.70)	0.47 (0.34,0.68)	0.48 (0.09,0.89)	0.42 (0.23,0.69)	0.55 (0.32,0.77)	0.19 (0.04,0.49)
30–49%	0.14 (0.10,0.16)	0.15 (0.10,0.17)	0.16 (0.10,0.17)	0.15 (0.11,0.17)	0.16 (0.14,0.17)	0.16 (0.11,0.17)	0.15 (0.12,0.17)	0.15 (0.12,0.17)	0.12 (0.04,0.16)	0.16 (0.11,0.17)	0.16 (0.08,0.17)	0.16 (0.12,0.17)	0.16 (0.13,0.17)	0.16 (0.05,0.17)	0.16 (0.12,0.17)	0.15 (0.10,0.17)	0.13 (0.05,0.16)
≥50%	0.22 (0.12,0.36)	0.30 (0.12,0.54)	0.38 (0.13,0.70)	0.30 (0.15,0.47)	0.40 (0.24,0.58)	0.43 (0.20,0.74)	0.30 (0.17,0.48)	0.30 (0.16,0.48)	0.18 (0.03,0.52)	0.46 (0.25,0.74)	0.39 (0.10,0.77)	0.39 (0.18,0.64)	0.37 (0.19,0.50)	0.36 (0.05,0.82)	0.42 (0.19,0.63)	0.30 (0.13,0.52)	0.68 (0.35,0.91)

[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

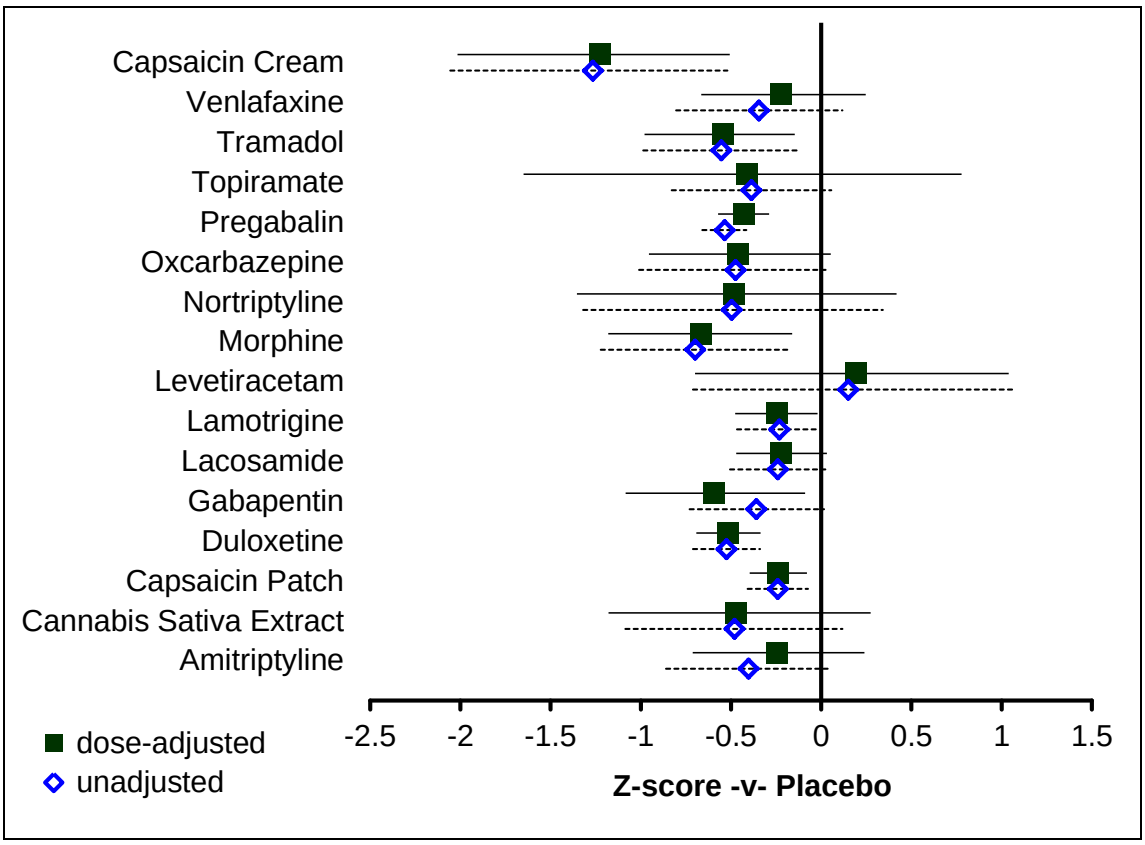
NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credible intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

1 **Table 5 30% and 50% pain relief – raw outputs of synthesis models**

	Unadjusted	Dose-adjusted	
	Z-score -v- placebo	Z-score -v- placebo	Coefficient for dose[a]
Amitriptyline	−0.412 (−0.885, −0.412)	−0.282 (−0.739, 0.166)	−0.824 (−4.268, 2.625)
Cannabis extract	−0.493 (−1.090, −0.493)	−0.466 (−1.043, 0.118)	−0.023 (−3.991, 3.903)
Capsaicin cream	−1.304 (−2.060, −1.304)	−1.223 (−2.001, −0.470)	0.020 (−3.878, 3.910)
Capsaicin patch	−0.240 (−0.408, −0.240)	−0.240 (−0.396, −0.080)	0.003 (−3.887, 3.918)
Duloxetine	−0.520 (−0.712, −0.520)	−0.527 (−0.705, −0.352)	−0.594 (−2.992, 1.830)
Gabapentin	−0.367 (−0.751, −0.367)	−0.351 (−0.718, 0.021)	0.275 (−0.164, 0.719)
Lacosamide	−0.237 (−0.507, −0.237)	−0.236 (−0.495, 0.015)	−0.275 (−1.155, 0.611)
Lamotrigine	−0.226 (−0.444, −0.226)	−0.232 (−0.453, −0.018)	−0.309 (−1.827, 1.149)
Levetiracetam	0.175 (−0.737, 0.175)	0.167 (−0.722, 1.023)	0.005 (−3.904, 3.852)
Morphine	−0.714 (−1.240, −0.714)	−0.739 (−1.274, −0.184)	−0.727 (−4.137, 2.736)
Nortriptyline	−0.499 (−1.318, −0.499)	−0.487 (−1.324, 0.321)	0.042 (−3.863, 3.822)
Oxcarbazepine	−0.475 (−1.010, −0.475)	−0.474 (−0.970, 0.038)	0.025 (−3.814, 3.976)
Pregabalin	−0.539 (−0.664, −0.539)	−0.513 (−0.635, −0.397)	−0.590 (−1.056, −0.127)
Topiramate	−0.396 (−0.839, −0.396)	−0.388 (−0.809, 0.031)	0.018 (−3.960, 3.852)
Tramadol	−0.558 (−0.980, −0.558)	−0.556 (−0.968, −0.145)	−0.793 (−4.184, 2.605)
Venlafaxine	−0.336 (−0.783, −0.336)	−0.361 (−0.789, 0.065)	−1.829 (−4.395, 0.748)

[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.

2



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 2 30% and 50% pain relief – relative effect of all options compared with placebo

Table 6 30% and 50% pain relief – 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 (14, 17)
Amitriptyline	0.006	9 (2, 16)	0.002	11 (3, 17)
Cannabis Extract	0.025	7 (2, 16)	0.024	7 (2, 16)
Capsaicin Cream	0.789	1 (1, 6)	0.762	1 (1, 7)
Capsaicin Patch	0.000	12 (8, 15)	0.000	12 (8, 15)
Duloxetine	0.001	6 (3, 11)	0.001	6 (3, 10)
Gabapentin	0.000	10 (3, 16)	0.001	10 (3, 16)
Lacosamide	0.000	12 (6, 16)	0.000	12 (6, 16)
Lamotrigine	0.000	12 (7, 16)	0.000	12 (7, 16)
Levetiracetam	0.003	17 (3, 17)	0.002	17 (3, 17)
Morphine	0.068	3 (1, 14)	0.102	3 (1, 13)
Nortriptyline	0.059	7 (1, 17)	0.062	7 (1, 17)
Oxcarbazepine	0.017	7 (2, 16)	0.019	7 (2, 16)
Pregabalin	0.001	6 (3, 10)	0.000	6 (3, 10)
Topiramate	0.005	9 (2, 16)	0.004	9 (2, 16)
Tramadol	0.019	6 (2, 14)	0.018	5 (2, 14)
Venlafaxine	0.006	10 (2, 17)	0.003	10 (2, 16)

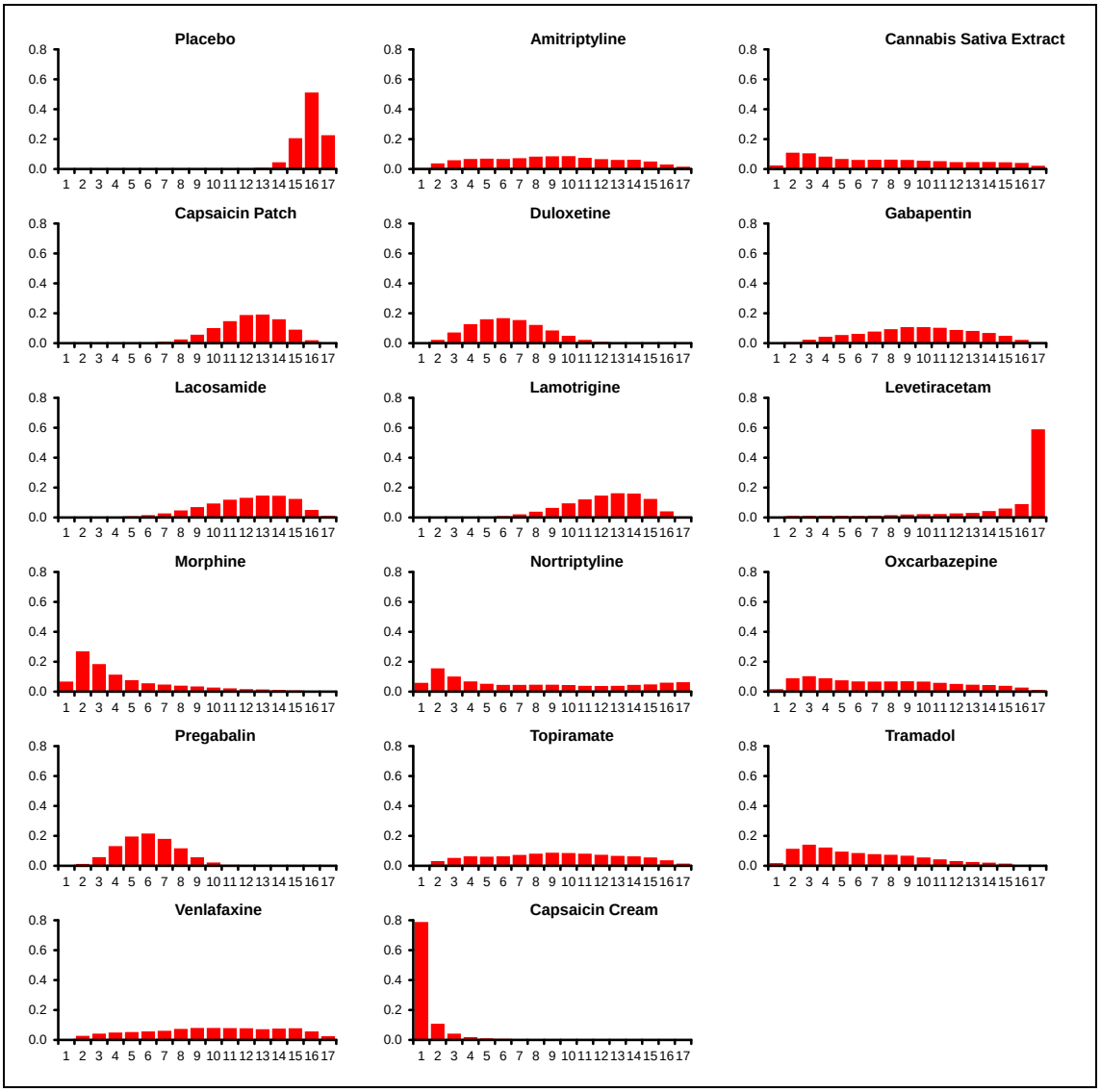


Figure 3 30% and 50% pain relief – rank probability histograms; no adjustment for dose

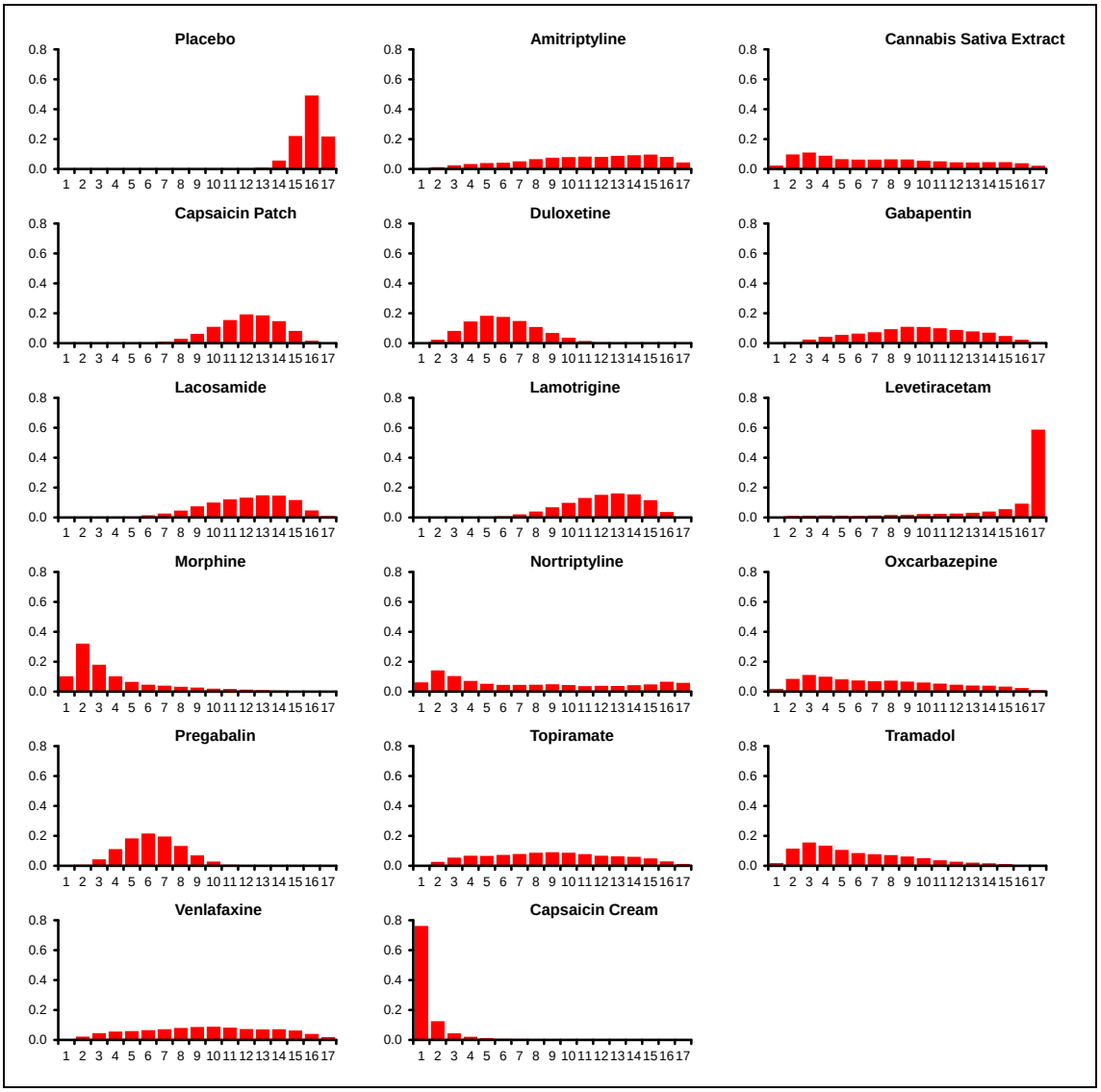


Figure 4 30% and 50% pain relief – rank probability histograms; dose-adjusted

Table 7 30% and 50% pain relief – model fit statistics

	Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
Unadjusted	226.4 (cf. 193 datapoints)	1069.8	975.8	94.0	1163.8	0.026 (95%CrI: 0.012, 0.059)
Dose-adjusted	226.2 (cf. 193 datapoints)	1069.6	974.9	94.7	1164.2	0.019 (95%CrI: 0.007, 0.053)

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 193 datapoints).

Because neither model was clearly superior, the health economic model was run with each in turn, to see whether cost–utility results were substantively affected by choice of synthesis model.

1.1.2 Validation of efficacy dataset

Only some of the included studies report pain relief data in the format required by the model (that is, proportion achieving 30% pain relief and/or proportion achieving 50% pain relief). Because of this, it is possible that an unrepresentative estimate of effect is relied on. This may be a particular concern for treatments with an older evidence-base: the reporting of 30% and 50% pain relief has become more common in recent years.

To investigate the possible impact of this issue, a series of analyses were performed taking advantage of a known relationship between dichotomous and continuous data. Odds ratios may be approximated from continuous data using the formula

$$\ln(OR) = SMD\frac{\pi}{\sqrt{3}},$$

where SMD indicates the standardised mean difference between arms, calculated as

$$SMD = \frac{m_1 - m_2}{s},$$

where m_1 and m_2 are the mean changes in pain from baseline to follow-up in arms 1 and 2 of each study, and s denotes the pooled standard deviation across both groups:

$$s = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{(n_1 + n_2) - 2}},$$

where *n* represents the numbers of particpants in each arm and *SD* the standard deviations of the mean changes (see Cochrane Handbook sections 9.2.3.2 and 9.4.6 for details).

This method relies on assumptions that are unlikely to be strictly applicable in the dataset at hand – most notably, that the underlying data follow a logistic distribution, where pain data are known to be more idiosyncratically distributed (see, for example, Moore et al., 2005). For this reason, it was not deemed appropriate to use continuous data to calculate odds ratios that could be directly used in the health economic model. However, a less formal analysis comparing the 2 types of data is useful to investigate the representativeness of data used in the model.

Accordingly, odds ratios (ORs) were approximated from the (larger) pool of studies reporting continuous measures of pain relief and compared with the directly reported odds ratios for 30% or 50% pain relief for the same comparisons. For each pair of treatments for which at least 1 study was available in each category, a stratified fixed-effects meta-analysis was undertaken to compare the pooled ORs estimated in each way and, most importantly, to explore evidence of heterogeneity between strata. If the set of trials reporting dichotomous pain relief does not agree with the results seen in the continuous studies, significant heterogeneity will be detected, suggesting the dichotomous data (and, by extension, the data used in the health economic model) may be a biased sample of the available evidence. See Table 8.

Table 8 Empirical and approximated odds ratios for all comparisons for which dichotomous and continuous pain data are available – exploratory fixed-effects[a] stratified meta-analyses with quantification of heterogeneity

	Dichotomous (30% or 50% pain relief[b,c])				Continuous (mean change in pain[c])				Inter-stratum
Comparison	**N**	**OR**	**(95%CI)**	**Heterogeneity**	**N**	**OR(SMD)[d]**	**(95%CI)**	**Heterogeneity**	**Heterogeneity**
placebo -v- cannabis	1	2.00	(0.81, 4.96)	N/A	3	1.88	(1.16, 3.06)	Q=2.53; p=0.282; I^2=21.0%	Q=0.01; p=0.906; I^2=0.0%
placebo -v- capsaicin cream	2	6.56	(1.69, 25.44)	Q=1.38; p=0.240; I^2=27.6%	2	2.57	(0.84, 7.92)	Q=0.43; p=0.514; I^2=0.0%	Q=1.08; p=0.298; I^2=7.8%
placebo -v- duloxetine	5	2.43	(1.96, 3.00)	Q=4.27; p=0.371; I^2=6.3%	5	2.34	(1.92, 2.87)	Q=1.50; p=0.826; I^2=0.0%	Q=0.05; p=0.816; I^2=0.0%
placebo -v- gabapentin	1	2.71	(1.41, 5.20)	N/A	13	2.73	(2.21, 3.37)	Q=79.05; p<0.001; I^2=84.8%	Q=0.00; p=0.984; I^2=0.0%
placebo -v- lacosamide	3	1.55	(1.11, 2.16)	Q=0.04; p=0.980; I^2=0.0%	1	1.88	(0.97, 3.62)	N/A	Q=0.27; p=0.604; I^2=0.0%
placebo -v- lamotrigine	5	1.37	(1.02, 1.84)	Q=9.32; p=0.054; I^2=57.1%	3	2.22	(1.34, 3.68)	Q=19.80; p<0.001; I^2=89.9%	Q=2.61; p=0.106; I^2=61.7%
placebo -v- oxcarbazepine	1	2.04	(1.03, 4.05)	N/A	1	1.92	(1.06, 3.47)	N/A	Q=0.02; p=0.893; I^2=0.0%
placebo -v- pregabalin	13	2.18	(1.86, 2.56)	Q=39.27; p<0.001; I^2=69.4%	10	2.26	(1.92, 2.66)	Q=26.05; p=0.002; I^2=65.4%	Q=0.08; p=0.774; I^2=0.0%
placebo -v- topiramate	1	1.81	(1.12, 2.91)	N/A	4	1.22	(1.01, 1.49)	Q=4.71; p=0.195; I^2=36.2%	Q=2.17; p=0.141; I^2=53.9%
placebo -v- tramadol	2	2.55	(1.49, 4.39)	Q=1.70; p=0.192; I^2=41.3%	3	2.61	(1.74, 3.90)	Q=2.45; p=0.293; I^2=18.5%	Q=0.00; p=0.952; I^2=0.0%
placebo -v- venlafaxine	1	1.77	(1.02, 3.08)	N/A	1	2.13	(0.87, 5.23)	N/A	Q=0.12; p=0.732; I^2=0.0%
amitriptyline -v- pregabalin	1	1.68	(0.74, 3.82)	N/A	1	4.02	(1.55, 10.42)	N/A	Q=1.85; p=0.174; I^2=45.9%
gabapentin -v- nortriptyline	1	1.29	(0.42, 3.95)	N/A	2	1.26	(0.73, 2.20)	Q=0.00; p=0.948; I^2=0.0%	Q=0.00; p=0.978; I^2=0.0%

[a] fixed-effects meta-analyses were used because, although random-effects models are used elsewhere in this analysis, it is inappropriate to estimate inter-stratum heterogeneity in a random-effects model

[b] to avoid double-counting issues, it was necessary to rely on one or other of 30% and 50% pain relief measures (which, in any case, approximate each other very closely); the 30% measure was preferred, where available, but the 50% measure was used instead if it was the only one reported

[c] where multiple arms in the same RCT addressed the same treatment, data from each were pooled to form a meta-arm for comparison with its common comparator; for dichotomous measures, the numbers and events in the separate arms can simply be summed; for continuous measures, a weighted mean of the relevant means and a pooled estimate of their variances were calculated and used to calculate the SMD

[d] odds ratios approximated from continuous data using standardised mean differences (see above)

A good degree of homogeneity was seen throughout the comparisons: none of the stratified analyses showed differences between dichotomous and continuous data that that would be considered significant by conventional standards (in tests of heterogeneity, p-values less than 0.1 are often seen as suggestive of non-random differences between strata). The greatest evidence for heterogeneity is for lamotrigine and topiramate: in comparisons with placebo, the former appears somewhat more effective according to the continuous data (suggesting the model inputs may potentially underestimate its efficacy), while the latter has the opposite relationship (so the model may overestimate its efficacy). The head-to-head comparison between amitriptyline and pregabalin also appears to imply some difference between evidence types. However, in none of these cases are the differences of a magnitude that cannot be explained by sampling error.

It is reassuring that treatments with older evidence do not appear to be systematically disadvantaged. In particular, while there is only 1 placebo-controlled RCT of gabapentin contributing dichotomous evidence to the dataset, it is very closely comparable to the OR approximated from the pooled continuous data (which means that the mean effect will be well estimated in the health economic model, although uncertainty will be much greater than would be the case if it were possible to derive an entirely robust estimate of effect from all trials). Finally, it is notable that the estimate of capsaicin cream's efficacy derived from dichotomous data is markedly higher than that approximated from the pooled continuous data. However, confidence intervals are broad and, once more, a null hypothesis of homogeneous effects cannot be rejected.

1.2 Safety

Basis of models

The models estimate the probability of experiencing adverse effects of interest with each of the drugs in the decision-set. An approach is used that accounts for varying time of follow-up in reported event-rates, assuming a constant rate over time (network meta-analysis for binomial data using a generalised linear model with complementary log–log link function; see Dias et al., NICE DSU Technical Support Document 2 for technical details). This method differs from that used in the analysis of adverse effects in the effectiveness review (see Appendix J), which relies on a logit link function to estimate odds ratios without adjustment for time of follow-up. Comparing the 2 sets of analyses shows that they are practically indistinguishable; however, the approach used in these analyses produces results that are more convenient for the health economic model structure that has been adopted.

Models presented

Sufficient data were available to estimate the incidence of 2 individual adverse effects: dizziness/vertigo and nausea. In addition, reported rates of withdrawal due to adverse effect(s) were synthesised to inform the health economic model (see Appendix F).

As for efficacy data, models incorporating a coefficient reflecting dose–response were explored. However, due to limited data availability, it was only possible to estimate this relationship for withdrawal due to adverse effect(s). Therefore, all individual AEs are estimated using models that do not adjust for dose.

Table 9 summarises all safety data used in the health economic model.

Table 9 Summary of safety outcomes included in health economic model

Drug	Withdrawal due to adverse effect(s)			Individual adverse effects – no adjustment for dose	
	Dose-variable		No adjustment for dose		
	(Assumed dose)	Probability	Probability	Dizziness	Nausea
placebo	-	0.09 (0.08,0.11)	0.09 (0.08,0.11)	0.12 (0.09,0.16)	0.10 (0.08,0.14)
amitriptyline	50mg/d[a]	0.23 (0.13,0.35)	0.24 (0.12,0.41)	0.12 (0.05,0.25)	0.09 (0.01,0.31)
cannabis extract	4 sprays/d[a]	0.49 (0.14,0.98)	0.48 (0.11,0.98)	0.37 (0.13,0.75)	0.20 (0.08,0.41)
capsaicin cream	4apps/d[a]	0.43 (0.22,0.69)	0.45 (0.22,0.78)	0.58 (0.02,1.00)	0.47 (0.03,1.00)
capsaicin patch	1 × 60-min	0.11 (0.04,0.25)	0.11 (0.03,0.25)	0.09 (0.03,0.21)	0.14 (0.07,0.23)
duloxetine	60mg/d[a]	0.21 (0.14,0.32)	0.23 (0.13,0.37)	0.26 (0.13,0.47)	0.28 (0.16,0.48)
gabapentin	1800mg/d[a]	0.18 (0.08,0.35)	0.17 (0.09,0.26)	0.40 (0.23,0.61)	0.11 (0.04,0.25)
lacosamide	400mg/d[a]	0.21 (0.13,0.32)	0.21 (0.11,0.36)	0.38 (0.18,0.66)	0.14 (0.06,0.27)
lamotrigine	400mg/d[a]	0.17 (0.11,0.27)	0.18 (0.10,0.29)	0.17 (0.06,0.35)	0.09 (0.05,0.16)
levetiracetam	3000mg/d[b]	0.44 (0.15,0.92)	0.40 (0.12,0.84)	0.57 (0.20,0.97)	0.25 (0.02,0.86)
morphine	120mg/d[a]	0.52 (0.09,1.00)	0.58 (0.08,1.00)	0.27 (0.05,0.74)	0.47 (0.11,0.99)
nortriptyline	50mg/d[a]	0.27 (0.03,0.83)	0.33 (0.03,0.97)	0.14 (0.03,0.40)	0.07 (0.00,0.34)
oxcarbazepine	1800mg/d[b]	0.30 (0.16,0.50)	0.34 (0.14,0.66)	0.65 (0.27,0.97)	0.18 (0.06,0.38)
pregabalin	300mg/d[a]	0.12 (0.08,0.17)	0.19 (0.12,0.26)	0.36 (0.24,0.50)	0.10 (0.04,0.17)
topiramate	100mg/d[a]	0.23 (0.15,0.34)	0.32 (0.16,0.53)	0.21 (0.04,0.59)	0.15 (0.07,0.25)
tramadol	400mg/d[a]	0.44 (0.20,0.81)	0.45 (0.17,0.88)	0.52 (0.18,0.93)	0.37 (0.20,0.65)
venlafaxine	75mg/d[a]	0.23 (0.09,0.48)	0.24 (0.08,0.55)	0.39 (0.01,1.00)	0.24 (0.11,0.45)

[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

1.2.1 Dizziness / vertigo

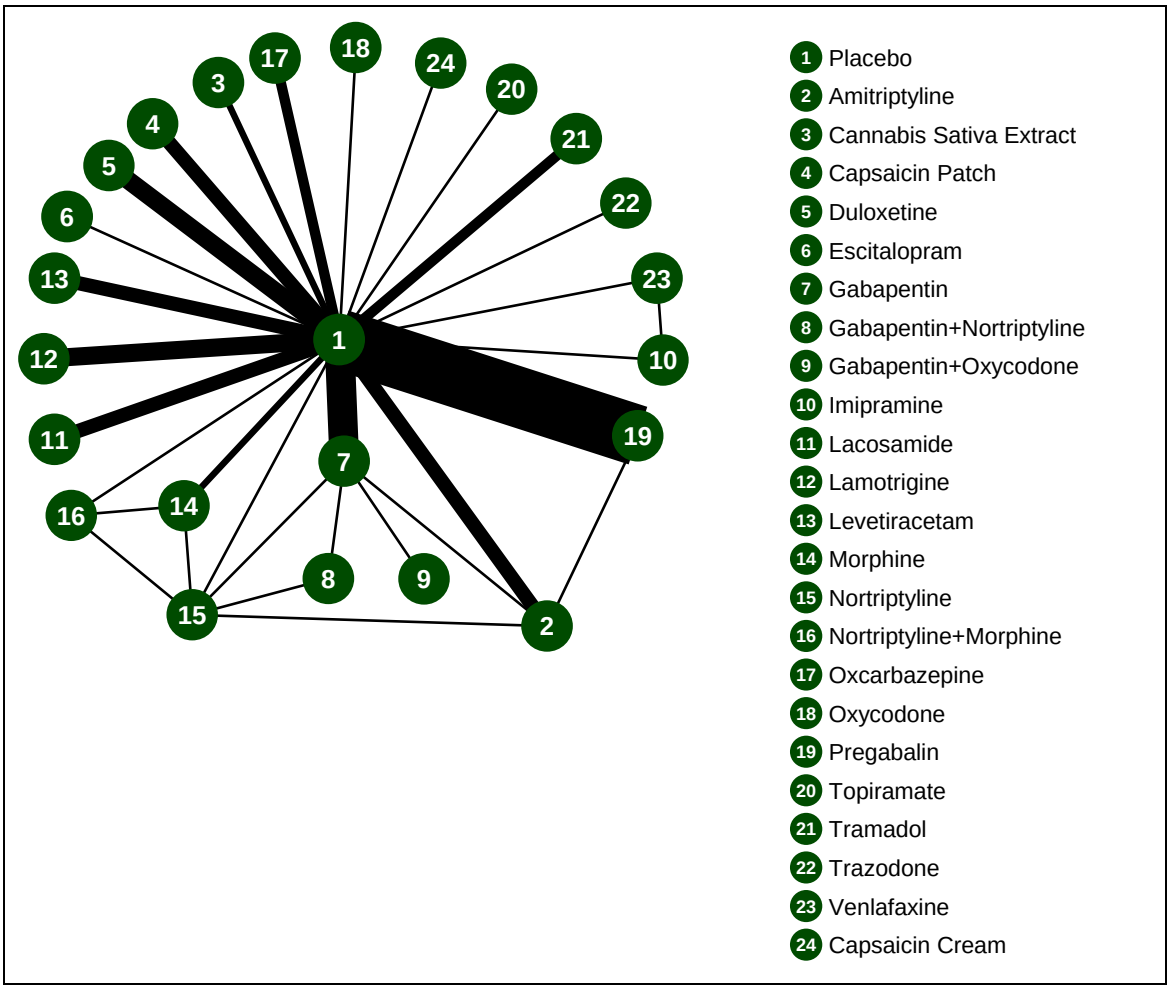


Figure 5 Dizziness – evidence network

1 **Table 10 Dizziness – trials included in analysis**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine
Amitriptyline	4 RCTs[8,28,32,43] total n=273																						
Cannabis Sativa Extract	2 RCTs[35,44] total n=191	-																					
Capsaicin Patch	4 RCTs[3,27,65,66] total n=1272	-	-																				
Duloxetine	5 RCTs[16,19,62,67,70] total n=1392	-	-	-																			
Escitalopram	1 RCT[36] total n=96	-	-	-	-																		
Gabapentin	8 RCTs[2,6,20,23,37,41,47,52] total n=1322	1 RCT[33] total n=50	-	-	-	-																	
Gabapentin +Nortriptyline	-	-	-	-	-	-	1 RCT[17] total n=112																
Gabapentin +Oxycodone	-	-	-	-	-	-	1 RCT[24] total n=338	-															
Imipramine	1 RCT[55] total n=80	-	-	-	-	-	-	-	-														
Lacosamide	4 RCTs[40,50,69,71] total n=1314	-	-	-	-	-	-	-	-	-													
Lamotrigine	5 RCTs[7,12,38,59,60] total n=934	-	-	-	-	-	-	-	-	-	-												
Levetiracetam	4 RCTs[13,14,26,46] total n=230	-	-	-	-	-	-	-	-	-	-	-											
Morphine	2 RCTs[29,68] total n=222	-	-	-	-	-	-	-	-	-	-	-	-										
Nortriptyline	1 RCT[29] total n=110	1 RCT[64] total n=66	-	-	-	-	1 RCT[17] total n=112	1 RCT[17] total n=112	-	-	-	-	-	1 RCT[29] total n=110									
Nortriptyline +Morphine	1 RCT[29] total n=110	-	-	-	-	-	-	-	-	-	-	-	-	1 RCT[29] total n=110	1 RCT[29] total n=110								

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine
Oxcarbazepine	3 RCTs[5,10,21] total n=634	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[18] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Pregabalin	16 RCTs[1,11,15,22,30,31,42,45,48,49,51,53,56,57,58,61] total n=3997	1 RCT[4] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Topiramate	1 RCT[39] total n=323	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Tramadol	3 RCTs[25,34,54] total n=256	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Trazodone	1 RCT[9] total n=18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	1 RCT[55] total n=80	-	-	-	-	-	-	-	-	1 RCT[55] total n=80	-	-	-	-	-	-	-	-	-	-	-	-	
Capsaicin Cream	1 RCT[63] total n=143	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(1) Arezzo et al. (2008); (2) Backonja et al. (1998); (3) Backonja et al. (2008); (4) Bansal et al. (2009); (5) Beydoun et al. (2006); (6) Bone et al. (2002); (7) Breuer et al. (2007); (8) Cardenas et al. (2002); (9) Davidoff et al. (1987); (10) Dogra et al. (2005); (11) Dworkin et al. (2003); (12) Eisenberg et al. (2001); (13) Falah et al. (2012); (14) Finnerup et al. (2009); (15) Freynhagen et al. (2005); (16) Gao et al. (2010); (17) Gilron et al. (2012); (18) Gimbel et al. (2003); (19) Goldstein et al. (2005); (20) Gordh et al. (2008); (21) Grosskopf et al. (2006); (22) Guan et al. (2011); (23) Hahn et al. (2004); (24) Hanna et al. (2008); (25) Harati et al. (1998); (26) Holbech et al. (2011); (27) Irving et al. (2011); (28) Kalso et al. (1995); (29) Khoromi et al. (2007); (30) Kim et al. (2011); (31) Lesser et al. (2004); (32) Max et al. (1988); (33) Morello et al. (1999); (34) Norrbrink & Lundeberg (2009); (35) Nurmikko et al. (2007); (36) Otto et al. (2008); (37) Rao et al. (2007); (38) Rao et al. (2008); (39) Raskin et al. (2004); (40) Rauck et al. (2007); (41) Rice & Maton (2001); (42) Richter et al. (2005); (43) Robinson et al. (2004); (44) Rog et al. (2005); (45) Rosenstock et al. (2004); (46) Rossi et al. (2009); (47) Rowbotham et al. (1998); (48) Sabatowski et al. (2004); (49) Satoh et al. (2011); (50) Shaibani et al. (2009); (51) Siddall et al. (2006); (52) Simpson (2001); (53) Simpson et al. (2010); (54) Sindrup et al. (1999); (55) Sindrup et al. (2003); (56) Stacey et al. (2008); (57) Tolle et al. (2008); (58) van Seventer et al. (2006); (59) Vinik et al. (2007); (60) Vinik et al. (2007); (61) Vranken et al. (2008); (62) Vranken et al. (2011); (63) Watson et al. (1993); (64) Watson et al. (1998); (65) Webster et al. (2010); (66) Webster et al. (2010); (67) Wernicke et al. (2006); (68) Wu et al. (2008); (69) Wymer et al. (2009); (70) Yasuda et al. (2011); (71) Ziegler et al. (2010)

1 **Table 11 Dizziness – relative effectiveness of all pairwise combinations (hazard ratios)**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amitriptyline	0.89 (0.37, 2.10)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cannabis Sativa Extract	3.12 (1.03, 9.56)	3.52 (0.87, 14.73)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Capsaicin Patch	0.67 (0.25, 1.75)	0.76 (0.21, 2.76)	0.21 (0.05, 0.95)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duloxetine	2.21 (1.11, 4.53)	2.51 (0.83, 7.64)	0.71 (0.18, 2.68)	3.30 (1.01, 11.20)		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	N/A	N/A	N/A	N/A	N/A	N/A
Escitalopram	0.34 (0.03, 2.80)	0.39 (0.03, 3.77)	0.11 (0.01, 1.17)	0.51 (0.04, 5.38)	0.15 (0.01, 1.40)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin	3.73 (2.10, 6.68)	4.23 (1.61, 11.27)	1.20 (0.34, 4.25)	5.56 (1.84, 17.39)	1.70 (0.67, 4.19)	10.94 (1.23, 137.6)		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 +Nortriptyline	2.86 (0.41, 18.74)	3.27 (0.42, 23.93)	0.92 (0.10, 8.13)	4.27 (0.48, 35.80)	1.29 (0.16, 9.60)	8.44 (0.48, 182.5)	0.77 (0.12, 4.82)		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	17.72 (3.31, 97.78)	19.99 (3.24, 129.7)	5.67 (0.77, 45.11)	26.39 (3.88, 188.5)	8.00 (1.30, 50.27)	52.94 (3.58, 1064)	4.73 (0.98, 23.74)	6.18 (0.58, 71.59)		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	3.86 (0.29, 138.7)	4.49 (0.28, 166.9)	1.27 (0.07, 51.04)	5.80 (0.34, 243.5)	1.75 (0.12, 66.87)	12.02 (0.37, 848.4)	1.04 (0.07, 38.85)	1.41 (0.05, 76.89)	0.22 (0.01, 10.89)		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	3.48 (1.59, 7.88)	3.93 (1.26, 12.69)	1.12 (0.28, 4.40)	5.19 (1.48, 18.81)	1.57 (0.54, 4.62)	10.26 (1.08, 133.0)	0.93 (0.35, 2.50)	1.22 (0.16, 9.93)	0.20 (0.03, 1.26)	0.90 (0.02, 13.51)		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	1.33 (0.57, 3.17)	1.51 (0.45, 5.18)	0.43 (0.10, 1.74)	1.99 (0.54, 7.45)	0.61 (0.20, 1.84)	3.91 (0.40, 52.22)	0.36 (0.13, 1.02)	0.46 (0.06, 3.93)	0.07 (0.01, 0.49)	0.34 (0.01, 5.54)	0.38 (0.12, 1.24)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream
Levetiracetam	6.37 (1.77, 28.47)	7.21 (1.52, 40.32)	2.04 (0.37, 13.24)	9.62 (1.92, 55.39)	2.89 (0.65, 14.55)	18.90 (1.53, 336.8)	1.71 (0.42, 8.34)	2.25 (0.22, 25.66)	0.36 (0.04, 3.32)	1.66 (0.04, 33.46)	1.85 (0.40, 9.51)	4.80 (1.02, 26.34)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	1.87 (0.38, 9.88)	2.13 (0.36, 13.05)	0.60 (0.08, 4.42)	2.80 (0.44, 18.81)	0.84 (0.15, 5.14)	5.57 (0.40, 101.0)	0.51 (0.09, 2.84)	0.66 (0.06, 7.39)	0.11 (0.01, 1.07)	0.48 (0.01, 10.52)	0.54 (0.09, 3.37)	1.41 (0.23, 9.07)	0.29 (0.03, 2.28)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	0.88 (0.19, 3.47)	0.99 (0.20, 4.23)	0.28 (0.04, 1.65)	1.31 (0.22, 7.12)	0.40 (0.07, 1.87)	2.55 (0.20, 44.04)	0.24 (0.05, 0.96)	0.31 (0.04, 2.34)	0.05 (0.01, 0.40)	0.22 (0.00, 4.20)	0.25 (0.05, 1.23)	0.66 (0.12, 3.39)	0.14 (0.02, 0.91)	0.47 (0.07, 2.81)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	0.39 (0.01, 4.79)	0.43 (0.01, 6.32)	0.12 (0.00, 2.03)	0.57 (0.01, 8.92)	0.17 (0.00, 2.39)	1.09 (0.02, 38.88)	0.10 (0.00, 1.39)	0.13 (0.00, 3.05)	0.02 (0.00, 0.47)	0.09 (0.00, 4.11)	0.11 (0.00, 1.56)	0.29 (0.01, 4.35)	0.06 (0.00, 1.07)	0.21 (0.01, 2.43)	0.45 (0.01, 6.15)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	8.35 (2.48, 34.10)	9.50 (2.17, 49.06)	2.71 (0.51, 16.16)	12.62 (2.61, 67.84)	3.81 (0.92, 17.79)	24.86 (2.14, 409.0)	2.24 (0.59, 10.40)	2.99 (0.31, 32.41)	0.48 (0.06, 4.17)	2.15 (0.05, 41.82)	2.41 (0.56, 12.16)	6.32 (1.40, 32.29)	1.32 (0.19, 8.61)	4.48 (0.58, 37.62)	9.64 (1.51, 76.11)	22.48 (1.29, 1057)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxycodone	3.58 (0.79, 16.74)	4.06 (0.71, 23.87)	1.16 (0.17, 7.59)	5.34 (0.90, 34.10)	1.62 (0.30, 8.57)	10.63 (0.78, 187.0)	0.96 (0.19, 4.90)	1.26 (0.11, 14.23)	0.20 (0.02, 1.96)	0.91 (0.02, 19.33)	1.03 (0.18, 5.83)	2.69 (0.47, 15.61)	0.56 (0.07, 4.23)	1.93 (0.20, 17.12)	4.11 (0.52, 34.66)	9.46 (0.49, 448.3)	0.42 (0.06, 3.12)		N/A	N/A	N/A	N/A	N/A	N/A
Pregabalin	3.39 (2.35, 4.91)	3.83 (1.52, 9.82)	1.09 (0.33, 3.49)	5.05 (1.79, 14.48)	1.53 (0.69, 3.35)	9.93 (1.19, 116.3)	0.91 (0.46, 1.80)	1.18 (0.17, 8.49)	0.19 (0.03, 1.05)	0.87 (0.02, 12.20)	0.98 (0.40, 2.32)	2.54 (0.99, 6.44)	0.53 (0.11, 2.01)	1.81 (0.33, 9.35)	3.85 (0.92, 18.59)	8.71 (0.68, 330.5)	0.40 (0.10, 1.46)	0.95 (0.19, 4.44)		N/A	N/A	N/A	N/A	N/A
Topiramate	1.34 (0.27, 7.04)	1.52 (0.25, 9.95)	0.43 (0.06, 3.20)	2.00 (0.31, 13.95)	0.61 (0.10, 3.65)	4.00 (0.27, 75.19)	0.36 (0.06, 2.07)	0.47 (0.04, 5.94)	0.08 (0.01, 0.82)	0.34 (0.01, 7.74)	0.39 (0.06, 2.38)	1.01 (0.16, 6.39)	0.21 (0.02, 1.71)	0.72 (0.07, 7.41)	1.54 (0.18, 14.45)	3.58 (0.17, 179.9)	0.16 (0.02, 1.27)	0.37 (0.04, 3.56)	0.40 (0.08, 2.17)		N/A	N/A	N/A	N/A
Tramadol	5.58 (1.67, 20.78)	6.32 (1.42, 31.47)	1.79 (0.35, 10.08)	8.35 (1.76, 42.74)	2.54 (0.61, 11.23)	16.62 (1.44, 264.3)	1.50 (0.39, 6.31)	1.98 (0.21, 20.65)	0.31 (0.04, 2.80)	1.45 (0.03, 27.11)	1.60 (0.37, 7.40)	4.20 (0.96, 19.91)	0.87 (0.13, 5.28)	2.98 (0.39, 23.12)	6.38 (1.04, 47.70)	14.73 (0.82, 702.6)	0.66 (0.11, 3.95)	1.56 (0.22, 11.63)	1.65 (0.47, 6.51)	4.17 (0.53, 32.56)		N/A	N/A	N/A
Trazodone	10.47 (0.42, 2818)	12.00 (0.42, 3289)	3.46 (0.11, 990.3)	15.67 (0.55, 4217)	4.76 (0.17, 1286)	33.42 (0.62, 12060)	2.82 (0.11, 757.0)	3.91 (0.09, 1167)	0.62 (0.02, 184.5)	2.77 (0.03, 907.7)	3.05 (0.11, 806.5)	7.89 (0.28, 2290)	1.66 (0.04, 497.8)	5.84 (0.15, 1700)	12.53 (0.35, 3791)	31.08 (0.45, 19980)	1.27 (0.04, 359.4)	3.04 (0.08, 891.2)	3.10 (0.12, 811.7)	8.08 (0.20, 2599)	1.90 (0.06, 553.2)		N/A	N/A
Venlafaxine	2.40 (0.13, 90.20)	2.76 (0.13, 112.4)	0.77 (0.03, 32.68)	3.62 (0.17, 154.4)	1.09 (0.05, 44.05)	7.35 (0.19, 547.0)	0.64 (0.03, 25.07)	0.86 (0.03, 50.04)	0.14 (0.00, 7.17)	0.62 (0.05, 6.14)	0.69 (0.03, 28.53)	1.81 (0.09, 73.04)	0.37 (0.01, 17.78)	1.30 (0.05, 65.11)	2.79 (0.11, 142.3)	6.88 (0.13, 929.6)	0.29 (0.01, 13.63)	0.68 (0.03, 31.46)	0.71 (0.04, 27.02)	1.82 (0.06, 95.05)	0.42 (0.02, 19.95)	0.22 (0.00, 27.12)		N/A
Capsaicin Cream	5.23 (0.13, 2668)	5.97 (0.14, 3325)	1.71 (0.03, 903.2)	7.86 (0.17, 4259)	2.36 (0.06, 1232)	16.41 (0.21, 12380)	1.40 (0.03, 695.4)	1.95 (0.03, 1147)	0.30 (0.01, 179.3)	1.35 (0.01, 1214)	1.51 (0.03, 785.3)	3.94 (0.09, 2030)	0.82 (0.02, 436.3)	2.88 (0.05, 1788)	6.19 (0.11, 3310)	16.20 (0.15, 22760)	0.62 (0.01, 363.7)	1.50 (0.03, 896.5)	1.55 (0.04, 784.7)	3.92 (0.06, 2307)	0.92 (0.02, 523.5)	0.48 (0.00, 582.5)	2.27 (0.01, 2243)	

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream

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). Numbers in parentheses are 95% credible intervals. Because it is not easily possible to derive analogous estimates of hazard ratios from a frequentist analysis of direct data only, the segment above and to the right of the shaded cells is left blank.

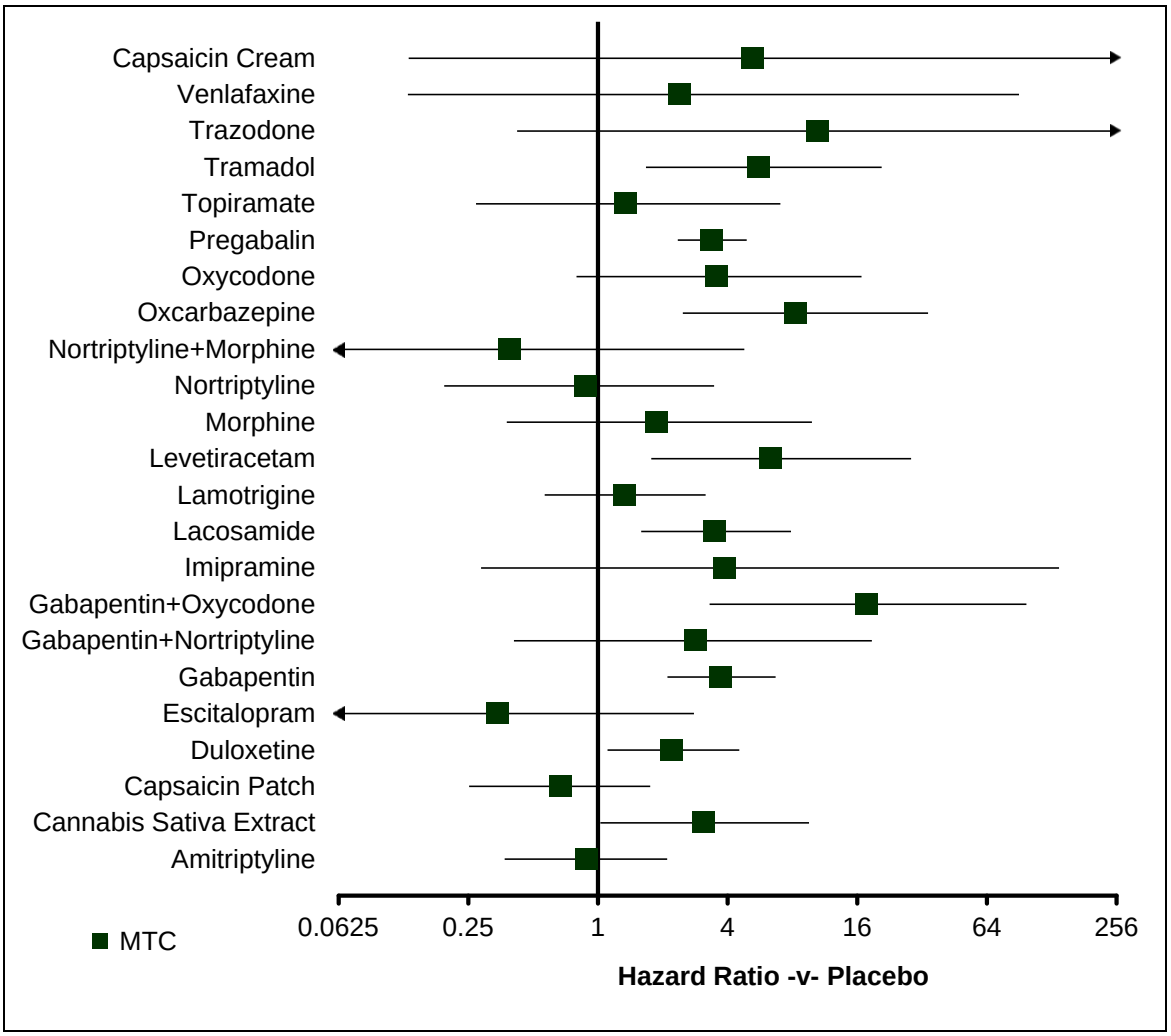


Figure 6 Dizziness – relative effect of all options compared with placebo

Table 12 Dizziness – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	6 (3, 10)
Amitriptyline	0.016	5 (2, 12)
Cannabis Sativa Extract	0.000	14 (6, 22)
Capsaicin Patch	0.060	4 (1, 11)
Duloxetine	0.000	12 (7, 18)
Escitalopram	0.367	2 (1, 13)
Gabapentin	0.000	16 (11, 20)
Gabapentin+Nortriptyline	0.007	14 (3, 23)
Gabapentin+Oxycodone	0.000	23 (15, 24)
Imipramine	0.013	16 (2, 24)
Lacosamide	0.000	15 (9, 21)
Lamotrigine	0.003	8 (3, 15)
Levetiracetam	0.000	19 (10, 24)
Morphine	0.006	11 (2, 21)
Nortriptyline	0.043	5 (1, 15)
Nortriptyline+Morphine	0.362	2 (1, 18)
Oxcarbazepine	0.000	21 (12, 24)
Oxycodone	0.001	16 (5, 23)
Pregabalin	0.000	15 (11, 19)
Topiramate	0.026	8 (1, 20)
Tramadol	0.000	19 (10, 23)
Trazodone	0.008	21 (3, 24)
Venlafaxine	0.045	12 (1, 24)
Capsaicin Cream	0.043	18 (1, 24)

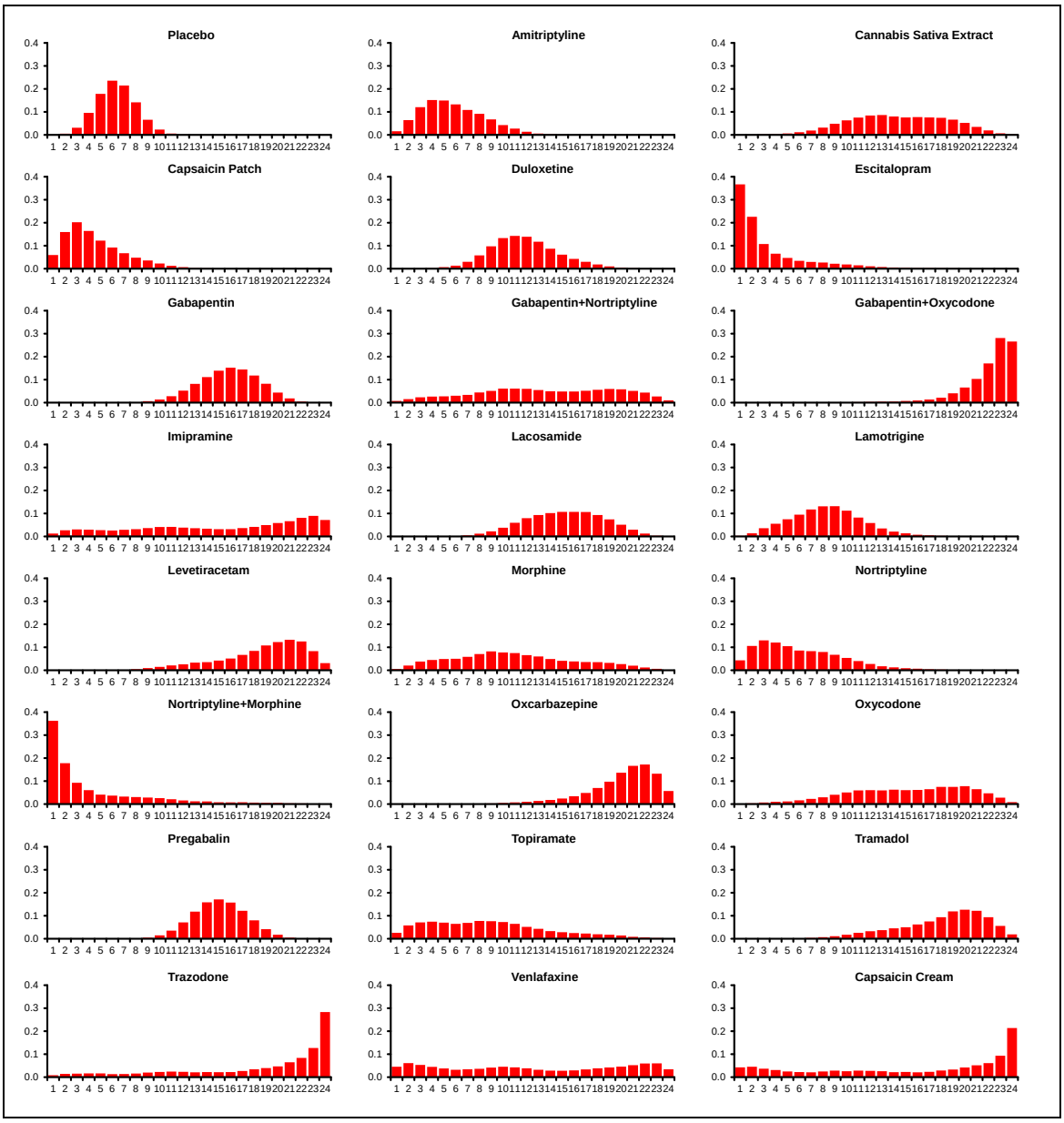


Figure 7 Dizziness – rank probability histograms

Table 13 Dizziness – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
167 (compared to 173 datapoints)	768.083	632.74	135.343	903.426	0.413 (95%CrI: 0.256, 0.704)

1.2.2 Nausea

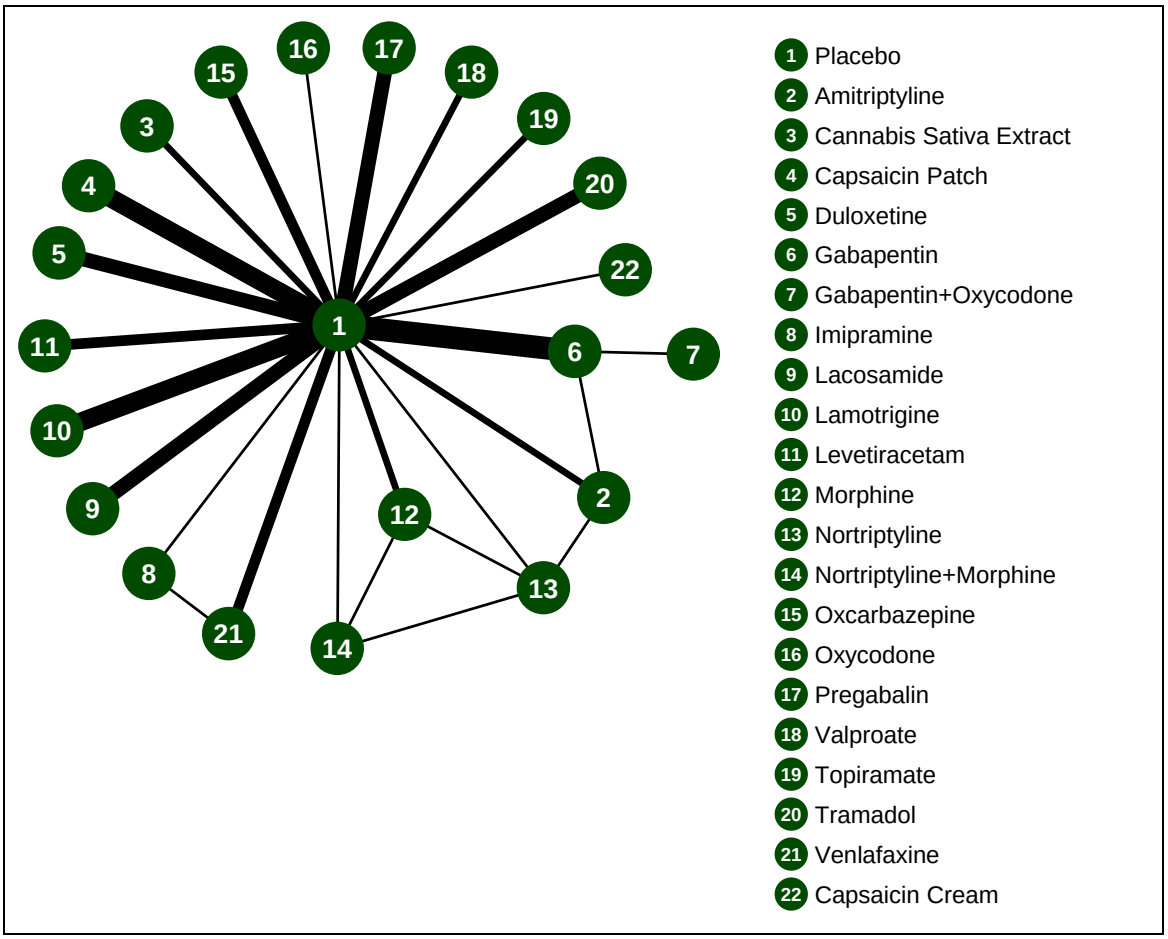


Figure 8 Nausea – evidence network

1 **Table 14 Nausea – trials included in analysis**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Amitriptyline	2 RCTs[22,48] total n=94																				
Cannabis Sativa Extract	2 RCTs[28,33] total n=191	-																			
Capsaicin Patch	5 RCTs[3,7,20,21,51] total n=2738	-	-																		
Duloxetine	4 RCTs[12,14,52,55] total n=1344	-	-	-																	
Gabapentin	6 RCTs[2,5,16,25,29,38] total n=559	1 RCT[26] total n=50	-	-	-																
Gabapentin +Oxycodone	-	-	-	-	-	1 RCT[17] total n=338															
Imipramine	1 RCT[41] total n=80	-	-	-	-	-	-														
Lacosamide	4 RCTs[32,37,54,56] total n=1314	-	-	-	-	-	-	-													
Lamotrigine	5 RCTs[9,30,39,45,46] total n=1125	-	-	-	-	-	-	-	-												
Levetiracetam	3 RCTs[10,19,35] total n=158	-	-	-	-	-	-	-	-	-											
Morphine	2 RCTs[23,53] total n=222	-	-	-	-	-	-	-	-	-	-										
Nortriptyline	1 RCT[23] total n=110	1 RCT[50] total n=66	-	-	-	-	-	-	-	-	-	1 RCT[23] total n=110									
Nortriptyline +Morphine	1 RCT[23] total n=110	-	-	-	-	-	-	-	-	-	-	1 RCT[23] total n=110	1 RCT[23] total n=110								
Oxcarbazepine	3 RCTs[4,8,15] total n=634	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[13] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Pregabalin	4 RCTs[11,34,44,47] total n=892	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Valproate	2 RCTs[1,24] total n=84	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine
Topiramate	2 RCTs[31,43] total n=1592	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	4 RCTs[6,18,27,40] total n=381	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	3 RCTs[36,41,42] total n=355	-	-	-	-	-	-	1 RCT[41] total n=80	-	-	-	-	-	-	-	-	-	-	-	-	
Capsaicin Cream	1 RCT[49] total n=143	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(1) Agrawal et al. (2009); (2) Backonja et al. (1998); (3) Backonja et al. (2008); (4) Beydoun et al. (2006); (5) Bone et al. (2002); (6) Boureau et al. (2003); (7) Clifford et al. (2012); (8) Dogra et al. (2005); (9) Eisenberg et al. (2001); (10) Falah et al. (2012); (11) Freynhagen et al. (2005); (12) Gao et al. (2010); (13) Gimbel et al. (2003); (14) Goldstein et al. (2005); (15) Grosskopf et al. (2006); (16) Hahn et al. (2004); (17) Hanna et al. (2008); (18) Harati et al. (1998); (19) Holbech et al. (2011); (20) Irving et al. (2011); (21) Irving et al. (2012); (22) Kalso et al. (1995); (23) Khoromi et al. (2007); (24) Kochar et al. (2004); (25) Levendoglu et al. (2004); (26) Morello et al. (1999); (27) Norrbrink & Lundeberg (2009); (28) Nurmikko et al. (2007); (29) Rao et al. (2007); (30) Rao et al. (2008); (31) Raskin et al. (2004); (32) Rauck et al. (2007); (33) Rog et al. (2005); (34) Rosenstock et al. (2004); (35) Rossi et al. (2009); (36) Rowbotham et al. (2004); (37) Shaibani et al. (2009); (38) Simpson (2001); (39) Simpson et al. (2003); (40) Sindrup et al. (1999); (41) Sindrup et al. (2003); (42) Tasmuth et al. (2002); (43) Thienel et al. (2004); (44) van Seventer et al. (2006); (45) Vinik et al. (2007); (46) Vinik et al. (2007); (47) Vranken et al. (2008); (48) Vrethem et al. (1997); (49) Watson et al. (1993); (50) Watson et al. (1998); (51) Webster et al. (2010); (52) Wernicke et al. (2006); (53) Wu et al. (2008); (54) Wymer et al. (2009); (55) Yasuda et al. (2011); (56) Ziegler et al. (2010)

1 **Table 15 Nausea – relative effectiveness of all pairwise combinations (hazard ratios)**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amitriptyline	0.76 (0.15, 3.94)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cannabis Sativa Extract	2.69 (1.00, 7.61)	3.53 (0.56, 24.37)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Capsaicin Patch	1.77 (1.07, 2.94)	2.39 (0.42, 11.29)	0.66 (0.22, 1.86)		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	3.98 (2.57, 6.43)	5.26 (0.97, 26.90)	1.49 (0.50, 4.22)	2.26 (1.20, 4.29)		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	1.36 (0.56, 3.61)	1.68 (0.34, 8.78)	0.50 (0.15, 1.74)	0.75 (0.29, 2.14)	0.34 (0.13, 0.94)		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	3.79 (0.25, 71.48)	4.38 (0.50, 73.49)	1.48 (0.08, 26.55)	2.14 (0.14, 40.90)	0.96 (0.07, 17.70)	2.92 (0.24, 33.16)		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	3.32 (0.75, 12.51)	4.36 (0.41, 33.13)	1.21 (0.20, 6.36)	1.88 (0.41, 7.30)	0.83 (0.18, 3.37)	2.40 (0.45, 11.51)	0.85 (0.04, 17.60)		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	1.77 (1.01, 3.28)	2.29 (0.40, 12.23)	0.65 (0.21, 2.12)	1.00 (0.49, 2.11)	0.44 (0.20, 0.95)	1.32 (0.42, 3.58)	0.48 (0.02, 7.61)	0.54 (0.13, 2.64)		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	1.20 (0.71, 2.07)	1.60 (0.28, 8.04)	0.45 (0.15, 1.27)	0.68 (0.34, 1.35)	0.30 (0.15, 0.59)	0.88 (0.30, 2.33)	0.31 (0.02, 4.98)	0.36 (0.09, 1.75)	0.68 (0.30, 1.39)		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	2.64 (0.28, 24.44)	3.27 (0.33, 41.99)	1.00 (0.09, 10.12)	1.47 (0.16, 14.20)	0.64 (0.07, 6.03)	1.93 (0.18, 18.81)	0.68 (0.04, 16.04)	0.82 (0.06, 9.76)	1.46 (0.14, 14.24)	2.21 (0.21, 20.99)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	7.25 (1.32, 61.70)	8.96 (0.94, 121.7)	2.67 (0.38, 25.74)	4.11 (0.73, 34.59)	1.79 (0.32, 16.49)	5.27 (0.79, 49.42)	2.04 (0.07, 52.73)	2.14 (0.28, 29.80)	4.24 (0.68, 38.48)	6.08 (1.08, 51.07)	2.97 (0.14, 51.88)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Nortriptyline	0.42 (0.01, 4.89)	0.48 (0.02, 6.09)	0.15 (0.00, 2.20)	0.23 (0.01, 2.84)	0.10 (0.00, 1.27)	0.30 (0.01, 3.75)	0.10 (0.00, 3.12)	0.12 (0.00, 2.26)	0.23 (0.01, 2.85)	0.34 (0.01, 4.24)	0.15 (0.00, 3.91)	0.06 (0.00, 0.73)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	3.90 (0.20, 60.99)	4.75 (0.22, 111.0)	1.47 (0.07, 27.22)	2.14 (0.11, 39.66)	0.99 (0.05, 17.10)	2.83 (0.16, 47.10)	1.02 (0.02, 42.67)	1.20 (0.05, 22.72)	2.21 (0.12, 33.61)	3.19 (0.18, 52.95)	1.59 (0.03, 52.23)	0.54 (0.05, 4.32)	8.64 (0.44, 580.7)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	2.48 (1.01, 6.28)	3.28 (0.48, 18.79)	0.92 (0.24, 3.93)	1.41 (0.50, 3.86)	0.62 (0.23, 1.69)	1.87 (0.45, 7.10)	0.67 (0.03, 11.80)	0.75 (0.16, 4.25)	1.39 (0.47, 3.89)	2.11 (0.73, 5.89)	1.03 (0.08, 10.57)	0.35 (0.03, 2.36)	6.09 (0.43, 220.0)	0.62 (0.03, 16.17)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxycodone	8.20 (2.97, 25.63)	10.72 (1.56, 68.23)	3.06 (0.83, 11.73)	4.67 (1.57, 14.88)	2.03 (0.69, 6.89)	6.08 (1.66, 23.04)	2.22 (0.11, 33.52)	2.49 (0.50, 14.30)	4.66 (1.42, 15.64)	6.82 (2.24, 23.38)	3.17 (0.29, 33.21)	1.14 (0.11, 7.87)	20.63 (1.44, 695.4)	2.11 (0.11, 43.43)	3.29 (0.83, 14.43)		N/A	N/A	N/A	N/A	N/A	N/A
Pregabalin	1.27 (0.64, 2.48)	1.62 (0.28, 9.10)	0.46 (0.15, 1.50)	0.72 (0.31, 1.58)	0.32 (0.14, 0.68)	0.94 (0.29, 2.76)	0.34 (0.02, 5.59)	0.39 (0.08, 1.86)	0.72 (0.28, 1.64)	1.06 (0.45, 2.45)	0.48 (0.04, 5.02)	0.18 (0.02, 0.98)	3.08 (0.23, 124.2)	0.33 (0.02, 6.22)	0.50 (0.17, 1.63)	0.15 (0.04, 0.53)		N/A	N/A	N/A	N/A	N/A
Valproate	3.93 (0.57, 48.93)	5.14 (0.45, 127.7)	1.50 (0.18, 22.74)	2.24 (0.28, 27.65)	0.96 (0.14, 13.82)	3.00 (0.35, 44.88)	1.13 (0.03, 48.84)	1.26 (0.12, 22.67)	2.25 (0.30, 29.31)	3.24 (0.45, 44.11)	1.64 (0.08, 51.22)	0.52 (0.03, 11.69)	10.08 (0.39, 844.7)	1.15 (0.03, 52.73)	1.63 (0.21, 21.44)	0.50 (0.05, 7.40)	3.14 (0.43, 44.21)		N/A	N/A	N/A	N/A
Topiramate	1.93 (1.17, 3.29)	2.54 (0.47, 13.12)	0.72 (0.23, 2.06)	1.09 (0.54, 2.20)	0.48 (0.25, 0.94)	1.44 (0.49, 3.82)	0.50 (0.03, 8.07)	0.58 (0.15, 2.81)	1.10 (0.50, 2.33)	1.60 (0.80, 3.31)	0.74 (0.07, 7.15)	0.27 (0.03, 1.52)	4.69 (0.38, 182.0)	0.49 (0.03, 9.46)	0.78 (0.27, 2.24)	0.24 (0.07, 0.70)	1.52 (0.69, 3.55)	0.50 (0.04, 3.56)		N/A	N/A	N/A
Tramadol	5.56 (2.65, 13.01)	7.28 (1.29, 40.93)	2.06 (0.68, 6.67)	3.12 (1.38, 8.03)	1.39 (0.58, 3.42)	4.12 (1.32, 12.30)	1.42 (0.08, 23.61)	1.70 (0.39, 8.83)	3.15 (1.21, 8.10)	4.56 (2.01, 12.30)	2.15 (0.21, 22.69)	0.78 (0.08, 4.72)	13.73 (1.17, 596.2)	1.48 (0.08, 24.55)	2.25 (0.65, 8.38)	0.67 (0.20, 2.23)	4.47 (1.62, 12.38)	1.36 (0.10, 11.85)	2.85 (1.24, 7.42)		N/A	N/A
Venlafaxine	3.40 (1.55, 8.17)	4.41 (0.73, 30.73)	1.26 (0.37, 4.73)	1.91 (0.78, 5.10)	0.85 (0.34, 2.23)	2.51 (0.79, 8.33)	0.89 (0.05, 16.38)	1.04 (0.30, 4.04)	1.94 (0.72, 5.56)	2.85 (1.12, 7.53)	1.24 (0.14, 13.81)	0.48 (0.05, 2.65)	8.24 (0.62, 324.5)	0.90 (0.06, 14.38)	1.39 (0.41, 4.76)	0.42 (0.12, 1.47)	2.71 (1.01, 7.81)	0.86 (0.06, 6.48)	1.77 (0.69, 4.64)	0.62 (0.21, 1.82)		N/A
Capsaicin Cream	5.88 (0.42, 3778)	7.87 (0.29, 4761)	2.29 (0.15, 1397)	3.29 (0.22, 2159)	1.45 (0.10, 967.8)	4.64 (0.29, 2486)	1.59 (0.05, 798.6)	1.88 (0.09, 1659)	3.48 (0.21, 2156)	4.90 (0.34, 3237)	2.36 (0.07, 1546)	0.83 (0.03, 771.8)	15.62 (0.35, 22700)	1.75 (0.03, 2033)	2.38 (0.14, 1988)	0.75 (0.04, 393.9)	4.82 (0.32, 2679)	1.36 (0.03, 795.1)	3.02 (0.21, 2037)	1.06 (0.07, 627.1)	1.78 (0.11, 1073)	

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). Numbers in parentheses are 95% credible intervals. Because it is not easily possible to derive analogous estimates of hazard ratios from a frequentist analysis of direct data only, the segment above and to the right of the shaded cells is left blank.

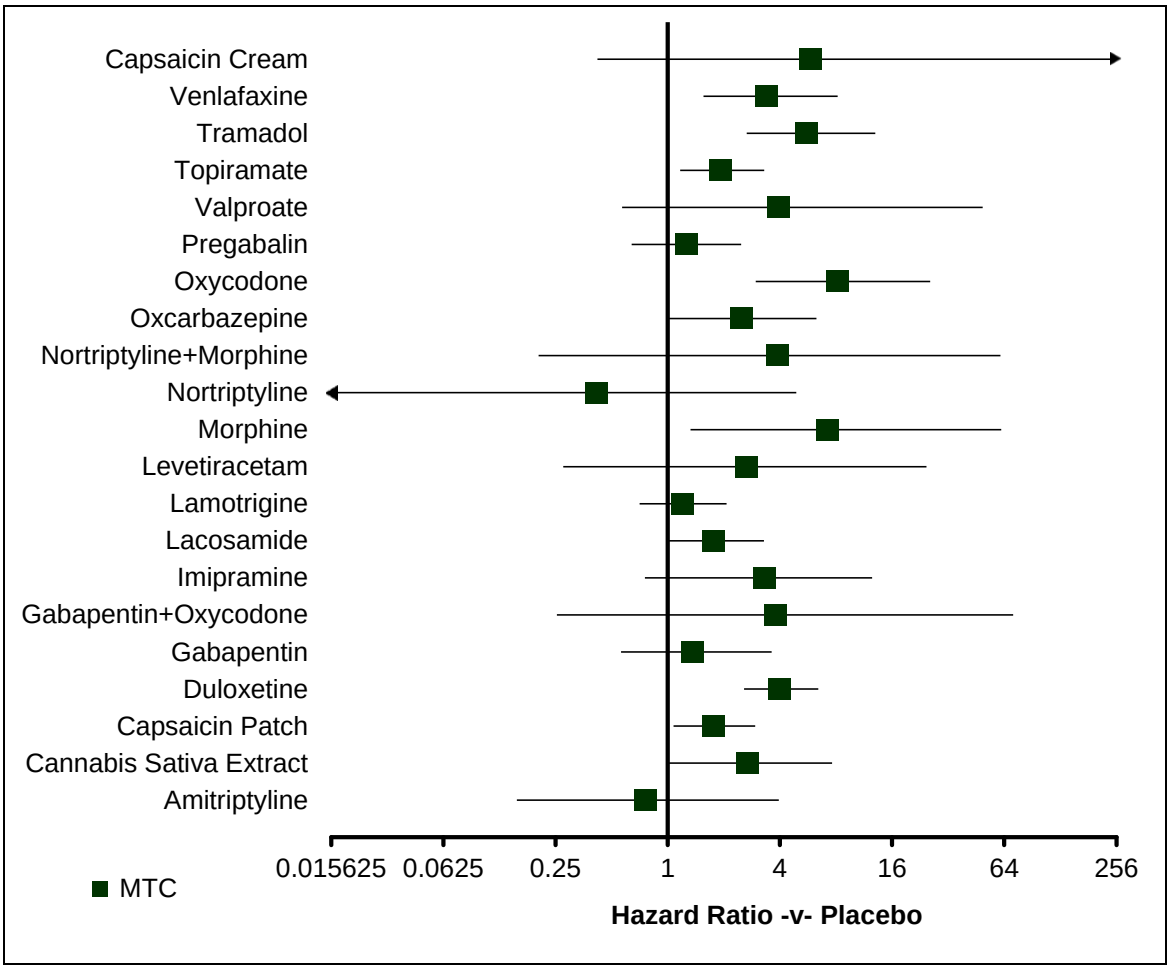


Figure 9 Nausea – relative effect of all options compared with placebo

Table 16 Nausea – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.038	4 (1, 7)
Amitriptyline	0.156	3 (1, 15)
Cannabis Sativa Extract	0.002	13 (4, 20)
Capsaicin Patch	0.000	9 (4, 14)
Duloxetine	0.000	16 (11, 20)
Gabapentin	0.026	6 (1, 14)
Gabapentin+Oxycodone	0.025	16 (2, 22)
Imipramine	0.012	14 (3, 21)
Lacosamide	0.001	9 (4, 15)
Lamotrigine	0.029	5 (1, 11)
Levetiracetam	0.044	13 (1, 22)
Morphine	0.000	19 (7, 22)
Nortriptyline	0.561	1 (1, 17)
Nortriptyline+Morphine	0.033	16 (1, 22)
Oxcarbazepine	0.006	12 (3, 20)
Oxycodone	0.000	20 (14, 22)
Pregabalin	0.022	6 (2, 12)
Valproate	0.017	16 (2, 22)
Topiramate	0.000	10 (5, 15)
Tramadol	0.000	18 (12, 22)
Venlafaxine	0.000	15 (8, 20)
Capsaicin Cream	0.027	19 (1, 22)

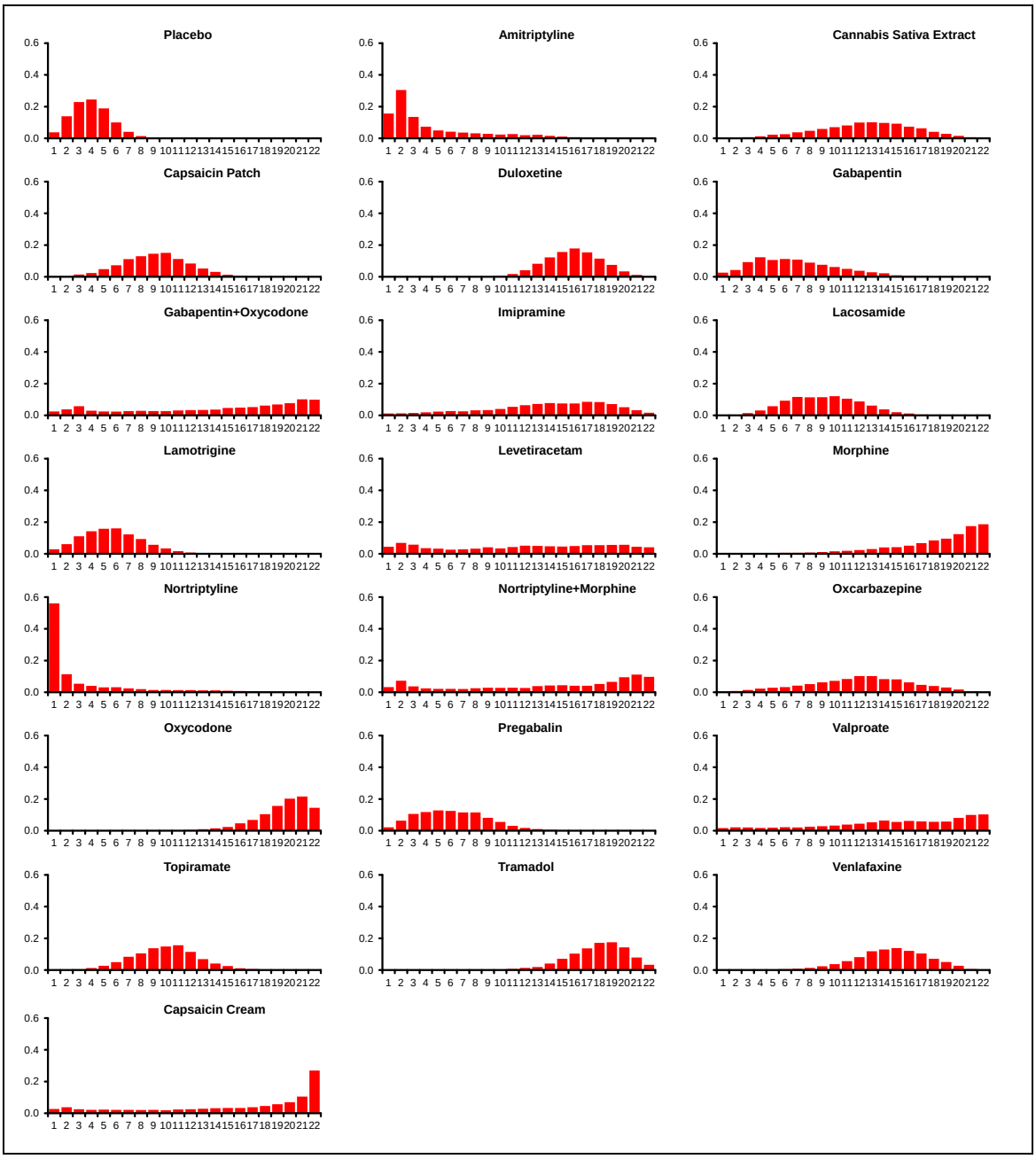


Figure 10 Nausea – rank probability histograms

Table 17 Nausea – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
139.8 (compared to 140 datapoints)	599.914	508.928	90.986	690.9	0.003 (95%CrI: 0.000, 0.221)

1.2.3 Withdrawal due to adverse effect(s)

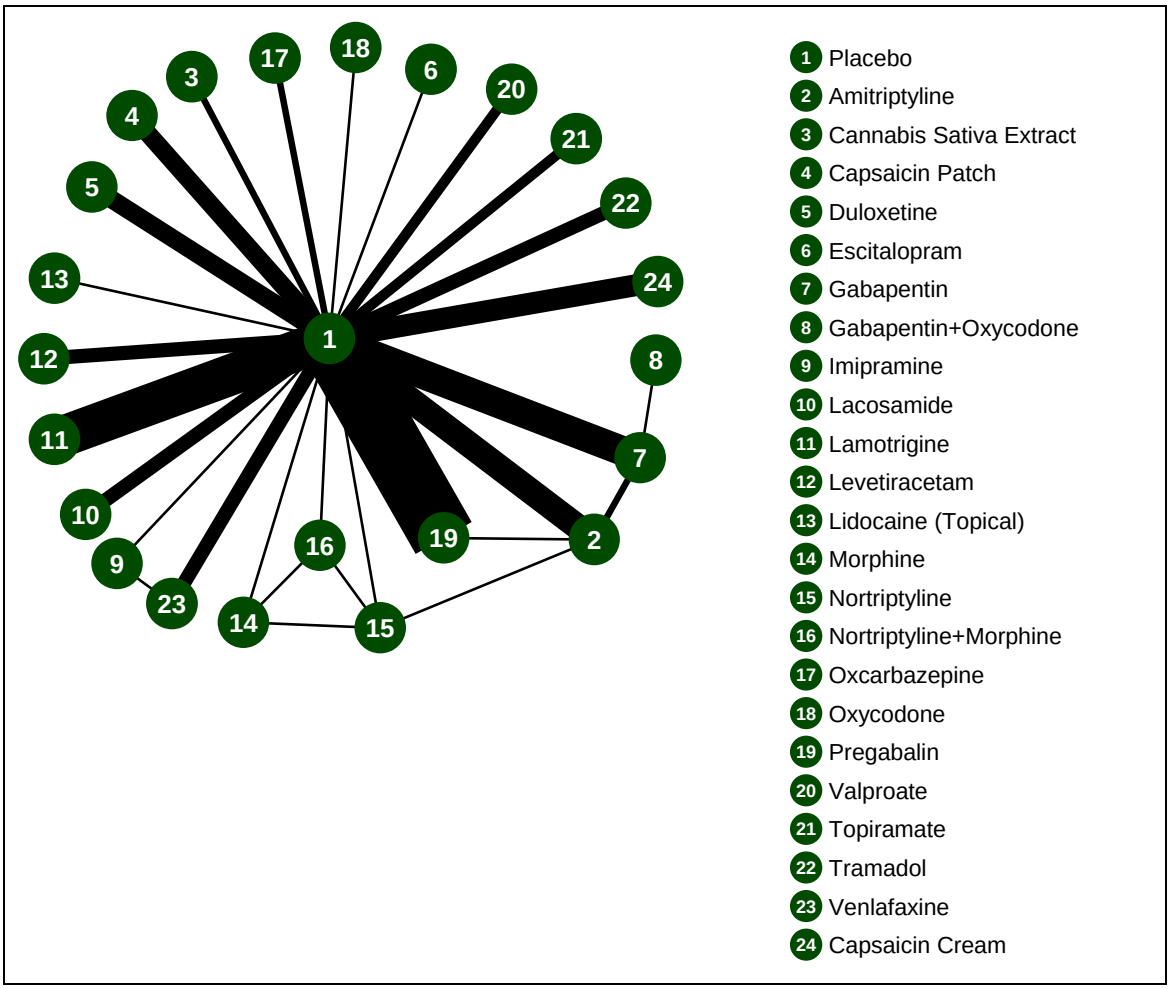


Figure 11 Withdrawal due to adverse effect(s) – evidence network

1 **Table 18 Withdrawal due to adverse effect(s) – 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[8,23,31,40,55,56,83] total n=449																						
Cannabis Sativa Extract	2 RCTs[46,57] total n=191	-																					
Capsaicin Patch	5 RCTs[4,10,29,30,87] total n=2738	-	-																				
Duloxetine	5 RCTs[19,21,51,88,90] total n=1692	-	-	-																			
Escitalopram	1 RCT[47] total n=96	-	-	-	-																		
Gabapentin	8 RCTs[3,22,25,44,53,55,60,67] total n=1176	2 RCTs[43,55] total n=126	-	-	-	-																	
Gabapentin +Oxycodone	-	-	-	-	-	-	1 RCT[26] total n=338																
Imipramine	1 RCT[72] total n=80	-	-	-	-	-	-	-															
Lacosamide	4 RCTs[52,65,89,92] total n=1314	-	-	-	-	-	-	-	-														
Lamotrigine	11 RCTs[7,14,16,39,41,49,68,69,79,80,81] total n=1463	-	-	-	-	-	-	-	-	-													
Levetiracetam	4 RCTs[15,17,28,59] total n=226	-	-	-	-	-	-	-	-	-	-												
Lidocaine (Topical)	1 RCT[9] total n=56	-	-	-	-	-	-	-	-	-	-	-											
Morphine	1 RCT[33] total n=110	-	-	-	-	-	-	-	-	-	-	-	-										
Nortriptyline	1 RCT[33] total n=110	1 RCT[86] total n=66	-	-	-	-	-	-	-	-	-	-	-	1 RCT[33] total n=110									
Nortriptyline +Morphine	1 RCT[33] total n=110	-	-	-	-	-	-	-	-	-	-	-	-	1 RCT[33] total n=110	1 RCT[33] total n=110								
Oxcarbazepine	2 RCTs[6,11] total n=493	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[20] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						

	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
Pregabalin	17 RCTs[2,13,18,24,34,38,42,54,58,62,63,66,70,73,77,78,82] total n=4236	1 RCT[5] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Valproate	3 RCTs[35,36,37] total n=145	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Topiramate	3 RCTs[32,50,76] total n=1674	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	4 RCTs[1,27,45,71] total n=292	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	4 RCTs[61,72,75,91] total n=415	-	-	-	-	-	-	-	1 RCT[72] total n=80	-	-	-	-	-	-	-	-	-	-	-	-	-	
Capsaicin Cream	6 RCTs[12,48,64,74,84,85] 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) Irving et al. (2012); (31) Kautio et al. (2008); (32) Khoromi et al. (2005); (33) Khoromi et al. (2007); (34) Kim et al. (2011); (35) Kochar et al. (2002); (36) Kochar et al. (2004); (37) Kochar et al. (2005); (38) Lesser et al. (2004); (39) Luria et al. (2000); (40) Max et al. (1988); (41) McCleane (1999); (42) Moon et al. (2010); (43) Morello et al. (1999); (44) Nikolajsen et al. (2006); (45) Norrbrink & Lundeberg (2009); (46) Nurmikko et al. (2007); (47) Otto et al. (2008); (48) Paice et al. (2000); (49) Rao et al. (2008); (50) Raskin et al. (2004); (51) Raskin et al. (2005); (52) Rauck et al. (2007); (53) Rice & Maton (2001); (54) Richter et al. (2005); (55) Rintala et al. (2007); (56) Robinson et al. (2004); (57) Rog et al. (2005); (58) Rosenstock et al. (2004); (59) Rossi et al. (2009); (60) Rowbotham et al. (1998); (61) Rowbotham et al. (2004); (62) Sabatowski et al. (2004); (63) Satoh et al. (2011); (64) Scheffler et al. (1991); (65) Shaibani et al. (2009); (66) Siddall et al. (2006); (67) Simpson (2001); (68) Simpson et al. (2000); (69) Simpson et al. (2003); (70) Simpson et al. (2010); (71) Sindrup et al. (1999); (72) Sindrup et al. (2003); (73) Stacey et al. (2008); (74) Tandan et al. (1992); (75) Tasmuth et al. (2002); (76) Thienel et al. (2004); (77) Tolle et al. (2008); (78) van Seventer et al. (2006); (79) Vestergaard et al. (2001); (80) Vinik et al. (2007); (81) Vinik et al. (2007); (82) Vranken et al. (2008); (83) Vrethem et al. (1997); (84) Watson & Evans (1992); (85) Watson et al. (1993); (86) Watson et al. (1998); (87) Webster et al. (2010); (88) Wernicke et al. (2006); (89) Wymer et al. (2009); (90) Yasuda et al. (2011); (91) Yucel et al. (2005); (92) Ziegler et al. (2010)

1 **Table 19 Withdrawal due to adverse effect(s) – relative effectiveness of all pairwise combinations (hazard ratios; unadjusted)**

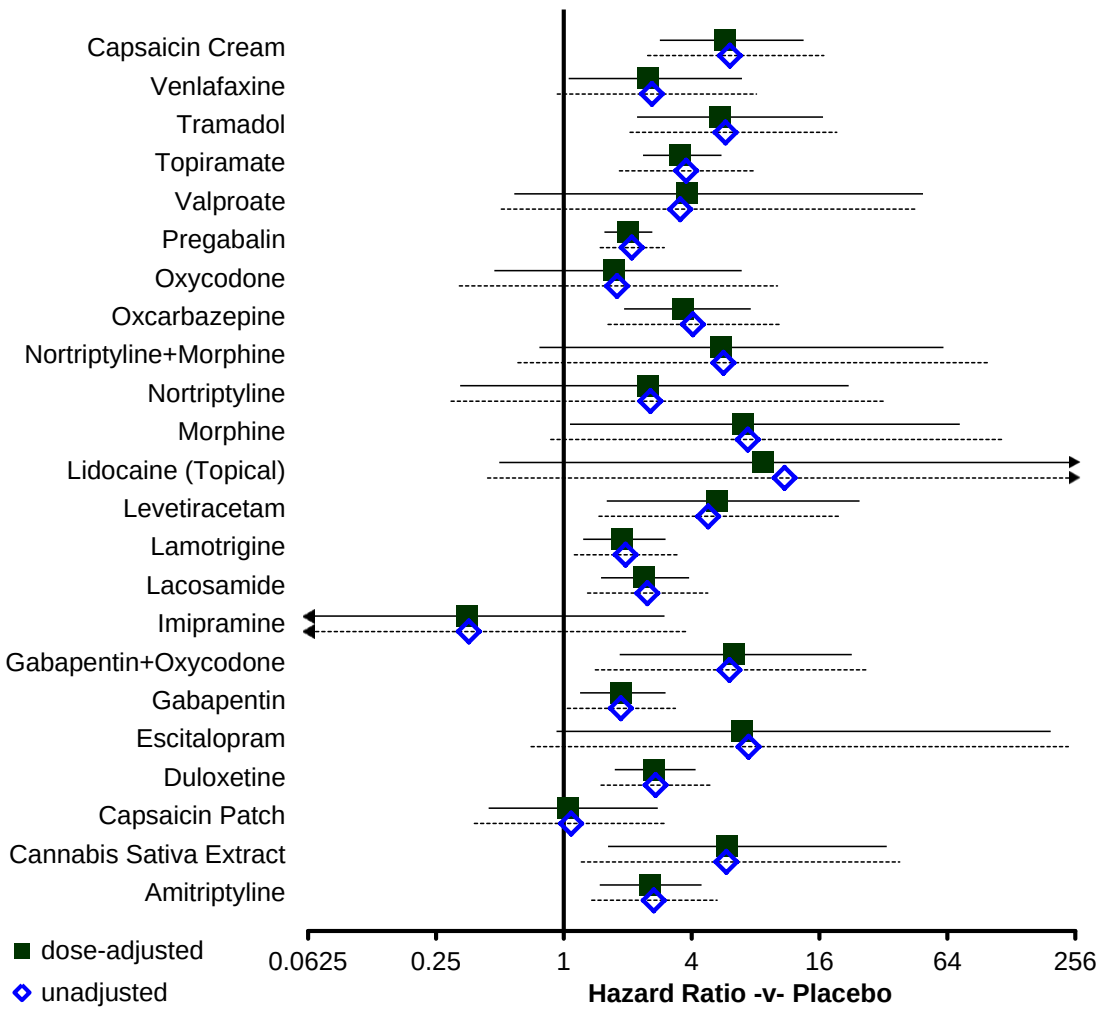
	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amitriptyline	2.65 (1.35, 5.27)		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	N/A	N/A	N/A
Cannabis Sativa Extract	5.82 (1.21, 38.14)	2.20 (0.39, 16.14)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Capsaicin Patch	1.08 (0.38, 3.06)	0.41 (0.12, 1.39)	0.18 (0.02, 1.23)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duloxetine	2.70 (1.50, 4.99)	1.02 (0.41, 2.55)	0.47 (0.06, 2.51)	2.51 (0.74, 8.30)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Escitalopram	7.41 (0.70, 237.9)	2.79 (0.24, 96.52)	1.28 (0.07, 54.24)	6.91 (0.53, 252.8)	2.75 (0.24, 92.46)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin	1.86 (1.04, 3.35)	0.70 (0.31, 1.59)	0.32 (0.04, 1.73)	1.72 (0.51, 5.66)	0.69 (0.29, 1.59)	0.25 (0.01, 2.82)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin +Oxycodone	6.03 (1.41, 26.99)	2.26 (0.48, 11.11)	1.02 (0.10, 9.15)	5.58 (0.93, 33.89)	2.22 (0.46, 11.24)	0.79 (0.02, 12.93)	3.23 (0.86, 12.56)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Imipramine	0.36 (0.01, 3.83)	0.13 (0.00, 1.60)	0.06 (0.00, 1.06)	0.32 (0.01, 4.58)	0.13 (0.00, 1.49)	0.04 (0.00, 1.32)	0.19 (0.01, 2.22)	0.06 (0.00, 0.95)		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
Lacosamide	2.47 (1.30, 4.77)	0.93 (0.36, 2.39)	0.42 (0.06, 2.31)	2.29 (0.67, 7.95)	0.91 (0.37, 2.24)	0.33 (0.01, 3.90)	1.33 (0.56, 3.20)	0.41 (0.08, 2.03)	6.98 (0.61, 264.0)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lamotrigine	1.95 (1.12, 3.51)	0.74 (0.30, 1.79)	0.33 (0.05, 1.81)	1.81 (0.56, 5.94)	0.72 (0.31, 1.66)	0.26 (0.01, 2.98)	1.05 (0.46, 2.41)	0.33 (0.07, 1.57)	5.54 (0.48, 210.2)	0.79 (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	N/A
Levetiracetam	4.79 (1.46, 19.82)	1.82 (0.45, 8.42)	0.84 (0.09, 6.66)	4.52 (0.93, 25.51)	1.78 (0.46, 8.03)	0.65 (0.02, 10.04)	2.59 (0.68, 12.02)	0.81 (0.12, 6.16)	14.27 (0.97, 576.6)	1.95 (0.51, 9.16)	2.46 (0.66, 11.13)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Lidocaine (Topical)	10.96 (0.44, 3740)	4.17 (0.15, 1499)	1.94 (0.04, 689.4)	10.54 (0.33, 3338)	4.07 (0.15, 1446)	1.50 (0.01, 729.5)	5.95 (0.22, 2067)	1.87 (0.05, 732.4)	37.30 (0.56, 26670)	4.49 (0.16, 1540)	5.66 (0.21, 1953)	2.34 (0.06, 742.1)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	7.35 (0.87, 118.8)	2.81 (0.30, 45.43)	1.26 (0.07, 31.90)	6.86 (0.64, 130.8)	2.71 (0.29, 47.58)	1.00 (0.02, 34.90)	4.00 (0.43, 67.76)	1.25 (0.09, 29.19)	22.92 (0.79, 1874)	2.97 (0.32, 51.04)	3.78 (0.41, 64.66)	1.52 (0.12, 30.92)	0.64 (0.00, 48.58)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	2.56 (0.29, 32.19)	0.97 (0.11, 11.79)	0.44 (0.02, 9.05)	2.39 (0.21, 36.62)	0.94 (0.10, 12.84)	0.33 (0.01, 10.37)	1.38 (0.15, 18.97)	0.42 (0.03, 7.95)	7.78 (0.28, 518.1)	1.03 (0.11, 13.86)	1.31 (0.14, 17.77)	0.52 (0.04, 8.67)	0.21 (0.00, 14.98)	0.34 (0.04, 2.32)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	5.65 (0.61, 98.68)	2.14 (0.21, 36.79)	0.98 (0.05, 25.08)	5.22 (0.45, 107.6)	2.08 (0.20, 38.44)	0.75 (0.01, 27.44)	3.05 (0.30, 56.36)	0.95 (0.06, 23.87)	17.52 (0.56, 1425)	2.30 (0.22, 42.67)	2.90 (0.29, 54.13)	1.18 (0.08, 25.04)	0.49 (0.00, 40.11)	0.78 (0.13, 4.27)	2.28 (0.30, 19.82)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	4.06 (1.62, 10.64)	1.53 (0.49, 4.89)	0.69 (0.09, 4.35)	3.77 (0.94, 15.07)	1.50 (0.49, 4.67)	0.54 (0.02, 6.98)	2.19 (0.73, 6.67)	0.67 (0.12, 3.85)	11.55 (0.90, 478.8)	1.64 (0.53, 5.16)	2.08 (0.70, 6.30)	0.84 (0.16, 3.78)	0.37 (0.00, 11.15)	0.55 (0.03, 5.81)	1.60 (0.11, 16.34)	0.71 (0.04, 8.26)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxycodone	1.78 (0.32, 10.14)	0.67 (0.11, 4.37)	0.30 (0.02, 3.28)	1.66 (0.22, 12.68)	0.66 (0.11, 4.14)	0.23 (0.01, 4.48)	0.96 (0.16, 6.11)	0.30 (0.03, 2.89)	5.24 (0.28, 252.4)	0.73 (0.12, 4.68)	0.92 (0.15, 5.58)	0.37 (0.04, 3.07)	0.16 (0.00, 6.33)	0.23 (0.01, 3.96)	0.70 (0.03, 11.02)	0.31 (0.01, 5.58)	0.44 (0.06, 3.19)		N/A	N/A	N/A	N/A	N/A	N/A
Pregabalin	2.09 (1.48, 2.97)	0.79 (0.38, 1.63)	0.36 (0.05, 1.79)	1.93 (0.65, 5.82)	0.77 (0.38, 1.53)	0.28 (0.01, 3.04)	1.13 (0.57, 2.20)	0.35 (0.08, 1.56)	5.92 (0.53, 223.3)	0.85 (0.40, 1.77)	1.07 (0.54, 2.08)	0.44 (0.10, 1.52)	0.19 (0.00, 5.07)	0.28 (0.02, 2.50)	0.82 (0.06, 7.26)	0.37 (0.02, 3.55)	0.51 (0.19, 1.39)	1.17 (0.20, 6.72)		N/A	N/A	N/A	N/A	N/A
Valproate	3.54 (0.51, 46.22)	1.33 (0.17, 18.86)	0.63 (0.04, 11.81)	3.28 (0.37, 50.11)	1.30 (0.17, 18.61)	0.46 (0.01, 15.63)	1.90 (0.26, 26.27)	0.60 (0.05, 10.88)	10.91 (0.47, 730.9)	1.44 (0.19, 19.86)	1.81 (0.24, 25.18)	0.74 (0.07, 11.85)	0.31 (0.00, 20.56)	0.48 (0.02, 12.10)	1.42 (0.06, 37.95)	0.64 (0.02, 17.62)	0.88 (0.10, 12.47)	2.03 (0.15, 41.66)	1.70 (0.23, 22.76)		N/A	N/A	N/A	N/A
Topiramate	3.76 (1.83, 7.92)	1.42 (0.53, 3.86)	0.65 (0.09, 3.68)	3.48 (0.99, 12.60)	1.39 (0.55, 3.58)	0.51 (0.01, 5.96)	2.02 (0.80, 5.17)	0.62 (0.12, 3.19)	10.75 (0.88, 406.2)	1.52 (0.57, 4.09)	1.93 (0.77, 4.86)	0.78 (0.16, 3.17)	0.34 (0.00, 9.53)	0.51 (0.03, 4.91)	1.47 (0.11, 14.20)	0.66 (0.04, 7.15)	0.93 (0.28, 3.03)	2.12 (0.33, 13.31)	1.81 (0.80, 4.10)	1.06 (0.08, 8.39)		N/A	N/A	N/A
Tramadol	5.78 (2.05, 19.31)	2.18 (0.63, 8.45)	0.99 (0.12, 7.34)	5.39 (1.18, 25.78)	2.13 (0.64, 8.14)	0.77 (0.02, 10.96)	3.11 (0.95, 11.74)	0.97 (0.16, 6.22)	16.66 (1.20, 770.9)	2.35 (0.69, 9.03)	2.93 (0.91, 11.00)	1.20 (0.21, 6.42)	0.52 (0.00, 16.79)	0.79 (0.04, 9.11)	2.27 (0.15, 26.44)	1.02 (0.05, 12.97)	1.44 (0.34, 6.32)	3.24 (0.43, 25.77)	2.77 (0.93, 9.64)	1.64 (0.10, 16.31)	1.54 (0.43, 6.25)		N/A	N/A
Venlafaxine	2.60 (0.93, 8.09)	0.98 (0.29, 3.66)	0.44 (0.05, 3.23)	2.42 (0.56, 11.67)	0.96 (0.29, 3.44)	0.35 (0.01, 4.76)	1.40 (0.43, 5.00)	0.43 (0.07, 2.70)	7.36 (0.78, 275.7)	1.05 (0.31, 3.87)	1.33 (0.41, 4.71)	0.54 (0.10, 2.80)	0.24 (0.00, 7.28)	0.36 (0.02, 3.88)	1.03 (0.07, 11.21)	0.47 (0.02, 5.61)	0.64 (0.16, 2.75)	1.46 (0.19, 11.36)	1.25 (0.42, 4.05)	0.73 (0.05, 6.97)	0.69 (0.20, 2.67)	0.45 (0.09, 2.13)		N/A
Capsaicin Cream	6.06 (2.49, 16.76)	2.29 (0.75, 7.67)	1.04 (0.13, 6.95)	5.63 (1.44, 23.69)	2.25 (0.76, 7.37)	0.82 (0.02, 10.64)	3.25 (1.14, 10.56)	1.02 (0.18, 5.70)	17.35 (1.35, 734.5)	2.47 (0.82, 8.10)	3.11 (1.07, 9.88)	1.27 (0.24, 5.94)	0.55 (0.00, 16.80)	0.83 (0.05, 8.68)	2.42 (0.17, 25.31)	1.08 (0.06, 12.16)	1.50 (0.41, 5.81)	3.42 (0.48, 24.68)	2.92 (1.10, 8.50)	1.71 (0.12, 14.97)	1.62 (0.50, 5.54)	1.06 (0.23, 4.42)	2.33 (0.57, 10.17)	

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Lidocaine (Topical)	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream

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). Numbers in parentheses are 95% credible intervals. Because it is not easily possible to derive analogous estimates of hazard ratios from a frequentist analysis of direct data only, the segment above and to the right of the shaded cells is left blank.



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 12 Withdrawal due to adverse effect(s) – relative effect of all options compared with placebo

Table 20 Withdrawal due to adverse effect(s) – rankings for each comparator

	No dose adjustment		Dose-adjusted	
	Probability best	**Median rank (95%CrI)**	**Probability best**	**Median rank (95%CrI)**
Placebo	0.051	3 (1, 6)	0.048	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 (6, 24)
Capsaicin Patch	0.098	3 (1, 13)	0.103	3 (1, 12)
Duloxetine	0.000	12 (5, 19)	0.000	12 (6, 18)
Escitalopram	0.009	20 (2, 24)	0.007	20 (3, 24)
Gabapentin	0.001	7 (3, 14)	0.000	7 (3, 14)
Gabapentin+Oxycodone	0.001	19 (5, 24)	0.000	19 (7, 24)
Imipramine	0.667	1 (1, 15)	0.711	1 (1, 13)
Lacosamide	0.000	11 (4, 18)	0.000	10 (5, 17)
Lamotrigine	0.001	8 (3, 15)	0.000	7 (3, 14)
Levetiracetam	0.000	17 (5, 23)	0.000	18 (5, 24)
Lidocaine (Topical)	0.022	22 (2, 24)	0.020	21 (2, 24)
Morphine	0.004	20 (3, 24)	0.002	20 (4, 24)
Nortriptyline	0.054	11 (1, 23)	0.047	11 (1, 22)
Nortriptyline+Morphine	0.011	18 (2, 24)	0.005	19 (3, 24)
Oxcarbazepine	0.000	16 (6, 22)	0.000	15 (7, 21)
Oxycodone	0.056	7 (1, 22)	0.038	6 (1, 20)
Pregabalin	0.000	9 (4, 14)	0.000	8 (4, 13)
Valproate	0.021	15 (2, 24)	0.019	16 (2, 24)
Topiramate	0.000	15 (7, 21)	0.000	15 (10, 20)
Tramadol	0.000	19 (8, 24)	0.000	18 (9, 24)
Venlafaxine	0.001	11 (3, 21)	0.001	11 (3, 21)
Capsaicin Cream	0.000	19 (11, 23)	0.000	19 (12, 23)

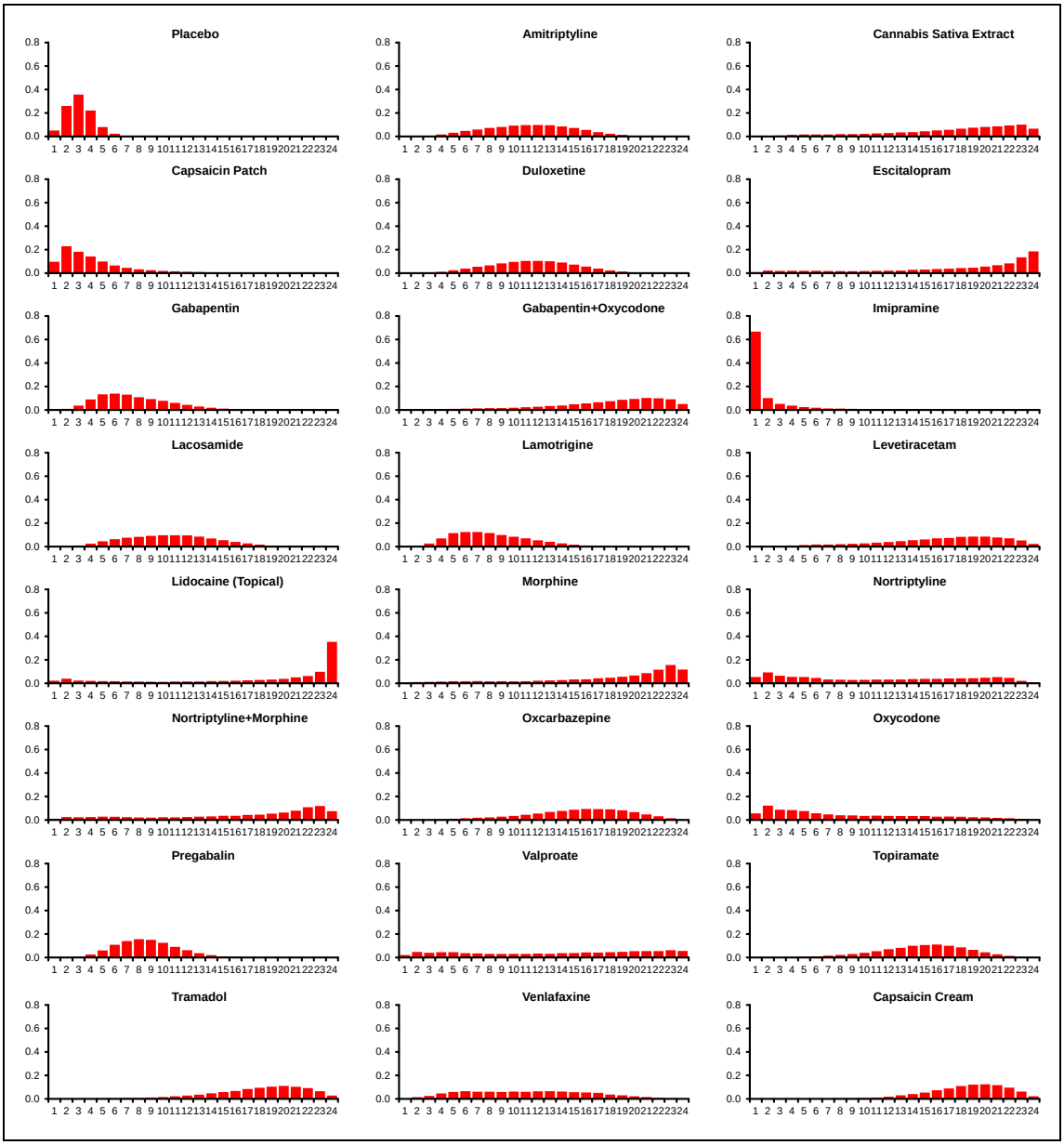


Figure 13 Withdrawal due to adverse effect(s) – rank probability histograms (no adjustment for dose)

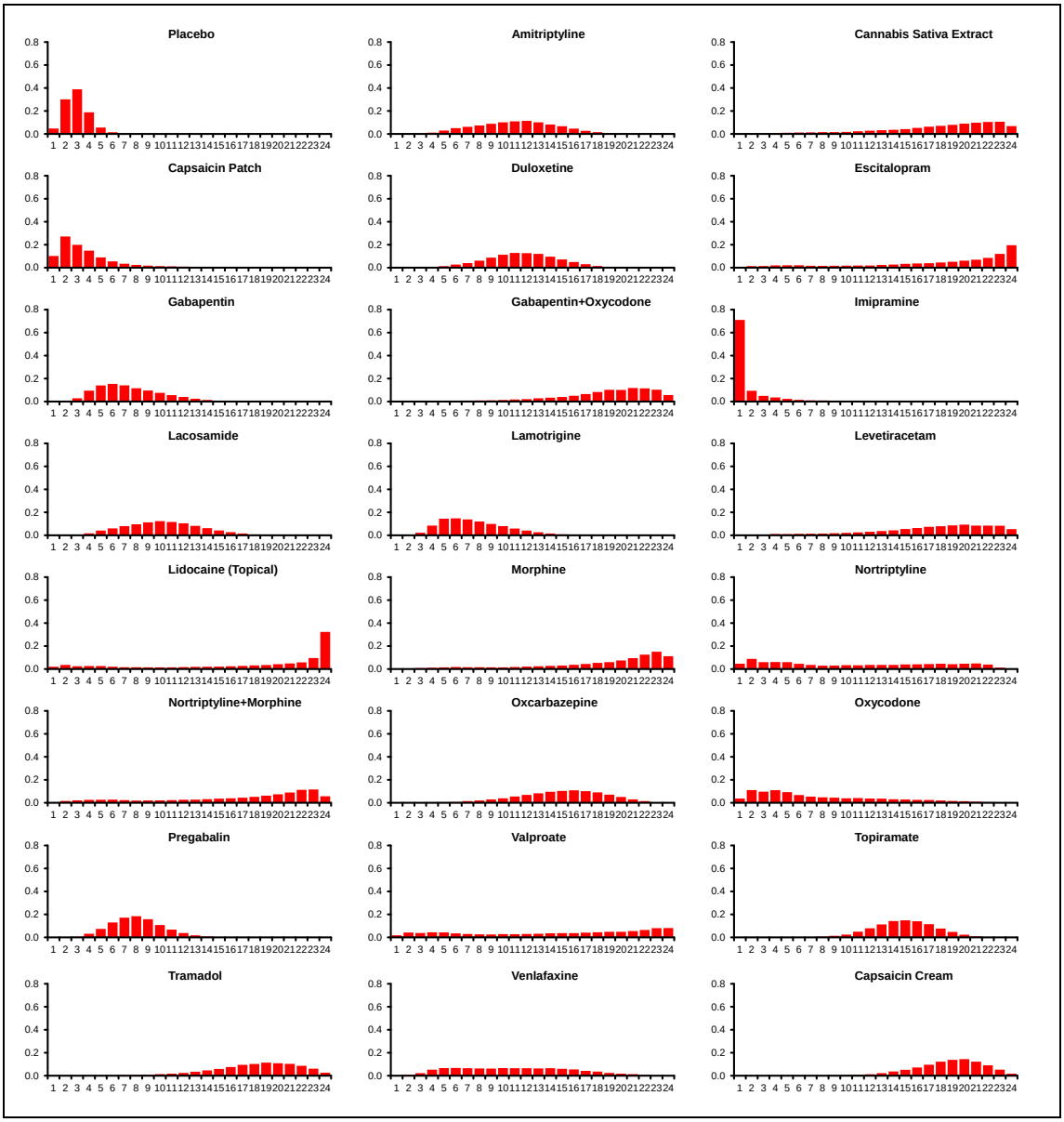


Figure 14 Withdrawal due to adverse effect(s) – rank probability histograms (dose-adjusted)

Table 21 Withdrawal due to adverse effect(s) – model fit statistics

	Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
Unadjusted	204.4 (cf. 199 datapoints)	918.7	763.0	155.6	1074.3	0.294 (95%CrI: 0.176, 0.507)
Dose-adjusted	214.9 (cf. 199 datapoints)	929.5	799.9	129.6	1059.2	0.007 (95%CrI: 0.001, 0.148)

As with efficacy data (see Table 7, above), 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 datapoints are poorly modelled in the dose-adjusted approach (this is particularly conspicuous for Stacey et al., 2008, which has the unusual feature of a much higher dropout rate in an arm with lower dosage).

2 Peripheral pain

2.1 Efficacy

2.1.1 30% and 50% pain relief

Data and results

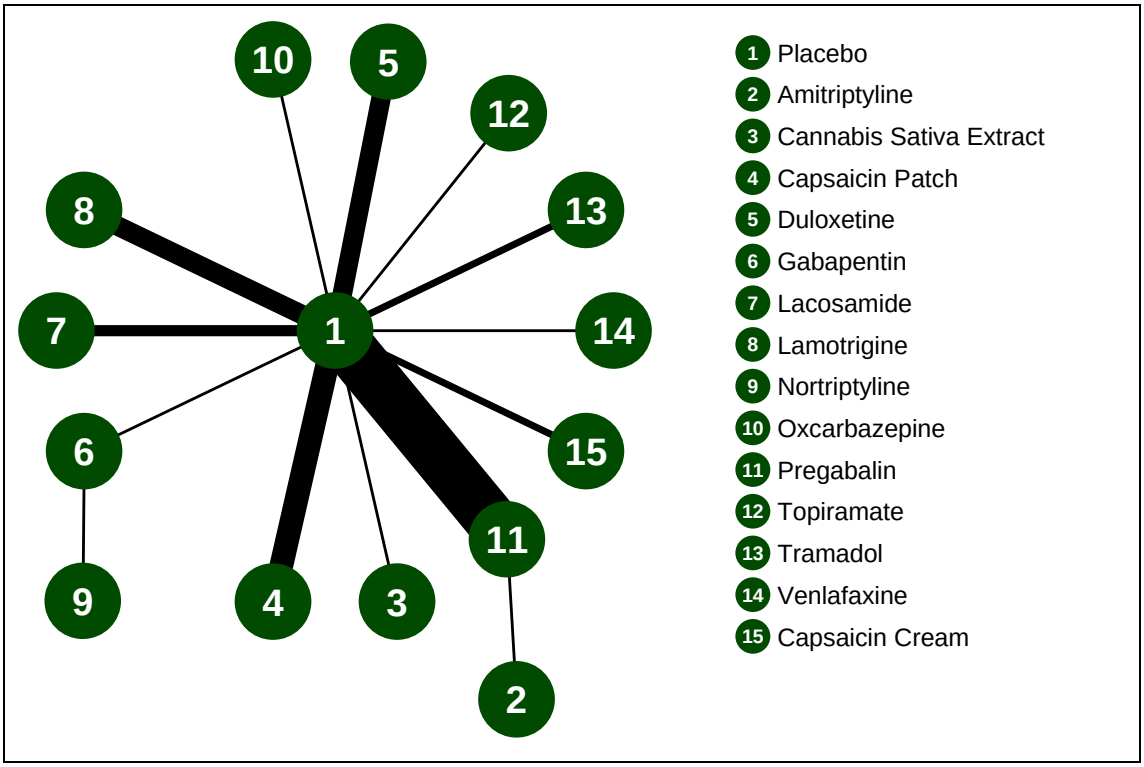


Figure 15 30% and 50% pain relief (peripheral only) – evidence network

1 **Table 22 30% and 50% pain relief (peripheral only) – trials included in analysis**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine
Amitriptyline	-													
Cannabis Sativa Extract	1 RCT[20] total n=250	-												
Capsaicin Patch	6 RCTs[1,4,7,15,16,33] total n=4890	-	-											
Duloxetine	5 RCTs[12,13,21,30,39] total n=2579	-	-	-										
Gabapentin	1 RCT[24] total n=334	-	-	-	-									
Lacosamide	3 RCTs[23,36,37] total n=1753	-	-	-	-	-								
Lamotrigine	5 RCTs[10,18,32,35,41] total n=1754	-	-	-	-	-	-							
Nortriptyline	-	-	-	-	-	1 RCT[5] total n=70	-	-						
Oxcarbazepine	1 RCT[8] total n=292	-	-	-	-	-	-	-	-					
Pregabalin	13 RCTs[6,9,11,14,17,19,25,26,28,29,31,34,40] total n=5542	1 RCT[42] total n=102	-	-	-	-	-	-	-	-				
Topiramate	1 RCT[22] total n=646	-	-	-	-	-	-	-	-	-	-			

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine
Tramadol	2 RCTs[3,43] 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) Boureau et al. (2003); (4) Webster et al. (2010); (5) Chandra et al. (2006); (6) Stacey et al. (2008); (7) Clifford et al. (2012); (8) Dogra et al. (2005); (9) Dworkin et al. (2003); (10) Eisenberg et al. (2001); (11) Freynhagen et al. (2005); (12) Gao et al. (2010); (13) Goldstein et al. (2005); (14) Guan et al. (2011); (15) Irving et al. (2012); (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) Vinik et al. (2007); (42) Bansal et al. (2009); (43) Sindrup et al. (1999)

1 **Table 23 30% and 50% pain relief (peripheral only) – relative effectiveness of all pairwise combinations (z-scores; unadjusted)**

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Lacosamide	Lamotrigine	Nortriptyline	Oxcarbazepine	Pregabalin	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amitriptyline	-0.20 (-0.82,0.43)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cannabis Sativa Extract	-0.47 (-1.08,0.13)	-0.27 (-1.15,0.59)		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	-0.24 (-0.40,-0.07)	-0.04 (-0.68,0.61)	0.23 (-0.39,0.86)		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)	-0.33 (-0.98,0.32)	-0.06 (-0.68,0.57)	-0.29 (-0.53,-0.04)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin	-0.57 (-1.03,-0.10)	-0.37 (-1.15,0.40)	-0.10 (-0.86,0.67)	-0.33 (-0.82,0.16)	-0.04 (-0.53,0.45)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lacosamide	-0.24 (-0.50,0.03)	-0.04 (-0.72,0.64)	0.23 (-0.42,0.89)	0.00 (-0.31,0.31)	0.29 (-0.03,0.61)	0.33 (-0.20,0.86)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lamotrigine	-0.21 (-0.45,0.02)	-0.02 (-0.69,0.64)	0.25 (-0.39,0.90)	0.02 (-0.27,0.30)	0.31 (0.01,0.60)	0.35 (-0.16,0.87)	0.02 (-0.33,0.37)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	-0.72 (-1.58,0.16)	-0.52 (-1.60,0.54)	-0.25 (-1.30,0.81)	-0.48 (-1.37,0.40)	-0.20 (-1.08,0.70)	-0.16 (-0.89,0.60)	-0.49 (-1.39,0.44)	-0.51 (-1.40,0.40)		N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	-0.48 (-1.01,0.05)	-0.28 (-1.10,0.53)	-0.01 (-0.81,0.80)	-0.24 (-0.80,0.32)	0.04 (-0.52,0.61)	0.08 (-0.62,0.79)	-0.25 (-0.83,0.35)	-0.27 (-0.85,0.33)	0.24 (-0.79,1.26)		N/A	N/A	N/A	N/A	N/A
Pregabalin	-0.51 (-0.65,-0.39)	-0.32 (-0.93,0.29)	-0.05 (-0.66,0.58)	-0.28 (-0.49,-0.07)	0.01 (-0.21,0.23)	0.05 (-0.43,0.53)	-0.28 (-0.57,0.02)	-0.30 (-0.57,-0.03)	0.20 (-0.69,1.08)	-0.03 (-0.59,0.51)		N/A	N/A	N/A	N/A
Topiramate	-0.39 (-0.83,0.06)	-0.19 (-0.96,0.58)	0.08 (-0.66,0.83)	-0.15 (-0.63,0.33)	0.14 (-0.35,0.62)	0.18 (-0.46,0.81)	-0.15 (-0.67,0.37)	-0.17 (-0.68,0.34)	0.33 (-0.66,1.31)	0.09 (-0.61,0.79)	0.13 (-0.33,0.60)		N/A	N/A	N/A
Tramadol	-0.55 (-0.99,-0.13)	-0.35 (-1.11,0.41)	-0.08 (-0.82,0.65)	-0.31 (-0.78,0.15)	-0.02 (-0.49,0.44)	0.02 (-0.62,0.65)	-0.31 (-0.82,0.19)	-0.34 (-0.83,0.16)	0.17 (-0.81,1.14)	-0.06 (-0.77,0.61)	-0.03 (-0.48,0.41)	-0.16 (-0.79,0.46)		N/A	N/A
Venlafaxine	-0.35 (-0.81,0.10)	-0.16 (-0.93,0.61)	0.11 (-0.64,0.87)	-0.12 (-0.60,0.36)	0.17 (-0.32,0.66)	0.21 (-0.43,0.85)	-0.12 (-0.65,0.41)	-0.14 (-0.65,0.37)	0.36 (-0.62,1.34)	0.13 (-0.58,0.83)	0.16 (-0.31,0.63)	0.03 (-0.60,0.67)	0.19 (-0.43,0.82)		N/A
Capsaicin Cream	-1.26 (-2.06,-0.50)	-1.06 (-2.08,-0.07)	-0.79 (-1.79,0.20)	-1.02 (-1.83,-0.24)	-0.73 (-1.55,0.06)	-0.69 (-1.60,0.19)	-1.02 (-1.85,-0.21)	-1.04 (-1.87,-0.24)	-0.54 (-1.73,0.62)	-0.78 (-1.73,0.15)	-0.74 (-1.54,0.03)	-0.87 (-1.78,0.01)	-0.71 (-1.61,0.17)	-0.90 (-1.82,-0.01)	

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). 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 24 Probability of pain relief over time as applied in the health economic model – peripheral pain only; no adjustment for dose

	placebo	amitriptyl-ine	cannabis sativa extract	capsaicin patch	duloxetine	gabapentin	lacosamide	lamotrigine	nortriptyl-ine	oxcarbaz-epine	pregabalin	topiramate	tramadol	venlafaxine	capsaicin cream
4 weeks															
<30%	0.78 (0.47,0.95)	0.71 (0.31,0.94)	0.62 (0.23,0.90)	0.70 (0.37,0.92)	0.60 (0.26,0.86)	0.58 (0.22,0.89)	0.70 (0.36,0.92)	0.71 (0.38,0.92)	0.52 (0.13,0.89)	0.61 (0.25,0.90)	0.60 (0.28,0.87)	0.65 (0.30,0.91)	0.58 (0.25,0.88)	0.66 (0.29,0.91)	0.31 (0.05,0.75)
30–49%	0.10 (0.03,0.16)	0.12 (0.03,0.16)	0.14 (0.05,0.16)	0.12 (0.05,0.16)	0.15 (0.07,0.16)	0.15 (0.06,0.16)	0.12 (0.04,0.16)	0.12 (0.04,0.16)	0.16 (0.06,0.16)	0.14 (0.05,0.16)	0.14 (0.07,0.16)	0.14 (0.05,0.16)	0.15 (0.06,0.16)	0.13 (0.05,0.16)	0.15 (0.06,0.17)
≥50%	0.12 (0.02,0.37)	0.17 (0.03,0.54)	0.24 (0.04,0.63)	0.18 (0.04,0.47)	0.26 (0.07,0.59)	0.27 (0.05,0.64)	0.18 (0.03,0.48)	0.17 (0.03,0.45)	0.33 (0.05,0.77)	0.25 (0.05,0.61)	0.26 (0.07,0.58)	0.22 (0.04,0.54)	0.27 (0.06,0.60)	0.21 (0.04,0.56)	0.54 (0.14,0.89)
8 weeks															
<30%	0.68 (0.57,0.78)	0.61 (0.33,0.83)	0.50 (0.25,0.73)	0.59 (0.46,0.71)	0.48 (0.35,0.61)	0.46 (0.26,0.68)	0.59 (0.44,0.73)	0.60 (0.46,0.73)	0.40 (0.11,0.74)	0.50 (0.28,0.73)	0.48 (0.35,0.61)	0.53 (0.33,0.75)	0.47 (0.27,0.66)	0.55 (0.33,0.75)	0.21 (0.05,0.52)
30–49%	0.13 (0.10,0.15)	0.14 (0.08,0.16)	0.16 (0.11,0.17)	0.15 (0.12,0.16)	0.16 (0.14,0.17)	0.16 (0.13,0.17)	0.15 (0.11,0.16)	0.14 (0.11,0.16)	0.16 (0.09,0.17)	0.16 (0.11,0.17)	0.16 (0.14,0.17)	0.15 (0.11,0.17)	0.16 (0.13,0.17)	0.15 (0.11,0.17)	0.13 (0.05,0.16)
≥50%	0.19 (0.12,0.28)	0.25 (0.09,0.52)	0.34 (0.16,0.61)	0.26 (0.17,0.38)	0.36 (0.25,0.50)	0.38 (0.19,0.59)	0.26 (0.15,0.40)	0.26 (0.15,0.39)	0.44 (0.15,0.80)	0.35 (0.15,0.57)	0.36 (0.25,0.49)	0.31 (0.15,0.52)	0.37 (0.20,0.58)	0.30 (0.14,0.51)	0.65 (0.32,0.90)
12 weeks															
<30%	0.62 (0.55,0.69)	0.54 (0.29,0.78)	0.44 (0.21,0.67)	0.53 (0.44,0.62)	0.42 (0.32,0.52)	0.40 (0.23,0.58)	0.53 (0.40,0.66)	0.54 (0.42,0.65)	0.34 (0.10,0.69)	0.43 (0.24,0.67)	0.42 (0.33,0.50)	0.47 (0.29,0.65)	0.41 (0.23,0.60)	0.48 (0.29,0.67)	0.17 (0.04,0.44)
30–49%	0.14 (0.12,0.15)	0.15 (0.10,0.16)	0.16 (0.12,0.17)	0.15 (0.14,0.16)	0.16 (0.15,0.17)	0.16 (0.13,0.17)	0.15 (0.13,0.17)	0.15 (0.13,0.16)	0.16 (0.09,0.17)	0.16 (0.13,0.17)	0.16 (0.15,0.17)	0.16 (0.13,0.17)	0.16 (0.14,0.17)	0.16 (0.13,0.17)	0.12 (0.05,0.16)
≥50%	0.24 (0.18,0.30)	0.30 (0.13,0.56)	0.40 (0.20,0.65)	0.32 (0.24,0.40)	0.42 (0.32,0.53)	0.44 (0.27,0.64)	0.32 (0.21,0.44)	0.31 (0.21,0.42)	0.50 (0.18,0.81)	0.41 (0.21,0.62)	0.42 (0.34,0.51)	0.37 (0.21,0.56)	0.43 (0.26,0.63)	0.36 (0.20,0.56)	0.71 (0.41,0.92)
16 weeks															
<30%	0.60 (0.08,0.96)	0.52 (0.05,0.95)	0.42 (0.02,0.93)	0.51 (0.05,0.93)	0.40 (0.03,0.90)	0.38 (0.02,0.91)	0.51 (0.05,0.93)	0.52 (0.06,0.94)	0.32 (0.01,0.90)	0.41 (0.03,0.92)	0.40 (0.03,0.89)	0.45 (0.03,0.93)	0.39 (0.03,0.90)	0.46 (0.04,0.94)	0.16 (0.00,0.75)
30–49%	0.14 (0.02,0.16)	0.15 (0.02,0.16)	0.16 (0.02,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.15 (0.03,0.16)	0.15 (0.01,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.02,0.16)	0.16 (0.03,0.16)	0.12 (0.01,0.16)
≥50%	0.25 (0.02,0.83)	0.32 (0.02,0.89)	0.42 (0.03,0.94)	0.33 (0.03,0.90)	0.44 (0.05,0.93)	0.46 (0.04,0.95)	0.33 (0.03,0.89)	0.33 (0.03,0.88)	0.52 (0.05,0.98)	0.43 (0.04,0.94)	0.44 (0.05,0.93)	0.39 (0.03,0.92)	0.45 (0.04,0.93)	0.38 (0.03,0.91)	0.73 (0.13,0.99)
20 weeks															
<30%	0.64 (0.51,0.76)	0.56 (0.26,0.81)	0.46 (0.22,0.72)	0.55 (0.39,0.69)	0.43 (0.29,0.59)	0.42 (0.23,0.64)	0.55 (0.38,0.71)	0.56 (0.40,0.72)	0.36 (0.10,0.71)	0.45 (0.23,0.71)	0.44 (0.30,0.59)	0.49 (0.28,0.72)	0.42 (0.23,0.65)	0.50 (0.29,0.71)	0.18 (0.04,0.46)
30–49%	0.14 (0.11,0.16)	0.15 (0.09,0.16)	0.16 (0.11,0.17)	0.15 (0.12,0.16)	0.16 (0.14,0.17)	0.16 (0.13,0.17)	0.15 (0.12,0.16)	0.15 (0.12,0.17)	0.16 (0.09,0.17)	0.16 (0.12,0.17)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.16 (0.13,0.17)	0.16 (0.12,0.17)	0.12 (0.05,0.16)
≥50%	0.22 (0.13,0.34)	0.29 (0.10,0.59)	0.39 (0.16,0.64)	0.30 (0.18,0.44)	0.41 (0.27,0.56)	0.42 (0.23,0.64)	0.30 (0.17,0.46)	0.29 (0.16,0.44)	0.48 (0.17,0.81)	0.39 (0.17,0.64)	0.40 (0.27,0.55)	0.35 (0.16,0.57)	0.42 (0.22,0.63)	0.34 (0.17,0.56)	0.69 (0.38,0.91)

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 25 Probability of pain relief over time as applied in the health economic model – peripheral pain only; dose-adjusted

	placebo	amitriptyline	cannabis sativa extract	capsaicin patch	duloxetine	gabapentin	lacosamide	lamotrigine	nortriptyline	oxcarbazepine	pregabalin	topiramate	tramadol	venlafaxine	capsaicin cream
	-	50mg/d[a]	4 sprays/d[a]	1×60-min[a]	60mg/d[a]	1800mg/d[a]	400mg/d[a]	400mg/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%	0.78 (0.45,0.95)	0.76 (0.35,0.96)	0.62 (0.19,0.92)	0.70 (0.36,0.92)	0.60 (0.27,0.87)	0.58 (0.20,0.89)	0.71 (0.36,0.92)	0.71 (0.37,0.93)	0.50 (0.00,1.00)	0.61 (0.25,0.91)	0.63 (0.27,0.87)	0.65 (0.00,1.00)	0.57 (0.25,0.91)	0.71 (0.42,0.99)	0.30 (0.01,0.92)
30–49%	0.10 (0.03,0.16)	0.11 (0.02,0.16)	0.14 (0.04,0.16)	0.12 (0.04,0.16)	0.14 (0.07,0.16)	0.15 (0.06,0.16)	0.12 (0.04,0.16)	0.12 (0.04,0.16)	0.16 (0.00,0.16)	0.14 (0.05,0.16)	0.14 (0.07,0.16)	0.14 (0.00,0.16)	0.15 (0.05,0.16)	0.12 (0.01,0.16)	0.15 (0.02,0.16)
≥50%	0.12 (0.02,0.39)	0.13 (0.01,0.49)	0.24 (0.03,0.68)	0.18 (0.03,0.48)	0.26 (0.06,0.59)	0.27 (0.05,0.67)	0.17 (0.03,0.48)	0.17 (0.03,0.48)	0.34 (0.00,1.00)	0.25 (0.04,0.60)	0.23 (0.06,0.59)	0.22 (0.00,1.00)	0.28 (0.04,0.61)	0.17 (0.00,0.42)	0.55 (0.04,0.97)
8 weeks															
<30%	0.68 (0.57,0.78)	0.66 (0.37,0.86)	0.51 (0.20,0.80)	0.59 (0.44,0.74)	0.48 (0.35,0.62)	0.47 (0.25,0.70)	0.60 (0.45,0.73)	0.60 (0.46,0.74)	0.39 (0.00,1.00)	0.49 (0.27,0.72)	0.51 (0.37,0.62)	0.53 (0.00,1.00)	0.45 (0.27,0.74)	0.60 (0.43,0.95)	0.21 (0.01,0.79)
30–49%	0.13 (0.10,0.15)	0.13 (0.07,0.16)	0.16 (0.09,0.17)	0.15 (0.11,0.16)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.14 (0.11,0.16)	0.14 (0.11,0.16)	0.16 (0.00,0.16)	0.16 (0.12,0.17)	0.16 (0.14,0.17)	0.15 (0.00,0.16)	0.16 (0.11,0.17)	0.14 (0.03,0.16)	0.13 (0.01,0.16)
≥50%	0.19 (0.12,0.28)	0.21 (0.07,0.47)	0.34 (0.11,0.67)	0.26 (0.15,0.40)	0.36 (0.24,0.49)	0.37 (0.17,0.61)	0.26 (0.15,0.40)	0.26 (0.15,0.38)	0.45 (0.00,1.00)	0.35 (0.16,0.58)	0.33 (0.24,0.47)	0.31 (0.00,1.00)	0.39 (0.15,0.57)	0.25 (0.02,0.42)	0.66 (0.11,0.98)
12 weeks															
<30%	0.62 (0.55,0.69)	0.60 (0.34,0.81)	0.44 (0.17,0.76)	0.53 (0.40,0.65)	0.42 (0.32,0.52)	0.40 (0.20,0.64)	0.53 (0.41,0.65)	0.53 (0.43,0.64)	0.33 (0.00,1.00)	0.43 (0.25,0.64)	0.45 (0.35,0.52)	0.47 (0.00,1.00)	0.39 (0.24,0.68)	0.54 (0.37,0.93)	0.17 (0.01,0.76)
30–49%	0.14 (0.12,0.15)	0.14 (0.09,0.16)	0.16 (0.11,0.17)	0.15 (0.13,0.16)	0.16 (0.15,0.17)	0.16 (0.13,0.17)	0.15 (0.13,0.17)	0.15 (0.13,0.16)	0.16 (0.00,0.15)	0.16 (0.13,0.17)	0.16 (0.15,0.17)	0.16 (0.00,0.16)	0.16 (0.13,0.17)	0.15 (0.04,0.16)	0.12 (0.01,0.16)
≥50%	0.24 (0.18,0.30)	0.26 (0.10,0.50)	0.40 (0.14,0.71)	0.32 (0.21,0.44)	0.42 (0.32,0.53)	0.44 (0.22,0.66)	0.31 (0.22,0.43)	0.31 (0.22,0.41)	0.52 (0.00,1.00)	0.41 (0.22,0.61)	0.39 (0.33,0.50)	0.37 (0.00,1.00)	0.45 (0.19,0.62)	0.31 (0.03,0.47)	0.72 (0.13,0.98)
16 weeks															
<30%	0.61 (0.10,0.97)	0.58 (0.07,0.97)	0.42 (0.03,0.95)	0.51 (0.06,0.94)	0.40 (0.03,0.91)	0.39 (0.02,0.92)	0.52 (0.05,0.95)	0.52 (0.06,0.95)	0.31 (0.00,1.00)	0.41 (0.03,0.93)	0.43 (0.04,0.92)	0.45 (0.00,1.00)	0.37 (0.03,0.93)	0.52 (0.07,0.99)	0.15 (0.00,0.89)
30–49%	0.14 (0.02,0.16)	0.15 (0.02,0.16)	0.16 (0.02,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.02,0.16)	0.16 (0.02,0.16)	0.16 (0.02,0.16)	0.15 (0.00,0.16)	0.16 (0.03,0.16)	0.16 (0.03,0.16)	0.16 (0.00,0.16)	0.16 (0.02,0.16)	0.15 (0.01,0.16)	0.12 (0.00,0.16)
≥50%	0.25 (0.01,0.82)	0.27 (0.01,0.85)	0.42 (0.02,0.94)	0.33 (0.02,0.88)	0.44 (0.04,0.93)	0.45 (0.03,0.94)	0.33 (0.02,0.89)	0.33 (0.02,0.87)	0.53 (0.00,1.00)	0.43 (0.03,0.92)	0.41 (0.04,0.92)	0.39 (0.00,1.00)	0.47 (0.03,0.93)	0.32 (0.00,0.86)	0.73 (0.05,1.00)
20 weeks															
<30%	0.64 (0.51,0.76)	0.61 (0.32,0.85)	0.46 (0.18,0.77)	0.55 (0.39,0.71)	0.44 (0.29,0.60)	0.42 (0.20,0.67)	0.55 (0.37,0.70)	0.55 (0.39,0.72)	0.34 (0.00,1.00)	0.45 (0.23,0.69)	0.47 (0.31,0.58)	0.48 (0.00,1.00)	0.40 (0.23,0.71)	0.56 (0.38,0.94)	0.18 (0.01,0.78)
30–49%	0.14 (0.11,0.16)	0.14 (0.07,0.16)	0.16 (0.10,0.17)	0.15 (0.12,0.16)	0.16 (0.14,0.17)	0.16 (0.12,0.17)	0.15 (0.12,0.17)	0.15 (0.12,0.16)	0.16 (0.00,0.16)	0.16 (0.12,0.17)	0.16 (0.14,0.17)	0.16 (0.00,0.16)	0.16 (0.12,0.17)	0.15 (0.03,0.16)	0.12 (0.01,0.16)
≥50%	0.22 (0.14,0.33)	0.24 (0.07,0.53)	0.38 (0.12,0.69)	0.30 (0.17,0.46)	0.40 (0.26,0.56)	0.42 (0.20,0.67)	0.30 (0.18,0.47)	0.30 (0.16,0.45)	0.50 (0.00,1.00)	0.39 (0.18,0.63)	0.37 (0.27,0.53)	0.36 (0.00,1.00)	0.44 (0.17,0.64)	0.29 (0.02,0.46)	0.70 (0.12,0.98)

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

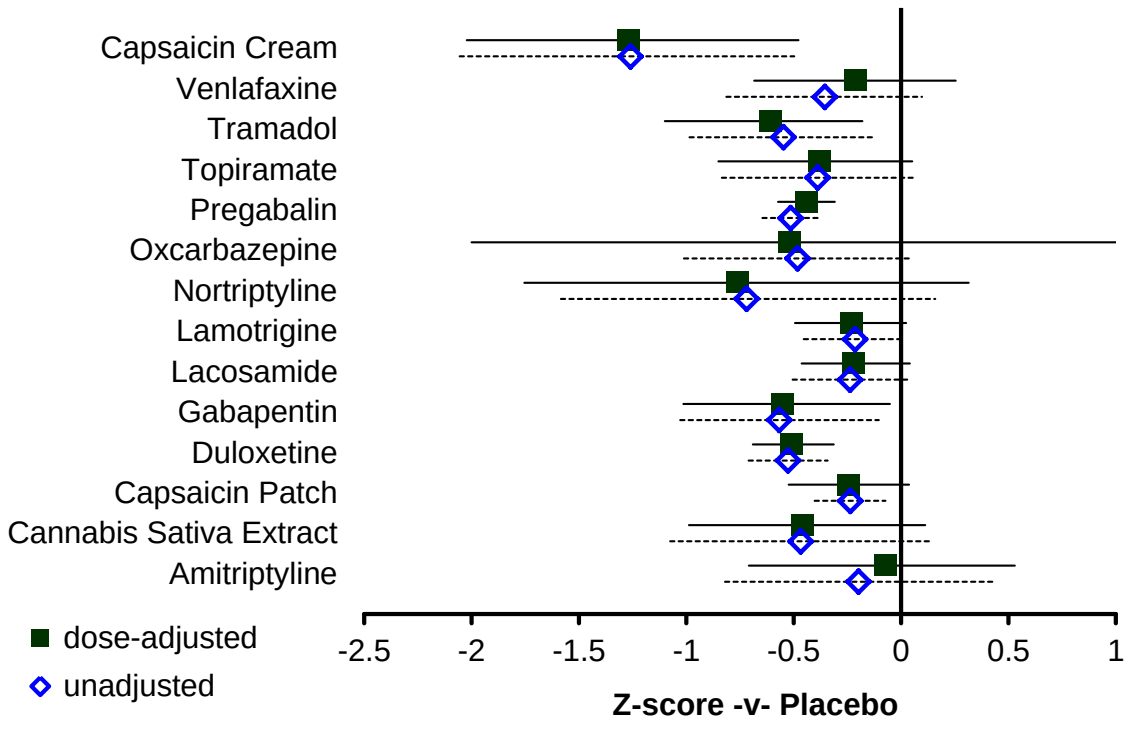
[b] GDG feel unable to comment based on own experience; weighted mean of dosages in trials contributing to evidence-base used instead

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 26 30% and 50% pain relief (peripheral only) – raw outputs of synthesis models

	Unadjusted	Dose−adjusted	
	Z−score −v− placebo	Z−score −v− placebo	Coefficient for dose[a]
amitriptyline	−0.204 (−0.827, 0.429)	−0.066 (−0.681, 0.535)	0.009 (−3.865, 3.947)
cannabis sativa extract	−0.470 (−1.080, 0.119)	−0.457 (−1.054, 0.131)	−0.027 (−3.919, 3.983)
capsaicin cream	−1.270 (−2.047, −0.536)	−1.283 (−2.081, −0.514)	0.001 (−3.961, 3.999)
capsaicin patch	−0.237 (−0.402, −0.075)	−0.239 (−0.396, −0.079)	0.018 (−3.911, 3.963)
duloxetine	−0.524 (−0.713, −0.340)	−0.524 (−0.699, −0.348)	−0.599 (−3.014, 1.845)
gabapentin	−0.567 (−1.035, −0.101)	−0.573 (−1.040, −0.094)	−0.042 (−0.830, 0.728)
lacosamide	−0.237 (−0.508, 0.032)	−0.234 (−0.488, 0.021)	−0.259 (−1.140, 0.639)
lamotrigine	−0.217 (−0.462, 0.017)	−0.207 (−0.437, 0.012)	−0.242 (−1.732, 1.247)
nortriptyline	−0.720 (−1.597, 0.154)	−0.755 (−1.721, 0.219)	0.014 (−3.836, 3.937)
oxcarbazepine	−0.483 (−1.021, 0.056)	−0.478 (−0.990, 0.023)	−0.021 (−3.888, 3.884)
pregabalin	−0.516 (−0.644, −0.390)	−0.495 (−0.620, −0.369)	−0.606 (−1.081, −0.141)
topiramate	−0.389 (−0.839, 0.058)	−0.391 (−0.801, 0.035)	0.037 (−3.966, 3.923)
tramadol	−0.551 (−0.988, −0.129)	−0.552 (−0.963, −0.142)	−0.768 (−4.153, 2.612)
venlafaxine	−0.353 (−0.816, 0.108)	−0.351 (−0.786, 0.075)	−1.816 (−4.303, 0.679)

[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 25 for details)

Figure 16 30% and 50% pain relief (peripheral only) – relative effect of all options compared with placebo

Table 27 30% and 50% pain relief (peripheral only) – rankings for each comparator

	No dose adjustment		Dose-adjusted	
	Probability best	**Median rank (95%CrI)**	**Probability best**	**Median rank (95%CrI)**
Placebo	0.000	15 (13, 15)	0.000	14 (13, 15)
Amitriptyline	0.004	12 (2, 15)	0.002	14 (3, 15)
Cannabis Extract	0.025	7 (1, 15)	0.023	7 (2, 15)
Capsaicin Cream	0.752	1 (1, 6)	0.740	1 (1, 6)
Capsaicin Patch	0.000	11 (7, 14)	0.000	11 (7, 14)
Duloxetine	0.002	6 (2, 10)	0.002	6 (2, 9)
Gabapentin	0.012	5 (2, 13)	0.010	5 (2, 13)
Lacosamide	0.000	11 (6, 15)	0.000	11 (6, 14)
Lamotrigine	0.000	12 (7, 14)	0.000	12 (7, 14)
Nortriptyline	0.156	3 (1, 15)	0.181	3 (1, 15)
Oxcarbazepine	0.019	7 (2, 15)	0.017	6 (2, 14)
Pregabalin	0.001	6 (3, 9)	0.000	6 (3, 9)
Topiramate	0.004	8 (2, 15)	0.004	8 (2, 14)
Tramadol	0.020	5 (2, 13)	0.017	5 (2, 13)
Venlafaxine	0.004	9 (2, 15)	0.004	9 (2, 15)

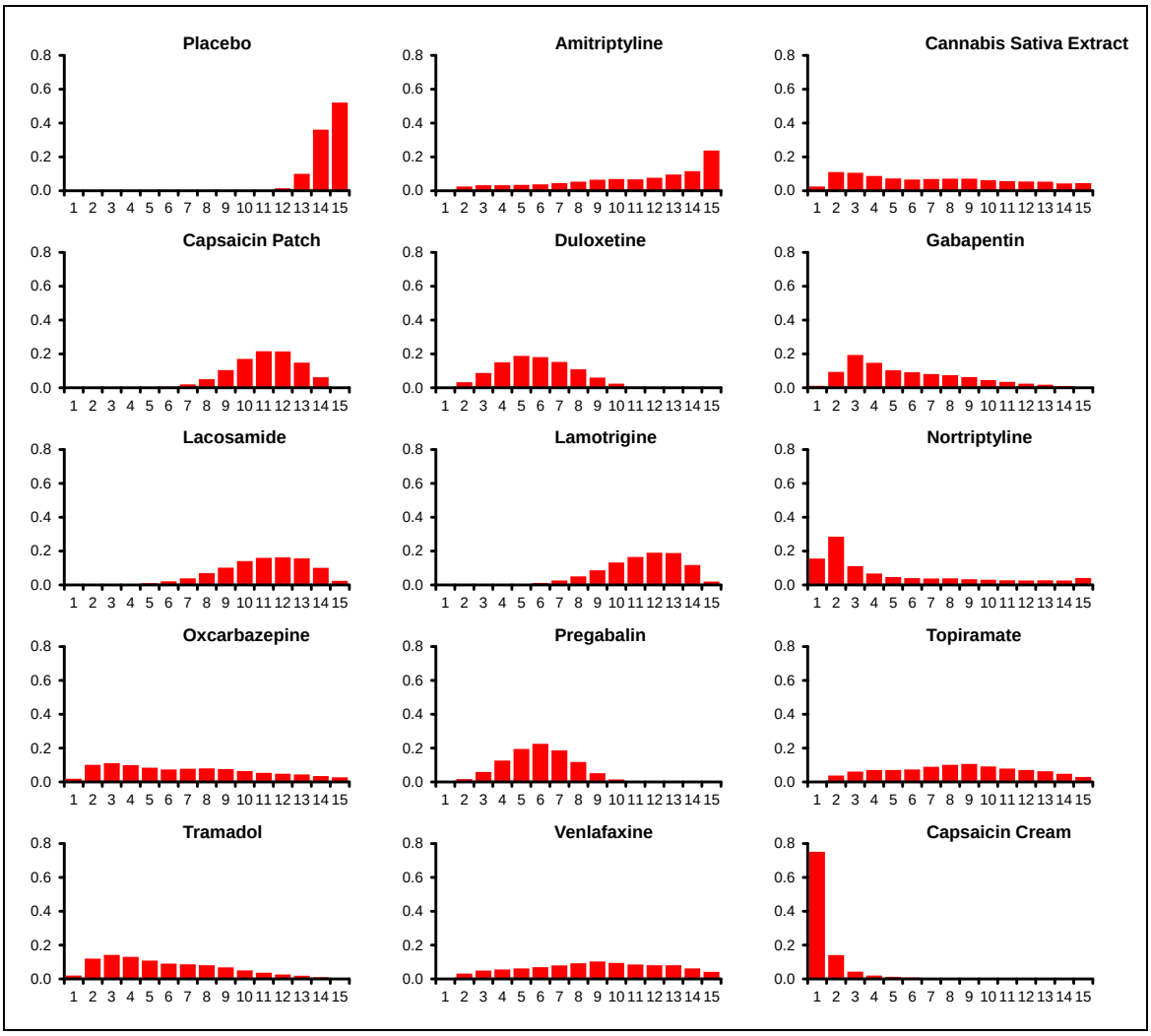


Figure 17 30% and 50% pain relief (peripheral only) – rank probability histograms; no adjustment for dose

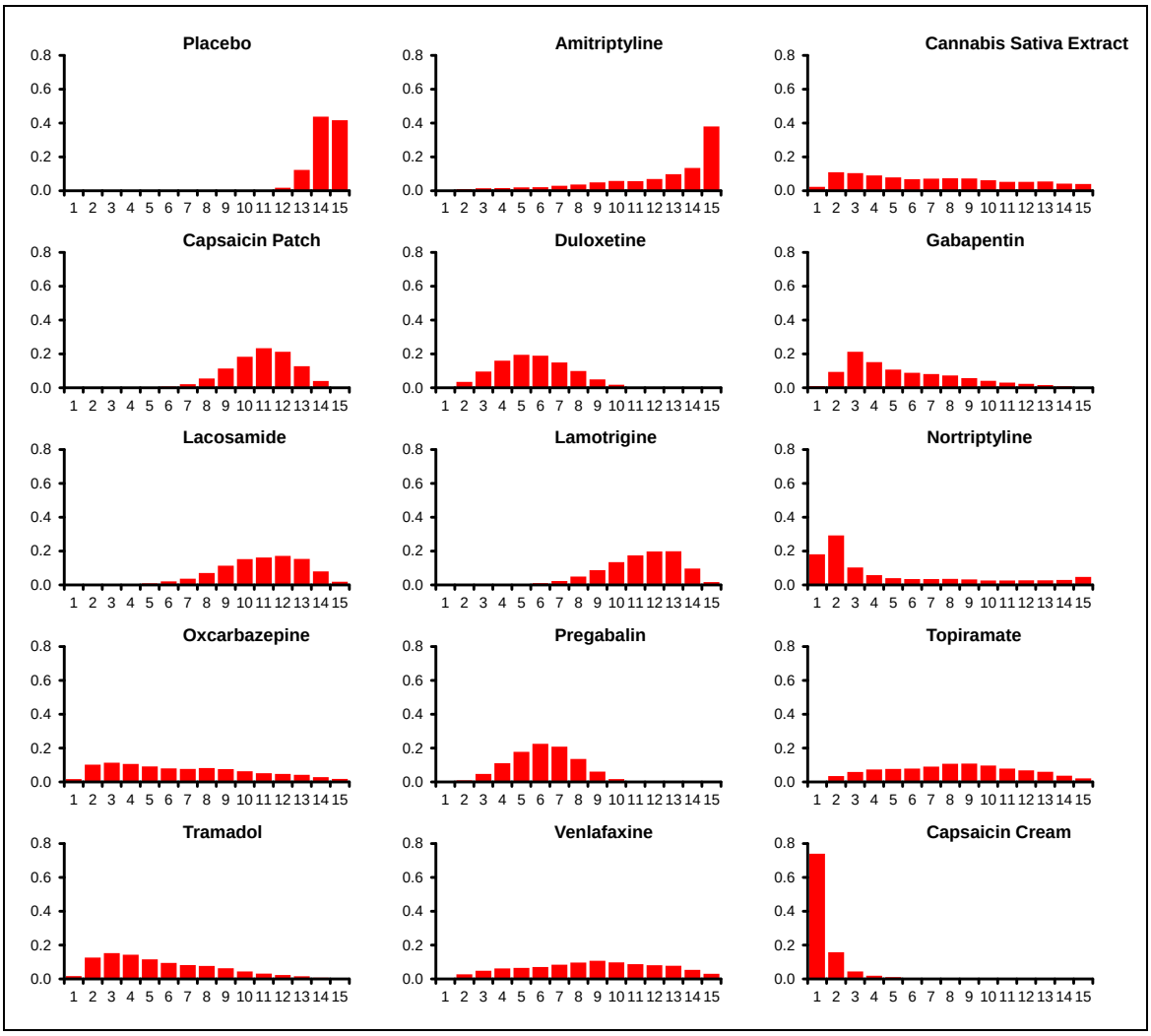


Figure 18 30% and 50% pain relief (peripheral only) – rank probability histograms; dose-adjusted

Table 28 30% and 50% pain relief (peripheral only) – model fit statistics

	Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
Unadjusted	211.7 (compared to 174 datapoints)	992.7	907.8	84.88	1077.5	0.025 (95%CrI: 0.010, 0.060)
Dose-adjusted	211.5 (compared to 174 datapoints)	992.4	907.4	85.09	1077.5	0.017 (95%CrI: 0.006, 0.053)

2.2 Safety

It was assumed that the incidence of adverse effects would not vary according to the type of neuropathic pain; therefore, no separate syntheses were performed using the peripheral-only dataset, and safety data derived from the whole evidence-base (see section 1.2, above) were used for the peripheral-only model.