Appendix J GRADE profiles and results for individual adverse effects for ‘all neuropathic pain’

T Gait disturbance (pg131)

Summary GRADE profile 3a: dizziness or vertigo

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Dizziness or vertigo	67 RCTs[a] n=12190	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] allocation concealment was inadequate in 1 study and unclear in 37 studies; there is uncertainty about comparability at baseline between groups in 42 studies and there are differences between groups in 7 studies (particularly for use of concomitant drugs); during 34 studies, it was unclear if the same care was received by each group and in 5 studies the same care was not received (these were usually to do with concomitant drug and rescue medication use); average baseline severity ranged from 3.9 to 8.8 on a 11-point scale across the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 41%, 37%, 37%, and 8% for amitriptyline vs placebo, cannabis sativa vs placebo, pregabalin vs placebo, and capsaicin patch vs placebo, respectively. This may indicate that moderate heterogeneity in the first 3 comparisons but any heterogeneity might not be important in any of these comparisons; indirect and direct estimates appear relatively similar

[3] all aspects of PICO conform to review protocol

[4] few head-to-head trials; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=341): Cardenas et al. (2002), Kalso et al. (1995), Max et al. (1988), Robinson et al. (2004), Vrethem et al. (1997)

Cannabis Sativa Extract (n=191): Nurmikko et al. (2007), Rog et al. (2005)

Capsaicin Patch (n=1579): Backonja et al. (2008), Irving et al. (2011), Simpson et al. (2008), Webster et al. (2010), Webster et al. (2010)

Duloxetine (n=1392): Gao et al. (2010), Goldstein et al. (2005), Vranken et al. (2011), Wernicke et al. (2006), Yasuda et al. (2011)

Escitalopram (n=96): Otto et al. (2008)

Gabapentin (n=1362): Backonja et al. (1998), Bone et al. (2002), Gordh et al. (2008), Hahn et al. (2004), Levendoglu et al. (2004), Rao et al. (2007), Rice & Maton (2001), Rowbotham et al. (1998), Simpson (2001)

Imipramine (n=80): Sindrup et al. (2003)

Lacosamide (n=119): Rauck et al. (2007),

Lamotrigine (n=898): Eisenberg et al. (2001), Rao et al. (2008), Vinik et al. (2007), Vinik et al. (2007)

Levetiracetam (n=170): Finnerup et al. (2009), Holbech et al. (2011), Rossi et al. (2009)

Morphine (n=222): Khoromi et al. (2007), Wu et al. (2008)

Nortriptyline, Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxcarbazepine (n=634): Beydoun et al. (2006), Dogra et al. (2005), Grosskopf et al. (2006)

Oxycodone (n=159): Gimbel et al. (2003)

Pregabalin (n=3333): Arezzo et al. (2008), Dworkin et al. (2003), Freynhagen et al. (2005), Guan et al. (2011), Kim et al. (2011), Lesser et al. (2004), Richter et al. (2005), Rosenstock et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Siddall et al. (2006), Simpson et al. (2010), van Seventer et al. (2006), Vranken et al. (2008)

Topiramate (n=323): Raskin et al. (2004)

Tramadol (n=256): Harati et al. (1998), Norrbrink & Lundeberg (2009), Sindrup et al. (1999)

Trazodone (n=18): Davidoff et al. (1987)

Venlafaxine (n=80): Sindrup et al. (2003)

Capsaicin Cream (n=143): Watson et al. (1993)

Head-to-head trials:

Amitriptyline vs Gabapentin (n=50): Morello et al. (1999)

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

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

Gabapentin vs Gabapentin+Nortriptyline Gabapentin vs Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012),

Gabapentin vs Gabapentin+Oxycodone (n=338): Hanna et al. (2008)

Imipramine vs Venlafaxine (n=80): Sindrup et al. (2003) Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine, Nortriptyline vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)
Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial.

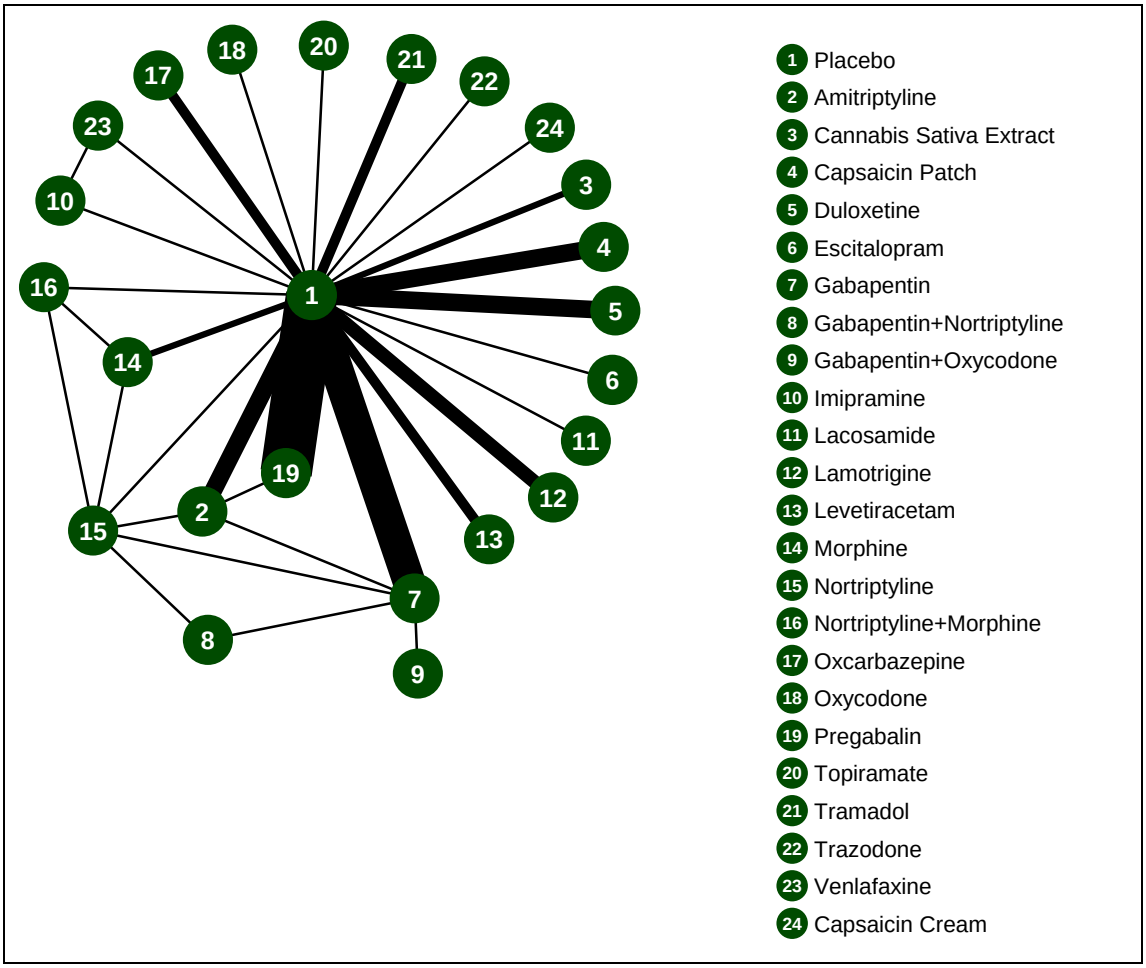

Figure 1 dizziness or vertigo - evidence network

Table 1 dizziness or vertigo - 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	5 RCTs[7,26,31,42,60] total n=341																						
Cannabis Sativa Extract	2 RCTs[34,43] total n=191	-																					
Capsaicin Patch	5 RCTs[3,25,51,63,64] total n=1579	-	-																				
Duloxetine	5 RCTs[14,17,59,65,67] total n=1392	-	-	-																			
Escitalopram	1 RCT[35] total n=96	-	-	-	-																		
Gabapentin	9 RCTs[2,6,18,21,30,36,40,46,50] total n=1362	1 RCT[32] total n=50	-	-	-	-																	
Gabapentin +Nortriptyline	-	-	-	-	-	-	1 RCT[15] total n=112																
Gabapentin +Oxycodone	-	-	-	-	-	-	1 RCT[22] total n=338	-															
Imipramine	1 RCT[54] total n=80	-	-	-	-	-	-	-	-														
Lacosamide	1 RCT[39] total n=119	-	-	-	-	-	-	-	-	-													
Lamotrigine	4 RCTs[11,37,56,57]	-	-	-	-	-	-	-	-	-	-												

	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
	total n=898																						
Levetiracetam	3 RCTs[12,24,45] total n=170	-	-	-	-	-	-	-	-	-	-	-											
Morphine	2 RCTs[27,66] total n=222	-	-	-	-	-	-	-	-	-	-	-	-										
Nortriptyline	1 RCT[27] total n=110	1 RCT[62] total n=66	-	-	-	-	1 RCT[15] total n=112	1 RCT[15] total n=112	-	-	-	-	-	1 RCT[27] total n=110									
Nortriptyline +Morphine	1 RCT[27] total n=110	-	-	-	-	-	-	-	-	-	-	-	-	1 RCT[27] total n=110	1 RCT[27] total n=110								
Oxcarbazepine	3 RCTs[5,9,19] total n=634	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[16] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Pregabalin	14 RCTs[1,10,13,20,28,29,41,44,47,48,49,52,55,58] total n=3333	1 RCT[4] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Topiramate	1 RCT[38] total n=323	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Tramadol	3 RCTs[23,33,53] total n=256	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Trazodone	1 RCT[8] total n=18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	1 RCT[54] total n=80	-	-	-	-	-	-	-	-	1 RCT[54]	-	-	-	-	-	-	-	-	-	-	-	-	

	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
										total n=80													
Capsaicin Cream	1 RCT[61] 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) Cardenas et al. (2002); (8) Davidoff et al. (1987); (9) Dogra et al. (2005); (10) Dworkin et al. (2003); (11) Eisenberg et al. (2001); (12) Finnerup et al. (2009); (13) Freynhagen et al. (2005); (14) Gao et al. (2010); (15) Gilron et al. (2012); (16) Gimbel et al. (2003); (17) Goldstein et al. (2005); (18) Gordh et al. (2008); (19) Grosskopf et al. (2006); (20) Guan et al. (2011); (21) Hahn et al. (2004); (22) Hanna et al. (2008); (23) Harati et al. (1998); (24) Holbech et al. (2011); (25) Irving et al. (2011); (26) Kalso et al. (1995); (27) Khoromi et al. (2007); (28) Kim et al. (2011); (29) Lesser et al. (2004); (30) Levendoglu et al. (2004); (31) Max et al. (1988); (32) Morello et al. (1999); (33) Norrbrink & Lundeberg (2009); (34) Nurmikko et al. (2007); (35) Otto et al. (2008); (36) Rao et al. (2007); (37) Rao et al. (2008); (38) Raskin et al. (2004); (39) Rauck et al. (2007); (40) Rice & Maton (2001); (41) Richter et al. (2005); (42) Robinson et al. (2004); (43) Rog et al. (2005); (44) Rosenstock et al. (2004); (45) Rossi et al. (2009); (46) Rowbotham et al. (1998); (47) Sabatowski et al. (2004); (48) Satoh et al. (2011); (49) Siddall et al. (2006); (50) Simpson (2001); (51) Simpson et al. (2008); (52) Simpson et al. (2010); (53) Sindrup et al. (1999); (54) Sindrup et al. (2003); (55) van Seventer et al. (2006); (56) Vinik et al. (2007); (57) Vinik et al. (2007); (58) Vranken et al. (2008); (59) Vranken et al. (2011); (60) Vrethem et al. (1997); (61) Watson et al. (1993); (62) Watson et al. (1998); (63) Webster et al. (2010); (64) Webster et al. (2010); (65) Wernicke et al. (2006); (66) Wu et al. (2008); (67) Yasuda et al. (2011)

Table 2 dizziness or vertigo - relative effectiveness of all pairwise combinations

	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	1.17 (0.55, 2.51)		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	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cannabis Sativa Extract	3.14 (1.06, 9.37)	2.68 (0.69, 10.09)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	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	0.84 (0.35, 2.05)	0.72 (0.22, 2.33)	0.27 (0.07, 1.09)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	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 (1.12, 4.49)	1.89 (0.67, 5.37)	0.70 (0.19, 2.63)	2.64 (0.86, 8.06)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	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, 2.67)	0.29 (0.02, 2.60)	0.11 (0.01, 1.16)	0.40 (0.03, 3.78)	0.15 (0.01, 1.36)		N/A	N/A	N/A	N/A	N/A	N/A	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	3.85 (2.22, 6.72)	3.30 (1.38, 7.91)	1.23 (0.36, 4.25)	4.61 (1.62, 12.93)	1.74 (0.72, 4.18)	11.36 (1.34, 126.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin +Nortriptyline	3.06 (0.47, 19.62)	2.62 (0.37, 18.03)	0.97 (0.11, 8.72)	3.64 (0.46, 29.02)	1.38 (0.19, 10.10)	9.15 (0.56, 177.60)	0.80 (0.13, 4.90)		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	N/A	N/A	N/A
Gabapentin +Oxycod	17.96 (3.53,	15.50 (2.65,	5.80 (0.79, 42.89	21.71 (3.35, 140.2	8.13 (1.40, 49.62	53.73 (3.77, 949.8	4.67 (1.02, 22.89	5.97 (0.56, 63.19		N/A	N/A	N/A	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
one	95.77)	92.04)	)	0)	)	0)	)	)																
Imipramine	4.10 (0.28, 145.50)	3.53 (0.21, 133.90)	1.32 (0.07, 56.49)	4.89 (0.30, 187.50)	1.84 (0.12, 69.09)	12.65 (0.41, 804.80)	1.06 (0.07, 39.08)	1.40 (0.05, 72.83)	0.23 (0.01, 11.30)		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
Lacosamide	1.87 (0.35, 10.58)	1.60 (0.26, 10.73)	0.60 (0.08, 4.64)	2.24 (0.33, 15.26)	0.85 (0.14, 5.54)	5.51 (0.39, 111.00)	0.48 (0.08, 3.06)	0.62 (0.05, 7.76)	0.10 (0.01, 1.11)	0.45 (0.01, 11.38)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lamotrigine	1.50 (0.63, 3.73)	1.29 (0.40, 4.18)	0.48 (0.12, 1.99)	1.79 (0.51, 6.34)	0.68 (0.22, 2.09)	4.46 (0.47, 56.65)	0.39 (0.14, 1.12)	0.49 (0.06, 3.94)	0.08 (0.01, 0.53)	0.36 (0.01, 6.50)	0.80 (0.11, 5.26)		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	4.12 (1.03, 20.63)	3.53 (0.73, 20.32)	1.33 (0.22, 8.87)	4.91 (0.94, 30.11)	1.87 (0.39, 10.55)	12.36 (0.98, 221.60)	1.07 (0.24, 5.75)	1.37 (0.14, 15.36)	0.23 (0.03, 2.21)	1.01 (0.02, 24.53)	2.21 (0.24, 22.12)	2.77 (0.51, 17.05)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	1.93 (0.41, 9.71)	1.66 (0.30, 9.43)	0.62 (0.09, 4.33)	2.31 (0.39, 14.69)	0.88 (0.16, 4.95)	5.72 (0.44, 99.54)	0.50 (0.10, 2.68)	0.64 (0.06, 6.62)	0.11 (0.01, 1.00)	0.46 (0.01, 10.93)	1.03 (0.10, 10.53)	1.29 (0.22, 8.13)	0.47 (0.05, 3.77)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	0.95 (0.22, 3.80)	0.82 (0.17, 3.41)	0.30 (0.05, 1.81)	1.14 (0.21, 5.84)	0.43 (0.08, 1.99)	2.82 (0.23, 44.29)	0.25 (0.06, 0.99)	0.31 (0.04, 2.26)	0.05 (0.01, 0.40)	0.22 (0.01, 4.96)	0.51 (0.05, 4.44)	0.63 (0.12, 3.21)	0.23 (0.03, 1.60)	0.49 (0.08, 2.88)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	0.43 (0.01, 4.88)	0.37 (0.01, 4.53)	0.13 (0.00, 2.03)	0.50 (0.01, 6.77)	0.19 (0.00, 2.50)	1.21 (0.02, 37.50)	0.11 (0.00, 1.33)	0.14 (0.00, 2.79)	0.02 (0.00, 0.43)	0.09 (0.00, 3.96)	0.22 (0.00, 4.50)	0.28 (0.01, 3.73)	0.10 (0.00, 1.74)	0.22 (0.01, 2.39)	0.45 (0.01, 5.74)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	8.33 (2.57,	7.15 (1.75,	2.69 (0.53,	10.05 (2.25,	3.80 (0.95,	25.25 (2.33,	2.17 (0.59,	2.80 (0.30,	0.47 (0.06,	2.04 (0.05,	4.51 (0.55,	5.60 (1.27,	2.03 (0.29,	4.35 (0.60,	8.92 (1.40,	20.32 (1.30,		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
	34.49)	36.34)	15.61)	52.82)	18.07)	394.60)	9.90)	27.12)	4.06)	40.97)	39.87)	28.88)	14.88)	35.26)	67.16)	927.20)								
Oxycodone	3.63 (0.85, 16.75)	3.12 (0.59, 17.29)	1.17 (0.18, 7.52)	4.33 (0.78, 25.62)	1.65 (0.32, 8.68)	10.87 (0.82, 183.60)	0.94 (0.20, 4.83)	1.19 (0.11, 13.26)	0.20 (0.02, 1.81)	0.88 (0.02, 19.12)	1.93 (0.20, 18.81)	2.43 (0.42, 14.38)	0.87 (0.10, 7.07)	1.87 (0.21, 16.50)	3.82 (0.51, 31.30)	8.83 (0.49, 408.60)	0.43 (0.06, 3.06)		N/A	N/A	N/A	N/A	N/A	N/A
Pregabalin	3.27 (2.23, 4.78)	2.80 (1.21, 6.53)	1.05 (0.32, 3.35)	3.89 (1.49, 10.23)	1.49 (0.66, 3.20)	9.63 (1.19, 105.70)	0.85 (0.44, 1.65)	1.07 (0.16, 7.24)	0.18 (0.03, 0.97)	0.80 (0.02, 11.94)	1.75 (0.29, 9.73)	2.19 (0.82, 5.67)	0.80 (0.15, 3.37)	1.69 (0.32, 8.28)	3.42 (0.84, 15.56)	7.65 (0.66, 291.00)	0.39 (0.09, 1.34)	0.90 (0.19, 4.09)		N/A	N/A	N/A	N/A	N/A
Topiramate	1.34 (0.28, 6.68)	1.15 (0.20, 6.95)	0.43 (0.06, 2.99)	1.60 (0.27, 10.07)	0.61 (0.11, 3.44)	3.98 (0.31, 69.89)	0.35 (0.07, 1.89)	0.44 (0.04, 5.26)	0.07 (0.01, 0.73)	0.32 (0.01, 7.21)	0.72 (0.07, 7.11)	0.89 (0.15, 5.58)	0.32 (0.04, 2.82)	0.69 (0.08, 6.39)	1.43 (0.17, 12.41)	3.23 (0.17, 154.90)	0.16 (0.02, 1.22)	0.37 (0.04, 3.19)	0.41 (0.08, 2.14)		N/A	N/A	N/A	N/A
Tramadol	5.64 (1.75, 20.27)	4.84 (1.19, 21.04)	1.80 (0.36, 9.93)	6.78 (1.55, 31.94)	2.55 (0.65, 10.98)	16.89 (1.51, 246.00)	1.48 (0.40, 5.82)	1.86 (0.20, 17.76)	0.31 (0.04, 2.43)	1.38 (0.03, 26.78)	3.02 (0.37, 24.33)	3.77 (0.85, 17.96)	1.37 (0.19, 9.00)	2.95 (0.40, 21.43)	6.04 (0.98, 39.72)	13.54 (0.86, 597.40)	0.67 (0.11, 3.87)	1.56 (0.23, 10.91)	1.72 (0.50, 6.61)	4.22 (0.57, 31.79)		N/A	N/A	N/A
Trazodone	12.90 (0.46, 18390.00)	11.27 (0.36, 15740.00)	4.24 (0.12, 6440.00)	15.39 (0.50, 23350.00)	5.92 (0.19, 8867.00)	42.42 (0.71, 85840.00)	3.38 (0.11, 4869.00)	4.51 (0.09, 7931.00)	0.74 (0.02, 1268.00)	3.32 (0.02, 5617.00)	7.08 (0.16, 11870.00)	8.84 (0.26, 13530.00)	3.11 (0.07, 5803.00)	7.02 (0.16, 10290.00)	14.43 (0.35, 22970.00)	37.94 (0.45, 93890.00)	1.57 (0.04, 2603.00)	3.62 (0.09, 6109.00)	3.94 (0.14, 5729.00)	9.90 (0.23, 17130.00)	2.34 (0.06, 3522.00)		N/A	N/A
Venlafaxine	2.46 (0.14, 101.40)	2.13 (0.11, 90.86)	0.80 (0.03, 38.77)	2.97 (0.14, 128.90)	1.12 (0.06, 48.45)	7.83 (0.20, 528.50)	0.64 (0.03, 27.60)	0.83 (0.03, 48.95)	0.14 (0.00, 7.14)	0.62 (0.05, 6.13)	1.34 (0.05, 74.46)	1.66 (0.08, 73.31)	0.59 (0.02, 32.39)	1.31 (0.05, 65.34)	2.71 (0.11, 131.30)	6.40 (0.13, 824.90)	0.29 (0.01, 13.31)	0.68 (0.03, 34.38)	0.75 (0.04, 31.39)	1.88 (0.07, 99.00)	0.44 (0.02, 21.12)	0.17 (0.00, 27.23)		N/A
Capsaicin Cream	5.05 (0.14, 3388.	4.31 (0.11, 3217.	1.65 (0.04, 1171.	6.14 (0.15, 4430.	2.29 (0.06, 1541.	16.52 (0.23, 16320	1.32 (0.03, 887.6	1.72 (0.03, 1560.	0.30 (0.01, 240.1	1.25 (0.01, 1533.	2.86 (0.05, 2256.	3.40 (0.08, 2516.	1.26 (0.02, 920.5	2.75 (0.05, 2251.	5.64 (0.11, 4446.	14.61 (0.14, 22380	0.60 (0.01, 500.3	1.44 (0.03, 1237.	1.55 (0.04, 1016.	3.89 (0.07, 3024.	0.91 (0.02, 650.5	0.38 (0.00,	2.09 (0.01, 2495.	

	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
	00)	00)	00)	00)	00)	.00)	0)	00)	0)	00)	00)	00)	0)	00)	00)	.00)	0)	00)	00)	00)	0)	725. 80)	00)	

Values given are hazard ratios.

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

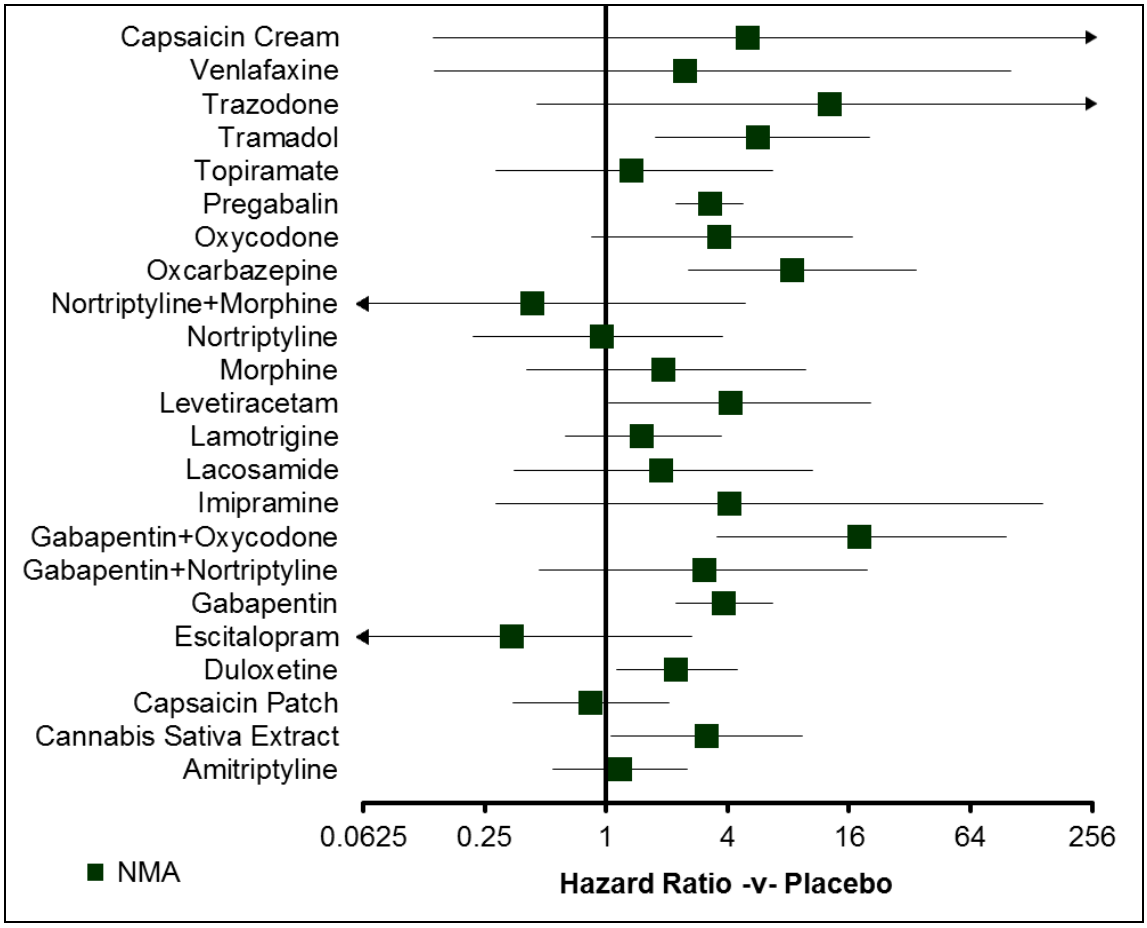

Figure 2 dizziness or vertigo - relative effect of all options compared with placebo

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

Table 3 dizziness or vertigo - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.001	6 (3, 9)
Amitriptyline	0.005	7 (2, 13)
Cannabis Sativa Extract	0.000	15 (6, 22)
Capsaicin Patch	0.031	5 (1, 12)
Duloxetine	0.000	12 (6, 18)
Escitalopram	0.396	2 (1, 13)
Gabapentin	0.000	17 (11, 21)
Gabapentin+Nortriptyline	0.007	15 (3, 23)
Gabapentin+Oxycodone	0.000	23 (16, 24)
Imipramine	0.015	17 (2, 24)
Lacosamide	0.016	11 (2, 22)
Lamotrigine	0.003	9 (3, 17)
Levetiracetam	0.000	17 (6, 23)
Morphine	0.006	11 (2, 21)
Nortriptyline	0.038	6 (1, 16)
Nortriptyline+Morphine	0.353	2 (1, 18)
Oxcarbazepine	0.000	21 (13, 24)
Oxycodone	0.001	16 (5, 23)
Pregabalin	0.000	15 (11, 19)
Topiramate	0.027	8 (1, 20)
Tramadol	0.000	19 (10, 23)
Trazodone	0.009	22 (3, 24)
Venlafaxine	0.049	13 (1, 24)
Capsaicin Cream	0.044	18 (1, 24)

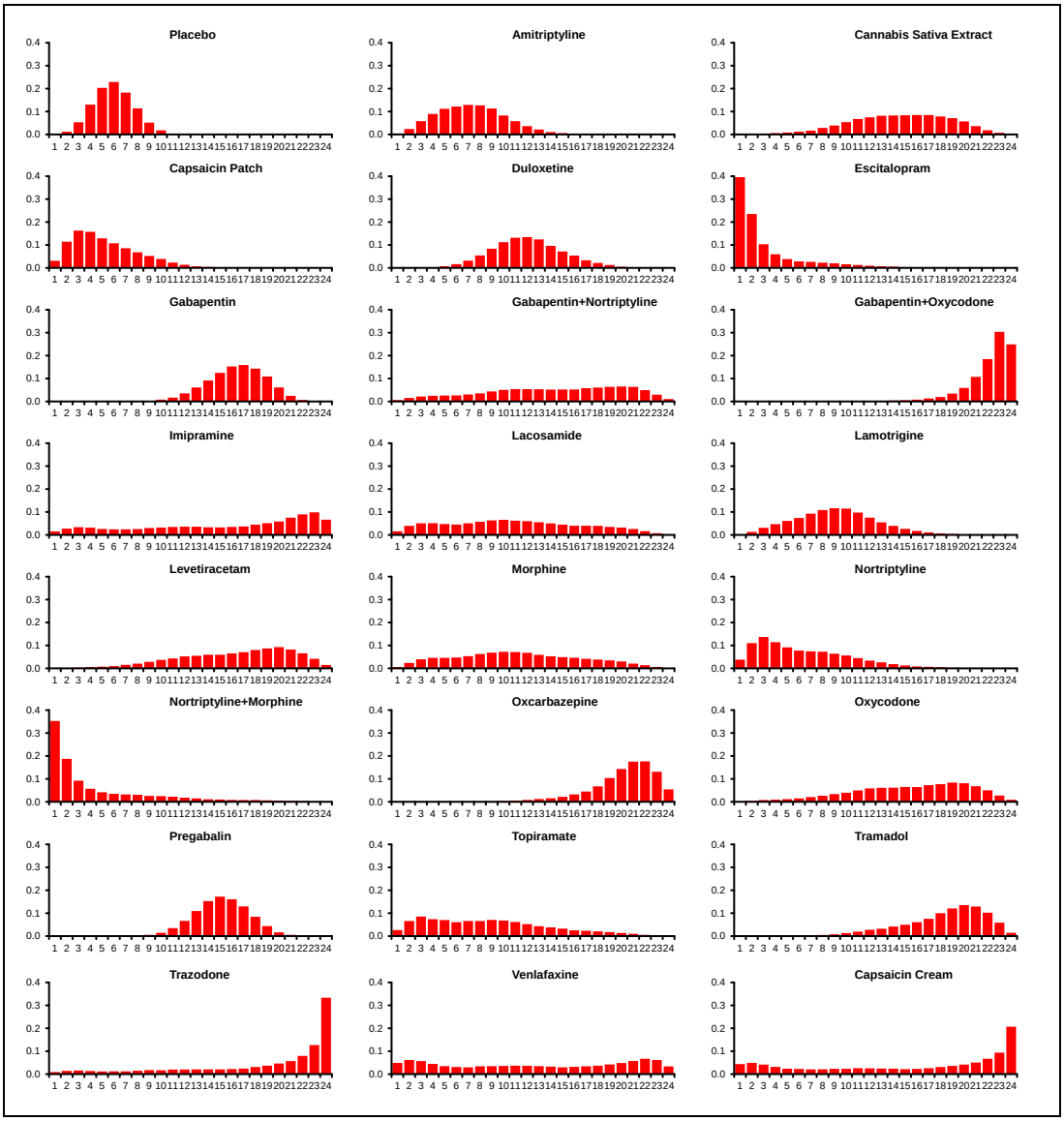

Figure 3 dizziness or vertigo - rank probability histograms

Table 4 dizziness or vertigo - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
153.7 (compared to 157 data-points)	689.426	566.942	122.484	811.909	0.371 (95%CI: 0.211, 0.705)

Table 5 dizziness or vertigo - notes

- Log–log ('cloglog') model used as the results from this analysis were used in the health economic model (this is explained in Appendix K)
- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 50000 burn-ins and 10000 iterations.
- For the seven studies which reported both dizziness and vertigo separately,

the results for dizziness were used (not vertigo) in the synthesis to avoid possible double counting (reasoning explained in the method section). These studies were Breuer (2007), Falah (2012), Shaibani (2009), Stacey (2008), Tolle (2008), Wymer (2009), Zeigler (2010)

- It was not possible to include the results from Huse (2001) in the synthesis because the study recorded the intensity of adverse events on a visual analogue scale (from 'not at all' to extremely) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.

Summary GRADE profile 3b: somnolence (including drowsiness and sedation)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Somnolence (including drowsiness and sedation)	66 RCTs[a] n=12112	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] allocation concealment was inadequate in 2 study and unclear in 33 studies; there is uncertainty about comparability at baseline between groups in 42 studies and there are differences between groups in 4 studies (particularly for use of concomitant drugs); during 32 studies, it was unclear if the same care was received by each group and in 5 studies the same care was not received (these were usually to do with concomitant drug and rescue medication use); average baseline severity ranged from 4.15 to 8.8 on a 11-point scale across the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 63%, 50%, 49%, 42%, and 31% for venlafaxine vs placebo, lacosamide vs placebo, tramadol vs placebo, topiramate vs placebo, and oxcarbazepine vs placebo, respectively. This may indicate that any heterogeneity in the first 2 comparisons may be moderate to substantial, in the third and fourth comparisons may be moderate, and in the fifth comparison might not be important; indirect and direct estimates appear relatively similar

[3] all aspects of PICO conform to review protocol

[4] few head-to-head trials; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=243): Graff-Radford et al. (2000), Kalso et al. (1995), Max et al. (1988), Vrethem et al. (1997)

Cannabis Sativa Extract (n=191): Nurmikko et al. (2007), Rog et al. (2005)

Duloxetine (n=1392): Gao et al. (2010), Goldstein et al. (2005), Vranken et al. (2011), Wernicke et al. (2006), Yasuda et al. (2011)

Escitalopram (n=96): Otto et al. (2008)

Gabapentin (n=892): Backonja et al. (1998), Bone et al. (2002), Hahn et al. (2004), Levendoglu et al. (2004), Rice & Maton (2001), Rowbotham et al. (1998), Simpson (2001)

Imipramine (n=80): Sindrup et al. (2003)

Lacosamide (n=587): Rauck et al. (2007), Shaibani et al. (2009)

Lamotrigine (n=129): Breuer et al. (2007), Eisenberg et al. (2001), Luria et al. (2000)

Levetiracetam (n=230): Falah et al. (2012), Finnerup et al. (2009), Holbech et al. (2011), Rossi et al. (2009)

Morphine (n=222): Khoromi et al. (2007), Wu et al. (2008)

Nortriptyline, Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxcarbazepine (n=493): Beydoun et al. (2006), Dogra et al. (2005)

Oxycodone (n=159): Gimbel et al. (2003)

Pregabalin (n=3997): Arezzo et al. (2008), Dworkin et al. (2003), Freynhagen et al. (2005), Guan et al. (2011), Kim et al. (2011), Lesser et al. (2004), Richter et al. (2005), Rosenstock et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Siddall et al. (2006), Simpson et al. (2010), Stacey et al. (2008), Tolle et al. (2008), van Seventer et al. (2006), Vranken et al. (2008)

Valproate (n=84): Agrawal et al. (2009), Kochar et al. (2004)

Topiramate (n=1674): Khoromi et al. (2005), Raskin et al. (2004), Thienel et al. (2004)

Tramadol (n=221): Harati et al. (1998), Sindrup et al. (1999)

Trazodone (n=18): Davidoff et al. (1987)

Venlafaxine (n=355): Rowbotham et al. (2004), Sindrup et al. (2003), Tasmuth et al. (2002)

Head-to-head trials:

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

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

Amitriptyline vs Capsaicin Cream (n=235): Biesbroeck et al. (1995)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Gabapentin vs Gabapentin+Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012) Gabapentin vs Gabapentin+Oxycodone (n=338): Hanna et al. (2008) Gabapentin vs Nortriptyline (n=182): Chandra et al. (2006), Gilron et al. (2012) Imipramine vs Venlafaxine (n=80): Sindrup et al. (2003) Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine, Nortriptyline vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)							
Abbreviations: PICO, patient intervention comparator outcome; RCT, randomised controlled trial.							

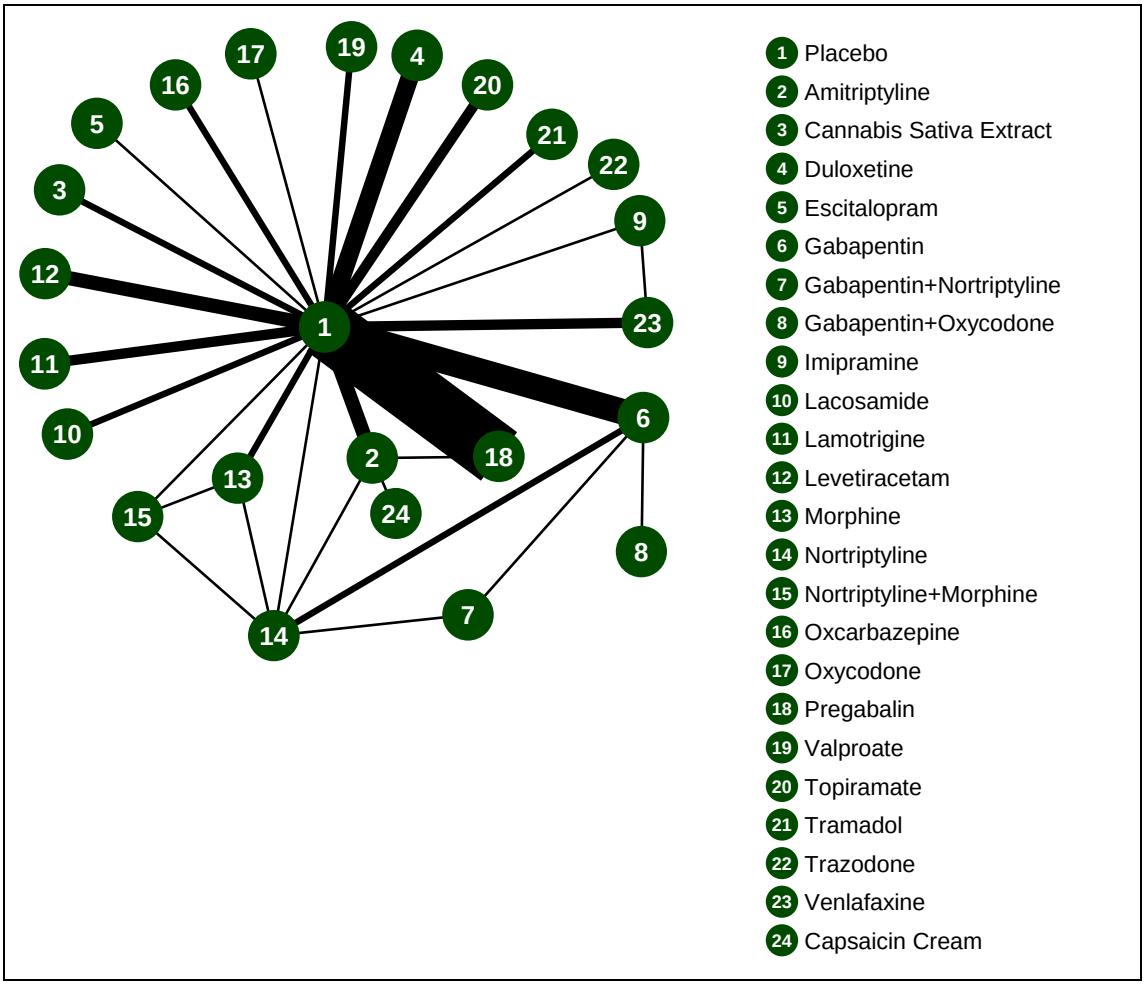

Figure 4 somnolence - evidence network

Table 6 somnolence - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine
Amitriptyline	4 RCTs[21,27,35,62] total n=243																						
Cannabis Sativa Extract	2 RCTs[36,42] total n=191	-																					
Duloxetine	5 RCTs[17,20,61,64,66] total n=1392	-	-																				
Escitalopram	1 RCT[37] total n=96	-	-	-																			
Gabapentin	7 RCTs[3,7,23,33,40,45,51] total n=892	-	-	-	-																		
Gabapentin +Nortriptyline	-	-	-	-	-	1 RCT[18] total n=112																	
Gabapentin +Oxycodone	-	-	-	-	-	1 RCT[24] total n=338	-																
Imipramine	1 RCT[54] total n=80	-	-	-	-	-	-	-															
Lacosamide	2 RCTs[39,49] total n=587	-	-	-	-	-	-	-	-														
Lamotrigine	3 RCTs[8,13,34] total n=129	-	-	-	-	-	-	-	-	-													
Levetiracetam	4 RCTs[14,15,26,44] total n=230	-	-	-	-	-	-	-	-	-	-												
Morphine	2 RCTs[29,65] total n=222	-	-	-	-	-	-	-	-	-	-	-											

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine
Nortriptyline	1 RCT[29] total n=110	1 RCT[63] total n=66	-	-	-	2 RCTs[9,18] total n=182	1 RCT[18] 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									
Oxcarbazepine	2 RCTs[5,11] total n=493	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
Oxycodone	1 RCT[19] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Pregabalin	16 RCTs[2,12,16,22,30,32,41,43,47,48,50,52,55,58,59,60] total n=3997	1 RCT[4] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Valproate	2 RCTs[1,31] total n=84	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Topiramate	3 RCTs[28,38,57] total n=1674	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Tramadol	2 RCTs[25,53] total n=221	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Trazodone	1 RCT[10] total n=18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	3 RCTs[46,54,56] total n=355	-	-	-	-	-	-	-	1 RCT[54] total n=80	-	-	-	-	-	-	-	-	-	-	-	-	-	

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine
Capsaicin Cream	-	1 RCT[6] total n=235	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(1) Agrawal et al. (2009); (2) Arezzo et al. (2008); (3) Backonja et al. (1998); (4) Bansal et al. (2009); (5) Beydoun et al. (2006); (6) Biesbroeck et al. (1995); (7) Bone et al. (2002); (8) Breuer et al. (2007); (9) Chandra et al. (2006); (10) Davidoff et al. (1987); (11) Dogra et al. (2005); (12) Dworkin et al. (2003); (13) Eisenberg et al. (2001); (14) Falah et al. (2012); (15) Finnerup et al. (2009); (16) Freynhagen et al. (2005); (17) Gao et al. (2010); (18) Gilron et al. (2012); (19) Gimbel et al. (2003); (20) Goldstein et al. (2005); (21) Graff-Radford et al. (2000); (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) Kalso et al. (1995); (28) Khoromi et al. (2005); (29) Khoromi et al. (2007); (30) Kim et al. (2011); (31) Kochar et al. (2004); (32) Lesser et al. (2004); (33) Levendoglu et al. (2004); (34) Luria et al. (2000); (35) Max et al. (1988); (36) Nurmikko et al. (2007); (37) Otto et al. (2008); (38) Raskin et al. (2004); (39) Rauck et al. (2007); (40) Rice & Maton (2001); (41) Richter et al. (2005); (42) Rog et al. (2005); (43) Rosenstock et al. (2004); (44) Rossi et al. (2009); (45) Rowbotham et al. (1998); (46) Rowbotham et al. (2004); (47) Sabatowski et al. (2004); (48) Satoh et al. (2011); (49) Shaibani et al. (2009); (50) Siddall et al. (2006); (51) Simpson (2001); (52) Simpson et al. (2010); (53) Sindrup et al. (1999); (54) Sindrup et al. (2003); (55) Stacey et al. (2008); (56) Tasmuth et al. (2002); (57) Thienel et al. (2004); (58) Tolle et al. (2008); (59) van Seventer et al. (2006); (60) Vranken et al. (2008); (61) Vranken et al. (2011); (62) Vrethem et al. (1997); (63) Watson et al. (1998); (64) Wernicke et al. (2006); (65) Wu et al. (2008); (66) Yasuda et al. (2011)

Table 7 somnolence - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream
Placebo		3.15 (1.72, 5.78)	5.04 (0.84, 30.03)	3.48 (2.24, 5.40)	2.09 (0.36, 12.0)	5.23 (3.25, 8.40)	-	-	1.0 (0.19, 5.28)	2.39 (0.26, 22.33)	0.56 (0.15, 2.14)	3.45 (1.72, 6.92)	4.32 (1.37, 13.65)	2.04 (0.18, 23.15)	3.12 (0.31, 30.92)	3.15 (0.59, 16.78)	51.18 (6.78, 386.45)	4.04 (3.09, 5.29)	3.15 (0.31, 31.52)	3.54 (1.57, 7.96)	4.11 (1.22, 13.79)	6.40 (0.55, 74.89)	2.94 (0.64, 13.42)	-
Amitriptyline	3.53 (1.61, 7.94)		-	-	-	-	-	-	-	-	-	-	-	1.61 (0.41, 6.34)	-	-	-	1.53 (0.24, 9.57)	-	-	-	-	-	-	0.0 (0.0, 0.05)
Cannabis Sativa Extract	6.58 (1.02, 87.93)	1.88 (0.24, 27.06)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duloxetine	4.13 (2.23, 7.92)	1.17 (0.42, 3.27)	0.63 (0.04, 4.63)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	2.32 (0.29, 24.97)	0.66 (0.07, 8.03)	0.34 (0.01, 7.38)	0.56 (0.06, 6.59)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	5.53 (2.97, 10.65)	1.57 (0.59, 4.21)	0.84 (0.06, 6.03)	1.34 (0.54, 3.27)	2.38 (0.20, 20.99)		4.23 (0.46, 39.10)	4.98 (2.32, 10.70)	-	-	-	-	-	1.39 (0.41, 4.72)	-	-	-	-	-	-	-	-	-	-
Gabapentin +Nortriptylin	25.92 (3.16,	7.36 (0.81,	3.81 (0.14	6.28 (0.69,	11.08 (0.48,	4.68 (0.59,		-	-	-	-	-	-	0.24 (0.03	-	-	-	-	-	-	-	-	-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream
e	284.40)	85.90)	, 82.26)	74.64)	263.30)	49.22)								, 2.18)										
Gabapentin +Oxycodone	28.68 (6.57, 131.70)	8.14 (1.54, 43.89)	4.28 (0.22, 48.59)	6.94 (1.40, 35.77)	12.25 (0.77, 163.20)	5.18 (1.36, 20.59)	1.10 (0.07, 13.44)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Imipramine	0.91 (0.13, 5.36)	0.26 (0.03, 1.80)	0.13 (0.01, 1.86)	0.22 (0.03, 1.43)	0.38 (0.02, 6.11)	0.16 (0.02, 1.08)	0.03 (0.0, 0.56)	0.03 (0.0, 0.32)		-	-	-	-	-	-	-	-	-	-	-	-	-	3.58 (0.89, 14.39)	-
Lacosamide	3.07 (0.81, 14.85)	0.88 (0.19, 4.97)	0.47 (0.03, 5.49)	0.75 (0.17, 4.0)	1.34 (0.09, 18.04)	0.56 (0.13, 2.98)	0.12 (0.01, 1.63)	0.11 (0.01, 0.92)	3.49 (0.36, 40.87)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lamotrigine	0.56 (0.12, 2.33)	0.16 (0.03, 0.80)	0.08 (0.0, 0.91)	0.13 (0.03, 0.64)	0.24 (0.01, 2.99)	0.10 (0.02, 0.47)	0.02 (0.0, 0.27)	0.02 (0.0, 0.15)	0.61 (0.06, 6.88)	0.18 (0.02, 1.27)		-	-	-	-	-	-	-	-	-	-	-	-	-
Levetiracetam	3.77 (1.53, 9.73)	1.07 (0.31, 3.63)	0.57 (0.04, 4.73)	0.91 (0.30, 2.81)	1.62 (0.13, 15.79)	0.68 (0.22, 2.12)	0.14 (0.01, 1.48)	0.13 (0.02, 0.76)	4.18 (0.57, 35.89)	1.22 (0.20, 6.27)	6.86 (1.23, 39.95)		-	-	-	-	-	-	-	-	-	-	-	-
Morphine	8.03 (2.18, 33.47)	2.29 (0.52, 10.83)	1.20 (0.07, 13.04)	1.94 (0.45, 9.12)	3.47 (0.23, 42.96)	1.45 (0.35, 6.47)	0.31 (0.02, 3.54)	0.28 (0.04, 2.09)	9.01 (0.98, 95.42)	2.60 (0.34, 17.83)	14.71 (2.08, 112)	2.14 (0.42, 11.59)		0.26 (0.05, 1.31)	0.40 (0.10, 1.62)	-	-	-	-	-	-	-	-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream
Nortriptyline	4.80 (1.60, 14.61)	1.35 (0.41, 4.43)	0.72 (0.04, 6.47)	1.16 (0.32, 4.13)	2.05 (0.15, 21.58)	0.86 (0.28, 2.62)	0.18 (0.02, 1.50)	0.17 (0.03, 0.94)	5.30 (0.65, 48.26)	1.54 (0.23, 8.77)	8.68 (1.42, 55.40)	1.27 (0.30, 5.29)	0.59 (0.14, 2.42)		1.53 (0.25, 9.53)	-	-	-	-	-	-	-	-	-
Nortriptyline +Morphine	3.95 (0.53, 25.74)	1.12 (0.14, 8.04)	0.57 (0.02, 8.82)	0.95 (0.12, 6.81)	1.66 (0.08, 28.04)	0.71 (0.09, 4.88)	0.15 (0.01, 2.24)	0.14 (0.01, 1.44)	4.37 (0.30, 63.11)	1.26 (0.11, 12.42)	7.13 (0.61, 78.67)	1.04 (0.11, 8.54)	0.49 (0.07, 2.79)	0.82 (0.12, 5.18)		-	-	-	-	-	-	-	-	-
Oxcarbazepine	3.61 (0.96, 17.05)	1.03 (0.21, 5.85)	0.54 (0.03, 6.17)	0.88 (0.20, 4.66)	1.57 (0.10, 20.52)	0.65 (0.15, 3.48)	0.14 (0.01, 1.94)	0.13 (0.02, 1.06)	4.11 (0.42, 46.59)	1.17 (0.15, 8.93)	6.63 (0.91, 56.61)	0.96 (0.19, 5.76)	0.45 (0.06, 3.41)	0.76 (0.13, 5.08)	0.94 (0.09, 11.61)		-	-	-	-	-	-	-	-
Oxycodone	73.14 (8.87, 2043)	20.87 (2.15, 616.60)	11.22 (0.39, 487)	17.83 (1.91, 503.10)	32.56 (1.31, 1438)	13.25 (1.46, 381.90)	2.94 (0.12, 139.90)	2.62 (0.19, 92.18)	86.19 (4.96, 3554)	24.02 (1.69, 847)	137 (10.41, 4797)	19.62 (1.92, 581.50)	9.29 (0.70, 317.20)	15.54 (1.39, 496)	19.72 (1.06, 844.70)	20.46 (1.44, 694.70)		-	-	-	-	-	-	-
Pregabalin	4.51 (3.12, 6.63)	1.28 (0.54, 3.01)	0.68 (0.05, 4.60)	1.09 (0.52, 2.27)	1.94 (0.18, 16.10)	0.82 (0.39, 1.70)	0.17 (0.02, 1.49)	0.16 (0.03, 0.73)	4.99 (0.81, 35.91)	1.46 (0.29, 5.88)	8.12 (1.84, 38.40)	1.20 (0.43, 3.20)	0.56 (0.13, 2.19)	0.94 (0.29, 3.0)	1.15 (0.17, 8.76)	1.25 (0.26, 4.96)	0.06 (0.0, 0.53)		-	-	-	-	-	-
Valproate	4.36 (0.37, 146)	1.24 (0.09, 44.90)	0.66 (0.02, 33.38)	1.06 (0.08, 36.64)	1.93 (0.06, 105)	0.79 (0.06, 27.10)	0.17 (0.01, 9.47)	0.15 (0.01, 6.50)	5.04 (0.22, 249.10)	1.42 (0.07, 59.02)	8.22 (0.43, 342.20)	1.17 (0.08, 42.59)	0.55 (0.03, 22.70)	0.92 (0.06, 35.02)	1.15 (0.05, 58.62)	1.20 (0.06, 50.74)	0.06 (0.0, 3.53)	0.97 (0.08, 32.59)		-	-	-	-	-
Topiramate	3.82 (1.75, 8.80)	1.09 (0.35, 3.38)	0.58 (0.04, 4.56)	0.92 (0.34, 2.60)	1.64 (0.14, 15.51)	0.69 (0.25, 1.95)	0.15 (0.01, 1.43)	0.13 (0.02, 0.73)	4.25 (0.61, 34.25)	1.24 (0.22, 5.90)	6.93 (1.34, 38.26)	1.01 (0.30, 3.47)	0.48 (0.10, 2.25)	0.80 (0.21, 3.17)	0.97 (0.13, 8.35)	1.06 (0.19, 5.01)	0.05 (0.0, 0.51)	0.85 (0.35, 2.10)	0.87 (0.02, 12.07)		-	-	-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Trazodone	Venlafaxine	Capsaicin Cream
Tramadol	4.50 (1.42, 15.10)	1.28 (0.31, 5.39)	0.67 (0.04, 6.44)	1.09 (0.29, 4.22)	1.93 (0.14, 21.74)	0.81 (0.22, 3.15)	0.17 (0.01, 2.02)	0.16 (0.02, 1.05)	5.01 (0.60, 48.58)	1.45 (0.21, 8.81)	8.15 (1.27, 56.03)	1.20 (0.27, 5.40)	0.56 (0.09, 3.29)	0.94 (0.19, 4.76)	1.15 (0.13, 11.73)	1.24 (0.18, 7.48)	0.06 (0.0, 0.72)	1.0 (0.30, 3.52)	1.02 (0.03, 16.35)	1.18 (0.28, 4.92)		-	-	-
Trazodone	9.13 (0.62, 358.90)	2.61 (0.16, 107.40)	1.36 (0.03, 81.17)	2.21 (0.14, 90.02)	3.99 (0.11, 251)	1.64 (0.10, 67.54)	0.36 (0.01, 22.87)	0.32 (0.01, 16.03)	10.50 (0.40, 618.90)	2.97 (0.13, 140.30)	17.03 (0.76, 828.10)	2.43 (0.14, 102.90)	1.14 (0.05, 53.66)	1.93 (0.10, 84.53)	2.41 (0.08, 144)	2.51 (0.11, 122.60)	0.12 (0.0, 8.43)	2.02 (0.13, 78.68)	2.08 (0.03, 170.30)	2.39 (0.14, 99.95)	2.06 (0.11, 92.70)		-	-
Venlafaxine	3.47 (1.28, 10.07)	0.98 (0.27, 3.70)	0.52 (0.03, 4.58)	0.84 (0.25, 2.87)	1.49 (0.12, 15.79)	0.63 (0.19, 2.15)	0.13 (0.01, 1.42)	0.12 (0.02, 0.74)	3.82 (0.72, 25.20)	1.12 (0.17, 6.22)	6.30 (1.09, 39.45)	0.92 (0.23, 3.67)	0.43 (0.08, 2.32)	0.73 (0.16, 3.36)	0.89 (0.10, 8.32)	0.96 (0.15, 5.27)	0.05 (0.0, 0.51)	0.77 (0.26, 2.37)	0.79 (0.02, 11.95)	0.91 (0.25, 3.37)	0.77 (0.16, 3.70)	0.38 (0.01, 6.90)		-
Capsaicin Cream	0.0 (0.0, 0.08)	0.0 (0.0, 0.02)	0.0 (0.0, 0.02)	0.0 (0.0, 0.02)	0.0 (0.0, 0.07)	0.0 (0.0, 0.02)	0.0 (0.0, 0.01)	0.0 (0.0, 0.0)	0.0 (0.0, 0.17)	0.0 (0.0, 0.04)	0.01 (0.0, 0.21)	0.0 (0.0, 0.02)	0.0 (0.0, 0.01)	0.0 (0.0, 0.02)	0.0 (0.0, 0.04)	0.0 (0.0, 0.03)	0.0 (0.0, 0.0)	0.0 (0.0, 0.02)	0.0 (0.0, 0.05)	0.0 (0.0, 0.02)	0.0 (0.0, 0.02)	0.0 (0.0, 0.03)	0.0 (0.0, 0.03)	

Values given are odds ratios.

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

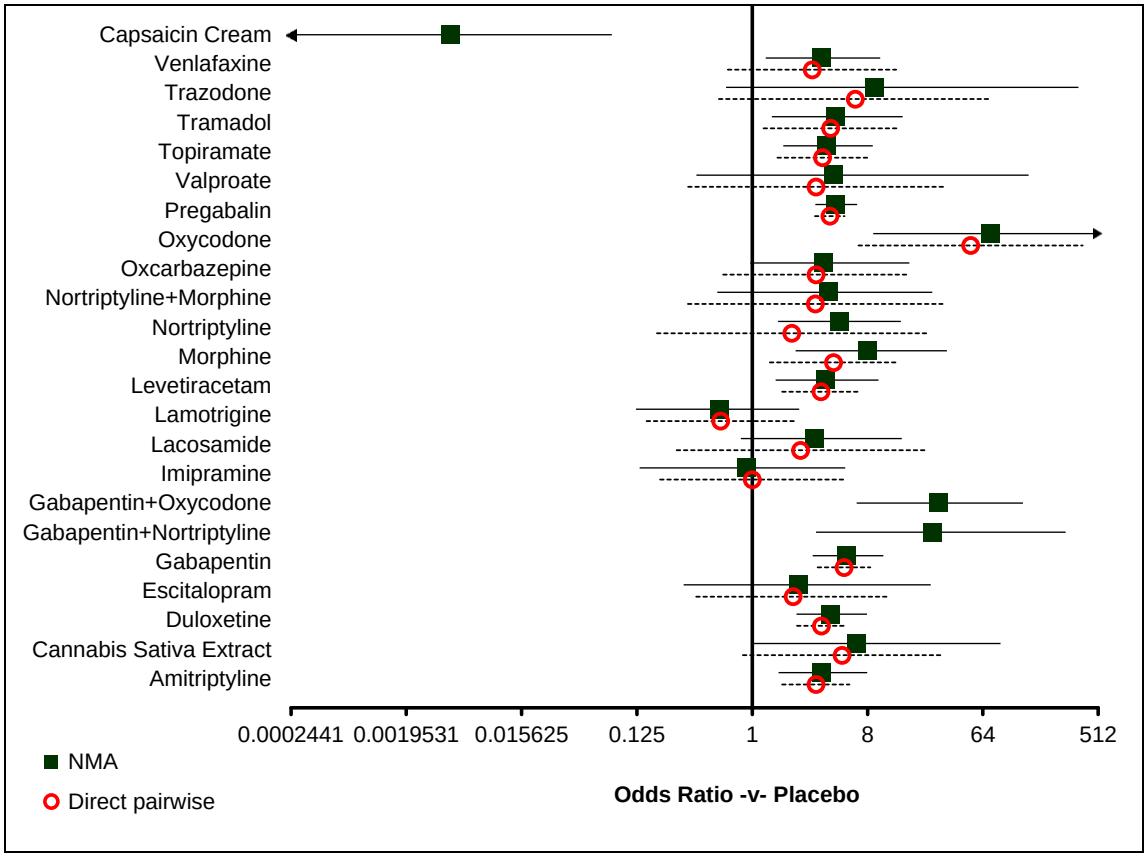

Figure 5 somnolence - relative effect of all options compared with placebo

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

Table 8 somnolence - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	4 (2, 6)
Amitriptyline	0.000	11 (5, 19)
Cannabis Sativa Extract	0.000	17 (4, 24)
Duloxetine	0.000	12 (6, 19)
Escitalopram	0.000	7 (2, 22)
Gabapentin	0.000	16 (9, 20)
Gabapentin+Nortriptyline	0.000	22 (10, 24)
Gabapentin+Oxycodone	0.000	22 (17, 24)
Imipramine	0.001	4 (2, 15)
Lacosamide	0.000	9 (3, 21)
Lamotrigine	0.001	2 (2, 7)
Levetiracetam	0.000	11 (5, 20)
Morphine	0.000	19 (7, 23)
Nortriptyline	0.000	14 (6, 21)
Nortriptyline+Morphine	0.000	12 (3, 22)
Oxcarbazepine	0.000	11 (4, 21)
Oxycodone	0.000	24 (19, 24)
Pregabalin	0.000	14 (8, 19)
Valproate	0.000	13 (2, 24)
Topiramate	0.000	12 (5, 20)
Tramadol	0.000	13 (5, 21)
Trazodone	0.000	19 (3, 24)
Venlafaxine	0.000	11 (5, 20)
Capsaicin Cream	0.998	1 (1, 1)

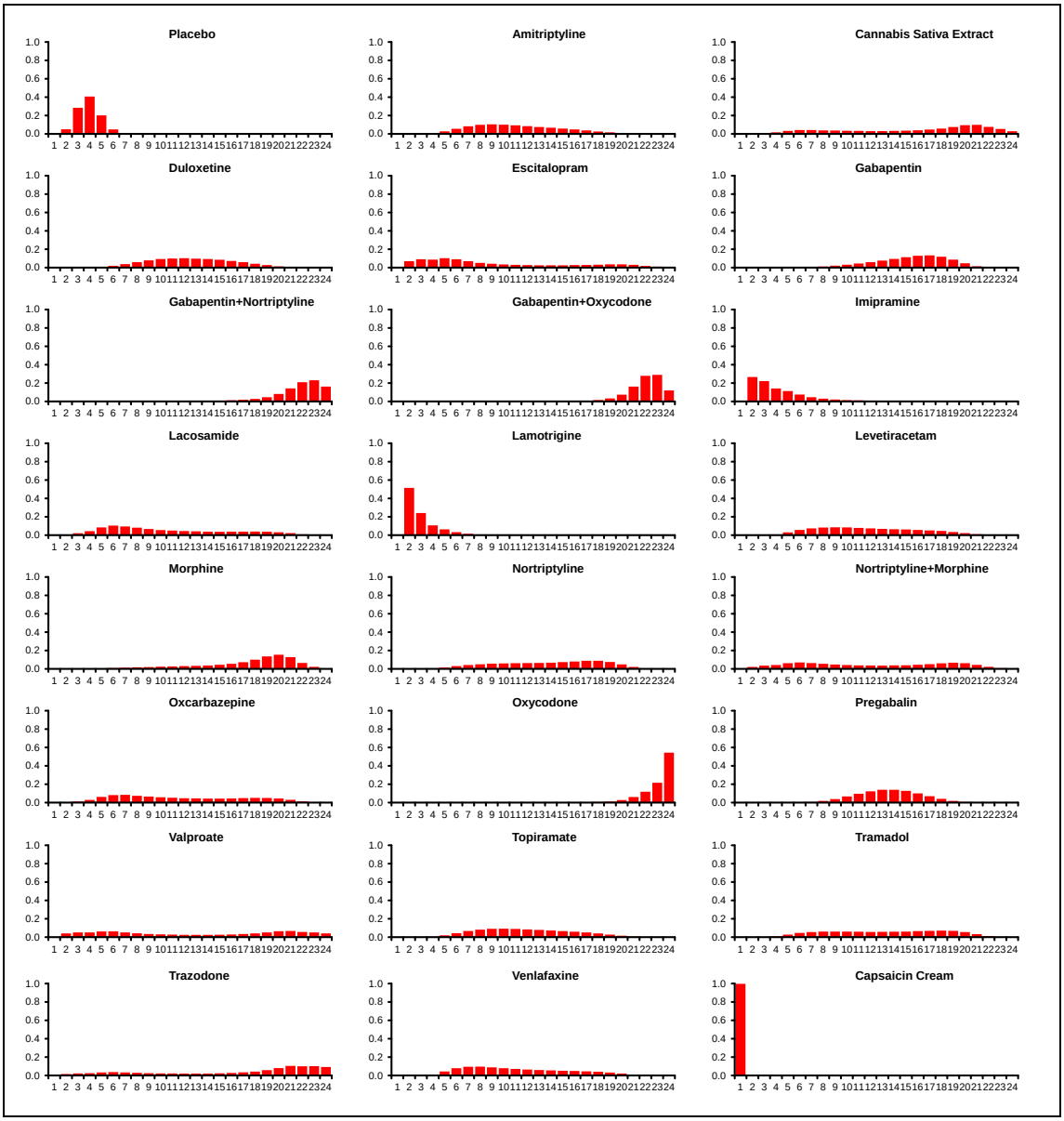

Figure 6 somnolence - rank probability histograms

Table 9 somnolence - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
157.7 (compared to 159 data-points)	696.756	578.142	118.615	815.371	0.267 (95%CrI: 0.127, 0.585)

Table 10 somnolence - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times)

rather than the proportion of patients who reported the event which the majority of the other studies reported.

- Model convergence: poor autocorrelation for capsaicin cream and oxycodone – both are only connected with one study.

Summary GRADE profile 3c: fatigue (or tiredness)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Fatigue (and tiredness)	25 RCTs[a] n=6397	Very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear about allocation concealment in 12 studies; there is uncertainty about comparability at baseline between groups in 17 studies and there are differences between groups at baseline in 4 studies (particularly for use of concomitant drugs); during 12 studies, it was unclear if the same care was received by each group and in 3 studies different care was received (these were usually to do with concomitant drug and rescue medication use); patients who completed the trials were not comparable between groups in 9 studies and in 4 studies it was unclear if they were comparable; mean baseline severity ranged from 3.9 to 7.4 on a normalised 11-point scale across the studies in the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 73% for duloxetine vs placebo, 61% for gabapentin vs placebo, 38% for gabapentin vs nortriptyline which may indicate substantial heterogeneity between the studies that form the comparisons in the first two and moderate or no heterogeneity between the studies that make the last; appears to be consistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] few head-to-head trials; more than half of the links had only one trial; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Cannabis Sativa Extract (n=191): Nurmikko et al. (2007), Rog et al. (2005)

Capsaicin Patch (n=307): Simpson et al. (2008)

Duloxetine (n=549): Gao et al. (2010), Wernicke et al. (2006)

Gabapentin (n=470): Gordh et al. (2008), Rao et al. (2007)

Lacosamide (n=1195): Shaibani et al. (2009), Wymer et al. (2009), Ziegler et al. (2010)

Lamotrigine (n=125): Rao et al. (2008)

Levetiracetam (n=60): Falah et al. (2012)

Morphine, Nortriptyline, Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxcarbazepine (n=493): Beydoun et al. (2006), Dogra et al. (2005)

Pregabalin (n=269): Stacey et al. (2008)

Topiramate (n=1674): Khoromi et al. (2005), Raskin et al. (2004), Thienel et al. (2004)

Tramadol (n=166): Harati et al. (1998), Norrbrink & Lundeberg (2009)

Head-to-head trials:

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

Gabapentin vs Gabapentin+Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012)

Gabapentin vs Gabapentin+Oxycodone (n=338): Hanna et al. (2008)

Gabapentin vs Nortriptyline (n=182): Chandra et al. (2006), Gilron et al. (2012)

Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

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

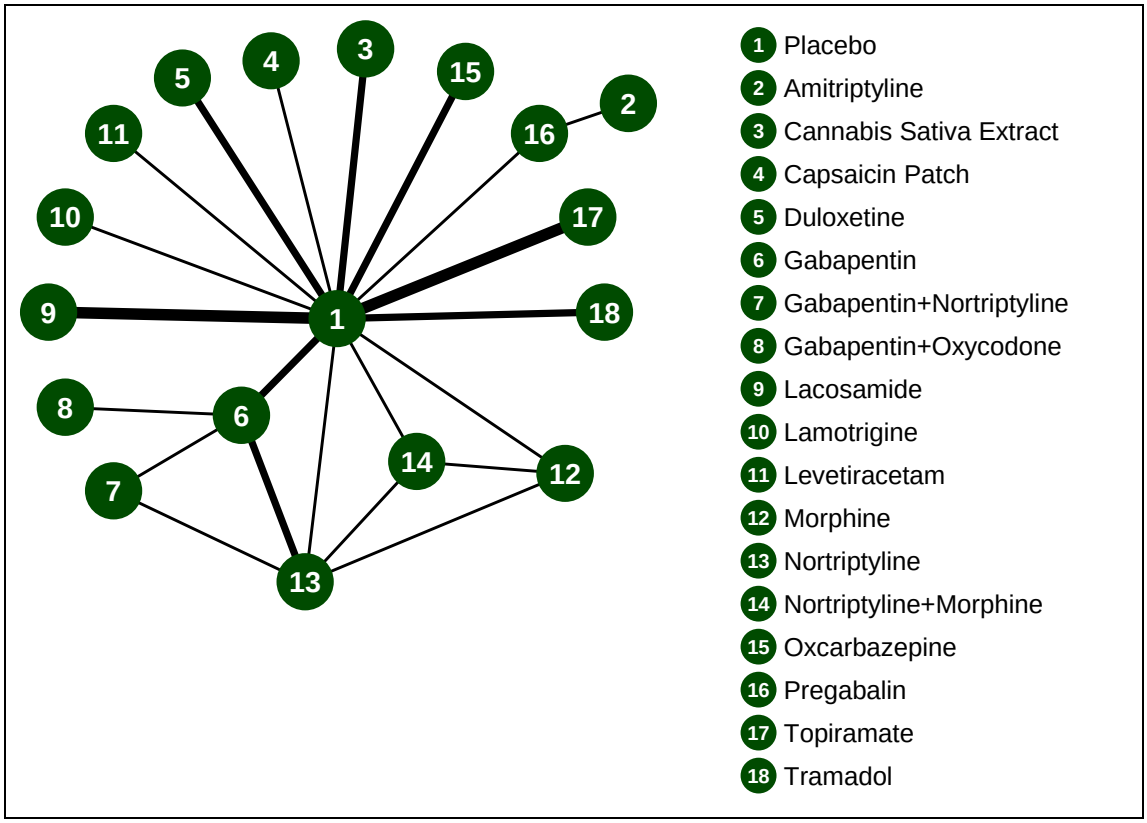

Figure 7 fatigue (or tiredness) - evidence network

Table 11 fatigue (or tiredness) - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate
Amitriptyline	-																
Cannabis Sativa Extract	2 RCTs[14,18] total n=191	-															
Capsaicin Patch	1 RCT[20] total n=307	-	-														
Duloxetine	2 RCTs[6,23] total n=549	-	-	-													
Gabapentin	2 RCTs[8,15] total n=470	-	-	-	-												
Gabapentin +Nortriptyline	-	-	-	-	-	1 RCT[7] total n=112											
Gabapentin +Oxycodone	-	-	-	-	-	1 RCT[9] total n=338	-										
Lacosamide	3 RCTs[19,24,25] total n=1195	-	-	-	-	-	-	-									
Lamotrigine	1 RCT[16] total n=125	-	-	-	-	-	-	-	-								
Levetiracetam	1 RCT[5] total n=60	-	-	-	-	-	-	-	-	-							
Morphine	1 RCT[12] total n=110	-	-	-	-	-	-	-	-	-	-						
Nortriptyline	1 RCT[12] total n=110	-	-	-	-	2 RCTs[3,7]	1 RCT[7] total	-	-	-	-	1 RCT[12] total					

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate
						total n=182	n=112					n=110					
Nortriptyline +Morphine	1 RCT[12] total n=110	-	-	-	-	-	-	-	-	-	-	1 RCT[12] total n=110	1 RCT[12] total n=110				
Oxcarbazepine	2 RCTs[2,4] total n=493	-	-	-	-	-	-	-	-	-	-	-	-	-			
Pregabalin	1 RCT[21] total n=269	1 RCT[1] total n=102	-	-	-	-	-	-	-	-	-	-	-	-	-		
Topiramate	3 RCTs[11,17,22] total n=1674	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Tramadol	2 RCTs[10,13] total n=166	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(1) Bansal et al. (2009); (2) Beydoun et al. (2006); (3) Chandra et al. (2006); (4) Dogra et al. (2005); (5) Falah et al. (2012); (6) Gao et al. (2010); (7) Gilron et al. (2012); (8) Gordh et al. (2008); (9) Hanna et al. (2008); (10) Harati et al. (1998); (11) Khoromi et al. (2005); (12) Khoromi et al. (2007); (13) Norrbrink & Lundeberg (2009); (14) Nurmikko et al. (2007); (15) Rao et al. (2007); (16) Rao et al. (2008); (17) Raskin et al. (2004); (18) Rog et al. (2005); (19) Shaibani et al. (2009); (20) Simpson et al. (2008); (21) Stacey et al. (2008); (22) Thienel et al. (2004); (23) Wernicke et al. (2006); (24) Wymer et al. (2009); (25) Ziegler et al. (2010)

Table 12 fatigue (or tiredness) - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate	Tramadol
Placebo		-	2.28 (0.87, 5.99)	0.72 (0.13, 4.03)	2.18 (0.47, 10.12)	1.36 (0.47, 3.92)	-	-	1.63 (0.82, 3.24)	0.48 (0.04, 5.48)	7.25 (0.82, 64.46)	0.38 (0.07, 2.03)	0.58 (0.13, 2.54)	0.58 (0.13, 2.54)	1.86 (0.79, 4.36)	6.97 (0.90, 54.15)	1.57 (1.11, 2.24)	11.96 (2.59, 55.20)
Amitriptyline	305.20 (6.97, 309900.00)		-	-	-	-	-	-	-	-	-	-	-	-	-	0.08 (0.00, 1.53)	-	-
Cannabis Sativa Extract	2.24 (0.69, 7.66)	0.01 (0.00, 0.40)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Capsaicin Patch	0.79 (0.11, 7.35)	0.00 (0.00, 0.22)	0.35 (0.04, 4.51)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duloxetine	2.33 (0.94, 6.21)	0.01 (0.00, 0.39)	1.04 (0.23, 4.88)	2.96 (0.27, 25.67)		-	-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	1.24 (0.51, 2.69)	0.00 (0.00, 0.19)	0.55 (0.12, 2.22)	1.56 (0.14, 12.50)	0.53 (0.14, 1.74)		2.08 (0.36, 11.83)	2.49 (1.27, 4.87)	-	-	-	-	1.53 (0.18, 13.18)	-	-	-	-	-
Gabapentin +Nortriptyline	1.23 (0.20, 6.55)	0.00 (0.00, 0.26)	0.54 (0.06, 4.12)	1.53 (0.09, 20.71)	0.53 (0.07, 3.52)	0.99 (0.19, 5.01)		-	-	-	-	-	1.56 (0.42, 5.86)	-	-	-	-	-
Gabapentin +Oxycodone	3.14 (0.73, 12.01)	0.01 (0.00, 0.58)	1.40 (0.21, 8.29)	3.94 (0.29, 42.49)	1.35 (0.23, 6.74)	2.54 (0.84, 7.87)	2.57 (0.36, 18.94)		-	-	-	-	-	-	-	-	-	-
Lacosamide	1.70 (0.77, 4.09)	0.01 (0.00, 0.28)	0.76 (0.18, 3.33)	2.16 (0.21, 17.93)	0.73 (0.21, 2.57)	1.39 (0.45, 4.81)	1.41 (0.22, 10.48)	0.54 (0.11, 2.99)		-	-	-	-	-	-	-	-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate	Tramadol
Lamotrigine	0.39 (0.01, 6.33)	0.00 (0.00, 0.15)	0.17 (0.00, 3.57)	0.47 (0.01, 14.94)	0.16 (0.00, 3.10)	0.32 (0.01, 5.93)	0.31 (0.01, 9.05)	0.12 (0.00, 2.91)	0.22 (0.01, 4.19)		-	-	-	-	-	-	-	-
Levetiracetam	10.07 (1.13, 333.90)	0.03 (0.00, 4.93)	4.56 (0.36, 177.00)	13.09 (0.57, 663.40)	4.35 (0.39, 157.40)	8.36 (0.80, 295.40)	8.70 (0.48, 404.40)	3.32 (0.24, 135.90)	5.94 (0.54, 213.50)	28.88 (0.73, 3779.00)		-	-	-	-	-	-	-
Morphine	0.48 (0.05, 2.90)	0.00 (0.00, 0.11)	0.21 (0.02, 1.84)	0.58 (0.03, 8.94)	0.20 (0.02, 1.56)	0.39 (0.04, 2.64)	0.39 (0.03, 4.05)	0.15 (0.01, 1.42)	0.28 (0.03, 2.04)	1.24 (0.03, 71.17)	0.04 (0.00, 0.85)		1.53 (0.25, 9.53)	1.53 (0.25, 9.53)	-	-	-	-
Nortriptyline	1.22 (0.35, 3.99)	0.00 (0.00, 0.22)	0.54 (0.10, 2.87)	1.53 (0.12, 15.33)	0.53 (0.10, 2.31)	0.99 (0.31, 3.26)	1.00 (0.21, 5.14)	0.39 (0.08, 1.98)	0.71 (0.16, 3.00)	3.17 (0.15, 144.20)	0.12 (0.00, 1.49)	2.52 (0.42, 22.94)		1.00 (0.19, 5.19)	-	-	-	-
Nortriptyline +Morphine	0.77 (0.11, 4.10)	0.00 (0.00, 0.17)	0.34 (0.04, 2.70)	0.96 (0.05, 12.77)	0.33 (0.04, 2.23)	0.63 (0.09, 3.77)	0.63 (0.06, 5.97)	0.25 (0.03, 2.03)	0.45 (0.06, 2.93)	1.99 (0.06, 113.70)	0.07 (0.00, 1.25)	1.62 (0.19, 16.60)	0.64 (0.10, 3.47)		-	-	-	-
Oxcarbazepine	1.99 (0.71, 6.07)	0.01 (0.00, 0.34)	0.89 (0.18, 4.46)	2.52 (0.23, 23.94)	0.85 (0.21, 3.61)	1.62 (0.45, 6.81)	1.64 (0.23, 13.92)	0.64 (0.12, 4.04)	1.16 (0.30, 4.64)	5.29 (0.26, 217.00)	0.19 (0.01, 2.40)	4.25 (0.52, 49.09)	1.64 (0.35, 8.96)	2.62 (0.36, 23.29)		-	-	-
Pregabalin	9.45 (1.31, 230.10)	0.04 (0.00, 0.67)	4.26 (0.41, 121.20)	12.48 (0.60, 440.30)	4.09 (0.45, 109.20)	7.80 (0.91, 210.60)	8.01 (0.57, 283.50)	3.10 (0.27, 96.96)	5.64 (0.63, 143.00)	27.18 (0.77, 2720.00)	0.94 (0.02, 41.36)	21.39 (1.26, 913.50)	7.97 (0.76, 231.70)	13.00 (0.86, 482.00)	4.83 (0.48, 127.40)		-	-
Topiramate	1.64 (0.90, 3.15)	0.01 (0.00, 0.25)	0.73 (0.19, 2.84)	2.09 (0.21, 16.26)	0.70 (0.23, 2.17)	1.32 (0.50, 4.12)	1.34 (0.23, 9.41)	0.52 (0.12, 2.64)	0.96 (0.34, 2.69)	4.26 (0.24, 170.00)	0.16 (0.00, 1.64)	3.44 (0.52, 34.93)	1.34 (0.36, 5.64)	2.14 (0.36, 16.23)	0.82 (0.24, 2.82)	0.17 (0.01, 1.42)		-
Tramadol	14.47 (2.74, 111.10)	0.05 (0.00, 3.59)	6.61 (0.80, 65.30)	18.41 (1.20, 295.50)	6.25 (0.91, 56.16)	11.84 (1.89, 106.50)	12.17 (1.12, 177.20)	4.69 (0.55, 54.72)	8.45 (1.32, 75.21)	40.14 (1.40, 2390.00)	1.43 (0.03, 29.20)	31.46 (2.58, 609.70)	11.96 (1.56, 128.50)	19.45 (1.71, 310.50)	7.30 (0.99, 69.25)	1.51 (0.05, 26.37)	8.77 (1.49, 73.56)	

Values given are odds ratios. The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate	Tramadol
above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.																		

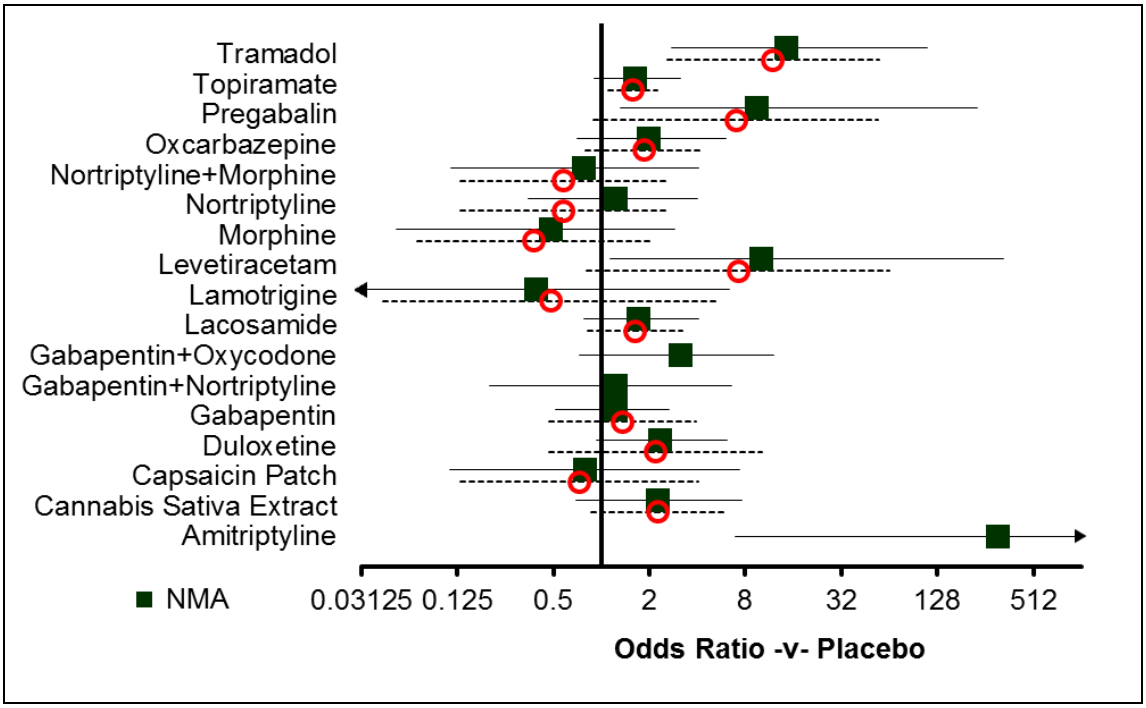

Figure 8 fatigue (or tiredness) - relative effect of all options compared with placebo

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

Table 13 fatigue (or tiredness) - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.004	5 (2, 9)
Amitriptyline	0.000	18 (16, 18)
Cannabis Sativa Extract	0.003	11 (3, 16)
Capsaicin Patch	0.137	4 (1, 15)
Duloxetine	0.001	12 (5, 15)
Gabapentin	0.005	7 (2, 12)
Gabapentin+Nortriptyline	0.044	7 (1, 15)
Gabapentin+Oxycodone	0.002	13 (4, 16)
Lacosamide	0.002	9 (3, 14)
Lamotrigine	0.421	2 (1, 15)
Levetiracetam	0.001	16 (6, 18)
Morphine	0.264	2 (1, 12)
Nortriptyline	0.009	7 (2, 14)
Nortriptyline+Morphine	0.105	4 (1, 14)
Oxcarbazepine	0.002	11 (3, 15)
Pregabalin	0.001	16 (7, 17)
Topiramate	0.001	9 (4, 14)
Tramadol	0.000	16 (12, 18)

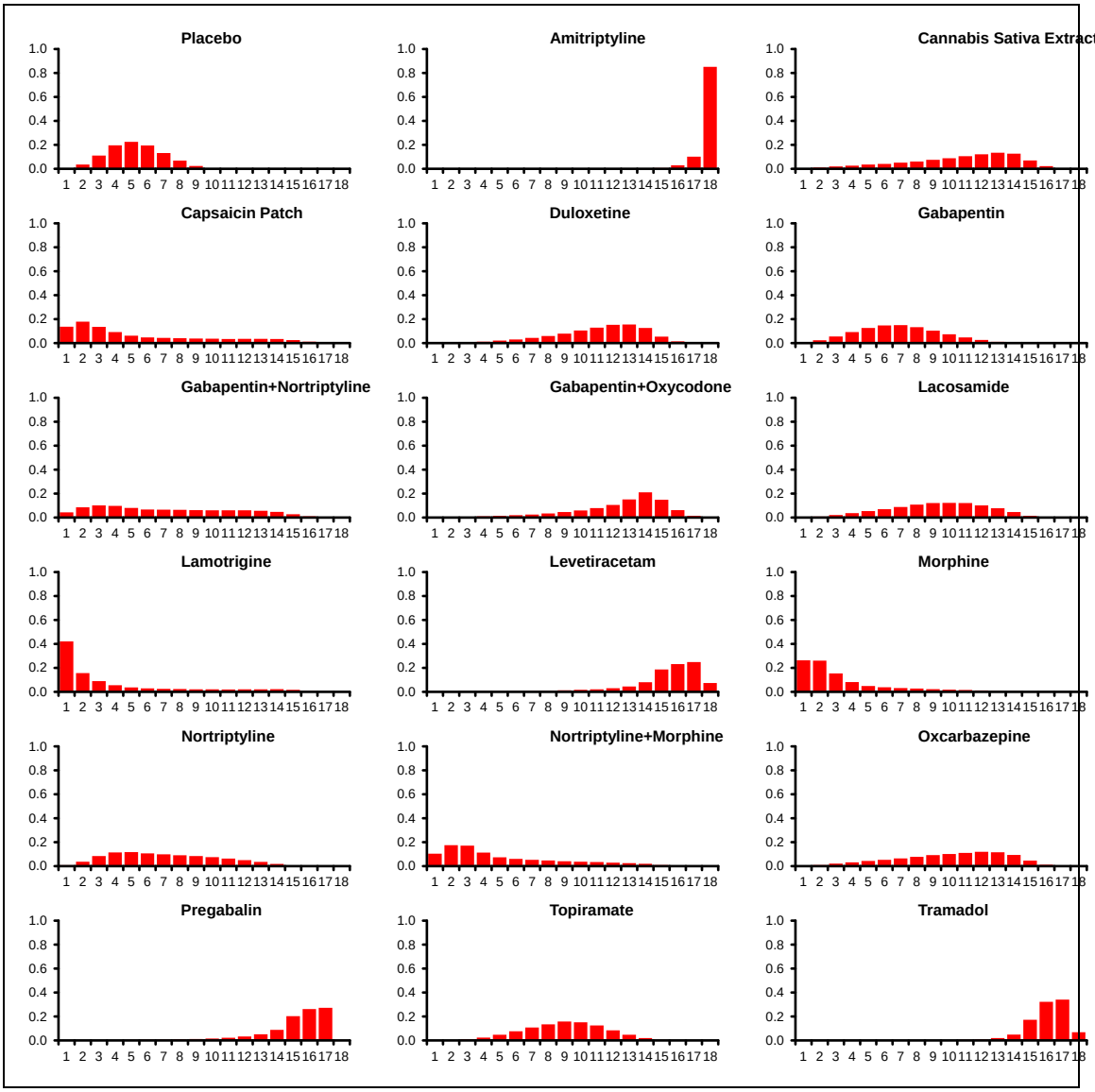

Figure 9 fatigue (or tiredness) - rank probability histograms

Table 14 fatigue (or tiredness) - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
65.31 (compared to 64 data-points)	284.883	235.738	49.145	334.029	0.010 (95%CI: 0.005, 0.629)

Table 15 fatigue (or tiredness) - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 10000 burn-ins and 50000 iterations.
- Since we were unable to include lethargy in this synthesis (for reasons stated in the methods section), the results from Watson (1998) which classified an event as ‘lethargy and fatigue’ were not included in either this

or the lethargy synthesis.

- It was not possible to include the results from Huse (2001) in the synthesis because the study recorded the intensity of adverse events on a visual analogue scale (from 'not at all' to extremely) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- Model convergence: amitriptyline and pregabalin have poor autocorrelation because they have only one study with low event rates for placebo.

Summary GRADE profile 3d: lethargy

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Lethargy	3 RCTs[a] n=792	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] randomisation method and allocation concealment were unclear in all 3 studies; there is uncertainty about comparability at baseline between groups in all 3 studies (particularly for use of concomitant drugs); during 2 studies, it was unclear if the same care was received by each group (these were usually to do with concomitant drug and rescue medication use); concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for pregabalin vs placebo which may indicate no heterogeneity between the studies that form this comparison (heterogeneity not possible for duloxetine vs placebo since there is only one trial for this comparison); no loops so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] no head-to-head trials; one of the two links has only one study; wide confidence intervals for the effect estimates of both interventions compared to placebo and for overall rankings within the network

[a] Duloxetine (n=215): Gao et al. (2010)

Pregabalin (n=577): Guan et al. (2011), Stacey et al. (2008)

(all compared to placebo)

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

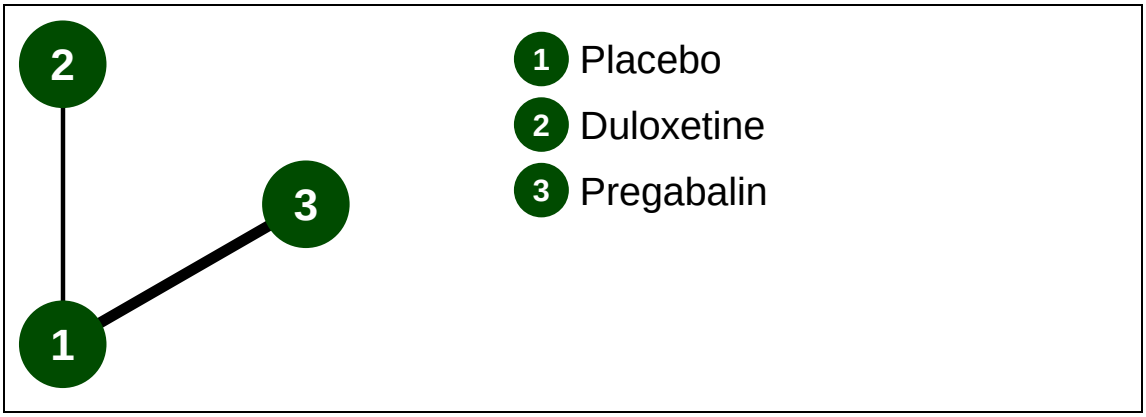

Figure 10 lethargy - evidence network

Table 16 lethargy - trials included in analysis

	Placebo	Duloxetine
Duloxetine	1 RCT[1] total n=215	
Pregabalin	2 RCTs[2,3] total n=577	-

(1) Gao et al. (2010); (2) Guan et al. (2011); (3) Stacey et al. (2008)

Table 17 lethargy - relative effectiveness of all pairwise combinations

	Placebo	Duloxetine	Pregabalin
Placebo		3.04 (0.94, 9.87)	2.74 (0.86, 8.77)
Duloxetine	3.32 (0.02, 524.40)		-
Pregabalin	3.29 (0.10, 143.10)	1.00 (0.00, 543.30)	

Values given are odds ratios.

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

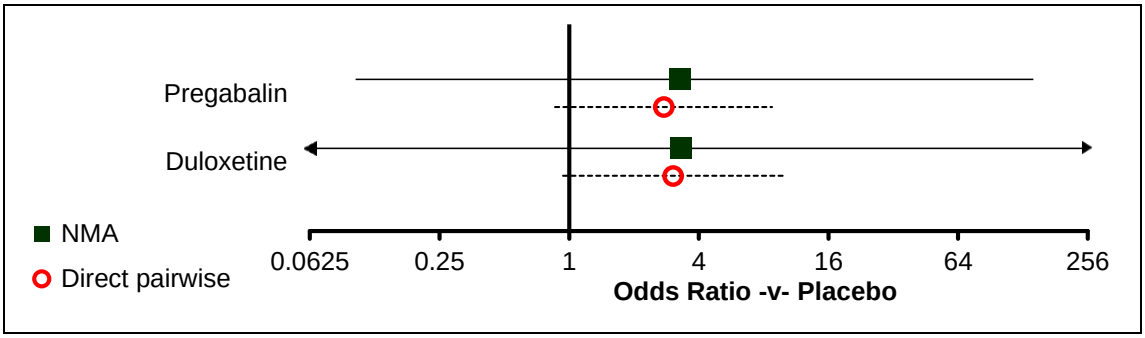

Figure 11 lethargy - relative effect of all options compared with placebo
(values less than 1 favour the treatment; values greater than 1 favour placebo; solid error bars are 95% credible intervals while dashed error bars are 95% confidence intervals)

Table 18 lethargy - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.666	1 (1, 3)
Duloxetine	0.194	2 (1, 3)
Pregabalin	0.140	2 (1, 3)

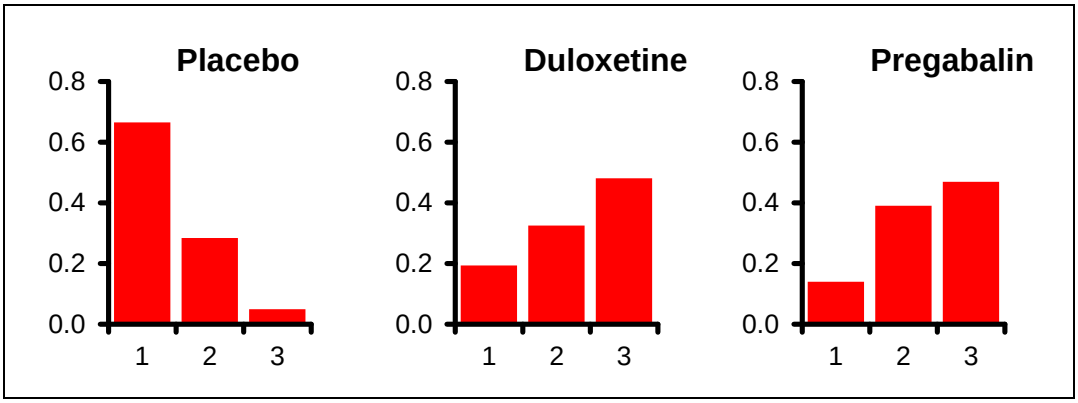

Figure 12 lethargy - rank probability histograms

Table 19 lethargy - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
6.677 (compared to 7 data-points)	27.233	21.326	5.907	33.14	0.002 (95%CrI: 0.006, 21.659)

Table 20 lethargy - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 10000 burn-ins and 50000 iterations.
- Removed Morello from the synthesis because it was not connected to the network

Summary GRADE profile 3e: constipation

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Constipation	34 RCTs[a] n=5172	Very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] there is uncertainty about comparability at baseline between groups in 22 studies and there are differences between groups in 5 studies (particularly for use of concomitant drugs); during 21 studies, it was unclear if the same care was received by each group and in 3 studies the same care was not received (these were usually to do with concomitant drug and rescue medication use); average baseline severity ranged from 3.4 to 7 on a 11-point scale across the network; concomitant drugs permitted varies across the studies in the network; insufficient follow-up in 18 studies

[2] I^2 was 53%, 52%, 50%, and 40% for gabapentin vs nortriptyline, duloxetine vs placebo, amitriptyline vs placebo, and levetiracetam vs placebo, respectively. This may indicate that any inconsistency in the first three comparisons may be moderate to substantial and that the last comparison could be moderate heterogeneity or that any heterogeneity might not be important; indirect and direct estimates appear relatively similar

[3] all aspects of PICO conform to review protocol

[4] the majority of links in the network have only one trial; few head-to-head trials; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=149): Cardenas et al. (2002), Kalso et al. (1995), Robinson et al. (2004)

Duloxetine (n=1392): Gao et al. (2010), Goldstein et al. (2005), Vranken et al. (2011), Wernicke et al. (2006), Yasuda et al. (2011)

Imipramine (n=80): Sindrup et al. (2003)

Lacosamide (n=119): Rauck et al. (2007)

Lamotrigine (n=36): Breuer et al. (2007)

Levetiracetam (n=138): Falah et al. (2012), Holbech et al. (2011)

Morphine (n=222): Khoromi et al. (2007), Wu et al. (2008)

Nortriptyline, Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxycodone (n=159): Gimbel et al. (2003)

Pregabalin (n=1547): Lesser et al. (2004), Richter et al. (2005), Rosenstock et al. (2004), Satoh et al. (2011), Siddall et al. (2006), van Seventer et al. (2006)

Topiramate (n=82): Khoromi et al. (2005)

Tramadol (n=256): Harati et al. (1998), Norrbrink & Lundeberg (2009), Sindrup et al. (1999)

Trazodone (n=18): Davidoff et al. (1987)

Venlafaxine (n=110): Sindrup et al. (2003), Tasmuth et al. (2002)

Head-to-head trials:

Amitriptyline vs Gabapentin (n=50): Morello et al. (1999)

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

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

Gabapentin vs Gabapentin+Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012)

Gabapentin vs Gabapentin+Oxycodone (n=338): Hanna et al. (2008)

Gabapentin vs Nortriptyline (n=182): Chandra et al. (2006), Gilron et al. (2012)

Imipramine vs Venlafaxine (n=80): Sindrup et al. (2003)

Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine, Nortriptyline vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

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

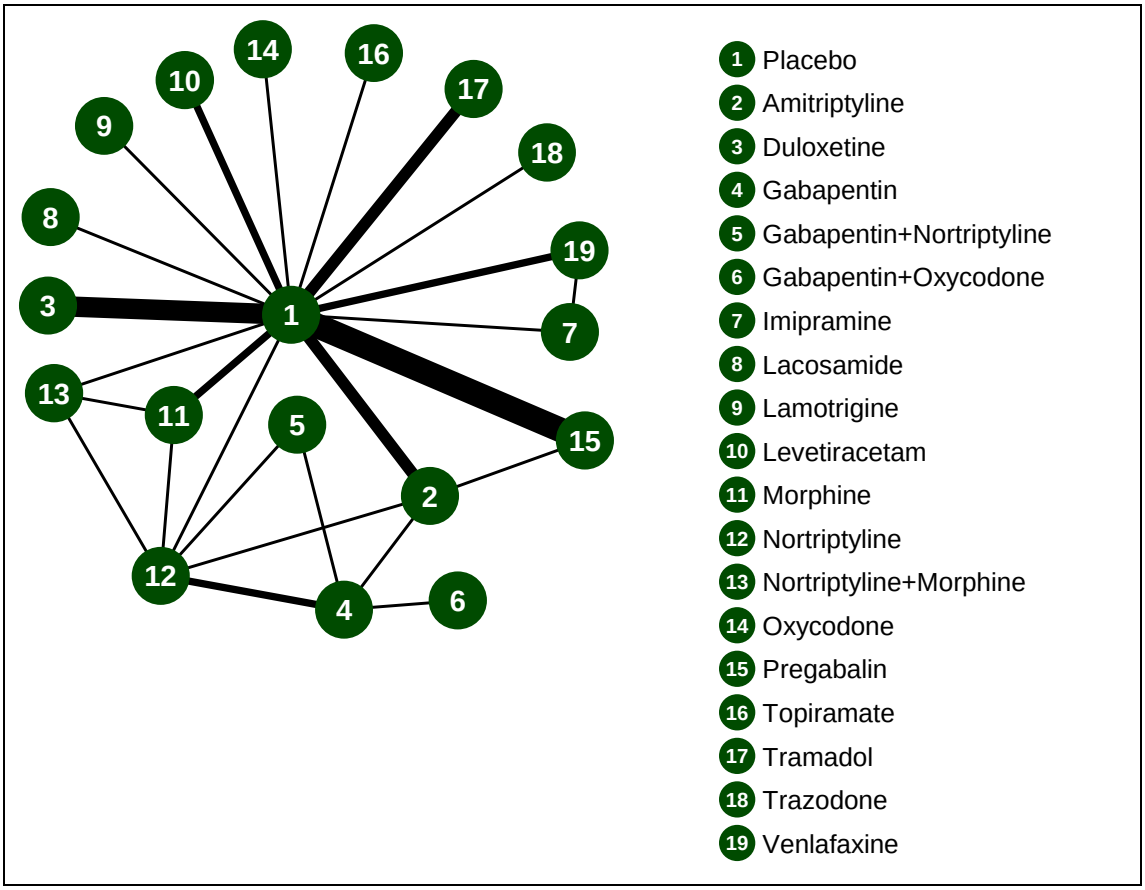

Figure 13 constipation - evidence network

Table 21 constipation - trials included in analysis

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone
Amitriptyline	3 RCTs[3,14,22] total n=149																	
Duloxetine	5 RCTs[7,10,30,32,34] total n=1392	-																
Gabapentin	-	1 RCT[18] total n=50	-															
Gabapentin +Nortriptyline	-	-	-	1 RCT[8] total n=112														
Gabapentin +Oxycodone	-	-	-	1 RCT[11] total n=338	-													
Imipramine	1 RCT[27] total n=80	-	-	-	-	-												
Lacosamide	1 RCT[20] total n=119	-	-	-	-	-	-											
Lamotrigine	1 RCT[2] total n=36	-	-	-	-	-	-	-										
Levetiracetam	2 RCTs[6,13] total n=138	-	-	-	-	-	-	-	-									
Morphine	2 RCTs[16,33] total n=222	-	-	-	-	-	-	-	-	-								
Nortriptyline	1 RCT[16] total n=110	1 RCT[31]	-	2 RCTs[4,8]	1 RCT[8] total	-	-	-	-	-	1 RCT[16]							

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone
		total n=66		total n=182	n=112						total n=110							
Nortriptyline +Morphine	1 RCT[16] total n=110	-	-	-	-	-	-	-	-	-	1 RCT[16] total n=110	1 RCT[16] total n=110						
Oxycodone	1 RCT[9] total n=159	-	-	-	-	-	-	-	-	-	-	-	-					
Pregabalin	6 RCTs[17,21,23,24,25,29] total n=1547	1 RCT[1] total n=102	-	-	-	-	-	-	-	-	-	-	-	-				
Topiramate	1 RCT[15] total n=82	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	3 RCTs[12,19,26] total n=256	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Trazodone	1 RCT[5] total n=18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Venlafaxine	2 RCTs[27,28] total n=110	-	-	-	-	-	1 RCT[27] total n=80	-	-	-	-	-	-	-	-	-	-	-

(1) Bansal et al. (2009); (2) Breuer et al. (2007); (3) Cardenas et al. (2002); (4) Chandra et al. (2006); (5) Davidoff et al. (1987); (6) Falah et al. (2012); (7) Gao et al. (2010); (8) Gilron et al. (2012); (9) Gimbel et al. (2003); (10) Goldstein et al. (2005); (11) Hanna et al. (2008); (12) Harati et al. (1998); (13) Holbech et al. (2011); (14) Kalso et al. (1995); (15) Khoromi et al. (2005); (16) Khoromi et al. (2007); (17) Lesser et al. (2004); (18) Morello et al. (1999); (19) Norrbrink & Lundeberg (2009); (20) Rauck et al. (2007); (21) Richter et al. (2005); (22) Robinson et al. (2004); (23) Rosenstock et al. (2004); (24) Satoh et al. (2011); (25) Siddall et al. (2006); (26) Sindrup et al. (1999); (27) Sindrup et al. (2003); (28) Tasmuth et al. (2002); (29) van Seventer et al. (2006); (30) Vranken et al. (2011); (31) Watson et al. (1998); (32) Wernicke et al. (2006); (33) Wu et al. (2008); (34) Yasuda et al. (2011)

Table 22 constipation - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine
Placebo		2.54 (0.70, 9.23)	1.92 (0.87, 4.24)	-	-	-	0.19 (0.01, 4.09)	0.13 (0.01, 2.64)	3.17 (0.12, 83.17)	0.95 (0.15, 6.05)	12.32 (4.20, 36.11)	3.86 (0.77, 19.51)	15.14 (3.33, 68.89)	4.47 (2.06, 9.69)	2.36 (1.23, 4.54)	7.55 (0.38, 150.87)	4.72 (1.92, 11.62)	1.00 (0.02, 55.80)	1.02 (0.25, 4.11)
Amitriptyline	2.35 (0.88, 6.59)		-	1.83 (0.39, 8.67)	-	-	-	-	-	-	-	1.69 (0.61, 4.67)	-	-	1.53 (0.24, 9.57)	-	-	-	-
Duloxetine	1.97 (0.88, 4.42)	0.84 (0.22, 2.96)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	1.82 (0.30, 11.16)	0.77 (0.15, 3.90)	0.92 (0.13, 6.72)		1.00 (0.06, 16.39)	5.77 (2.80, 11.91)	-	-	-	-	-	4.43 (0.23, 85.75)	-	-	-	-	-	-	-
Gabapentin +Nortriptyline	3.09 (0.07, 83.83)	1.32 (0.03, 32.08)	1.56 (0.03, 46.26)	1.72 (0.04, 39.19)		-	-	-	-	-	-	1.00 (0.06, 16.39)	-	-	-	-	-	-	-
Gabapentin +Oxycodone	10.83 (0.98, 132.80)	4.61 (0.46, 48.71)	5.51 (0.44, 76.87)	6.01 (1.14, 32.58)	3.55 (0.10, 205.40)		-	-	-	-	-	-	-	-	-	-	-	-	-
Imipramine	0.12 (0.00, 3.19)	0.05 (0.00, 1.58)	0.06 (0.00, 1.80)	0.06 (0.00, 2.91)	0.04 (0.00, 5.89)	0.01 (0.00, 0.68)		-	-	-	-	-	-	-	-	-	-	-	3.08 (0.12, 77.80)
Lacosamide	0.07 (0.00, 1.68)	0.03 (0.00, 0.82)	0.03 (0.00, 0.93)	0.03 (0.00, 1.50)	0.02 (0.00, 3.12)	0.01 (0.00, 0.34)	0.52 (0.00, 464.20)		-	-	-	-	-	-	-	-	-	-	-

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine
Lamotrigine	5.83 (0.13, 2442.00)	2.51 (0.05, 1079.00)	2.99 (0.06, 1299.00)	3.33 (0.05, 1719.00)	2.19 (0.01, 1831.00)	0.57 (0.01, 336.00)	62.39 (0.30, 246500.00)	121.50 (0.55, 451800.00)		-	-	-	-	-	-	-	-	-	-
Levetiracetam	0.94 (0.16, 5.36)	0.40 (0.05, 2.93)	0.47 (0.07, 3.24)	0.51 (0.04, 6.28)	0.31 (0.01, 19.38)	0.09 (0.00, 1.71)	8.08 (0.18, 3933.00)	15.20 (0.35, 8448.00)	0.15 (0.00, 10.70)		-	-	-	-	-	-	-	-	-
Morphine	16.29 (4.05, 72.91)	6.96 (1.43, 35.08)	8.27 (1.65, 45.64)	9.03 (1.17, 71.66)	5.33 (0.18, 252.30)	1.51 (0.10, 21.14)	140.40 (3.82, 68640.00)	262.90 (7.13, 146200.00)	2.74 (0.01, 170.10)	17.55 (1.86, 177.60)		0.30 (0.11, 0.79)	1.17 (0.53, 2.58)	-	-	-	-	-	-
Nortriptyline	5.72 (1.49, 23.55)	2.43 (0.68, 8.88)	2.90 (0.61, 14.85)	3.12 (0.67, 15.97)	1.83 (0.09, 68.97)	0.52 (0.05, 5.30)	48.96 (1.35, 22430.00)	90.81 (2.59, 49500.00)	0.96 (0.00, 58.32)	6.13 (0.68, 59.63)	0.35 (0.08, 1.64)		3.92 (1.49, 10.28)	-	-	-	-	-	-
Nortriptyline +Morphine	20.19 (3.66, 120.70)	8.61 (1.40, 54.02)	10.25 (1.57, 73.31)	11.14 (1.26, 102.40)	6.58 (0.21, 335.40)	1.86 (0.12, 28.77)	175.50 (4.12, 85310.00)	328.90 (7.70, 194200.00)	3.34 (0.01, 237.30)	21.69 (1.88, 265.90)	1.24 (0.24, 6.38)	3.55 (0.66, 18.79)		-	-	-	-	-	-
Oxycodone	4.60 (0.85, 25.42)	1.96 (0.27, 13.83)	2.33 (0.37, 15.58)	2.54 (0.21, 29.87)	1.51 (0.04, 92.93)	0.42 (0.02, 8.19)	39.29 (0.93, 19270.00)	73.95 (1.80, 43000.00)	0.77 (0.00, 51.47)	4.92 (0.44, 58.28)	0.28 (0.03, 2.53)	0.81 (0.09, 6.94)	0.23 (0.02, 2.51)		-	-	-	-	-
Pregabalin	2.86 (1.29, 6.69)	1.22 (0.36, 4.03)	1.45 (0.47, 4.72)	1.58 (0.23, 10.78)	0.93 (0.03, 44.42)	0.26 (0.02, 3.29)	23.62 (0.81, 10690.00)	44.56 (1.56, 22920.00)	0.49 (0.00, 24.52)	3.07 (0.45, 22.15)	0.18 (0.03, 0.88)	0.50 (0.10, 2.35)	0.14 (0.02, 0.93)	0.62 (0.10, 4.16)		-	-	-	-
Topiramate	15.78 (0.58, 9676.0	6.79 (0.21, 4340.0	8.12 (0.26, 5163.0	9.08 (0.20, 6728.0	5.91 (0.05, 8425.0	1.56 (0.02, 1356.0	178.90 (1.07, 885500.0	343.30 (2.10, 1496000.0	2.90 (0.00, 4023.0	17.80 (0.40, 12610.0	0.98 (0.03, 683.8	2.80 (0.07, 1908.0	0.81 (0.02, 580.7	3.60 (0.08, 2561.0	5.54 (0.18, 3549.0		-	-	-

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Gabapentin +Nortriptyline	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Topiramate	Tramadol	Trazodone	Venlafaxine
	0)	0)	0)	0)	0)	0)	0)	0)	0)	0)	0)	0)	0)	0)	0)				
Tramadol	5.37 (1.56, 19.74)	2.28 (0.46, 11.52)	2.73 (0.63, 12.59)	2.97 (0.33, 27.07)	1.76 (0.05, 96.29)	0.50 (0.03, 7.71)	45.53 (1.33, 21240.00)	85.62 (2.55, 46180.00)	0.91 (0.00, 52.36)	5.78 (0.68, 51.75)	0.33 (0.05, 2.22)	0.94 (0.14, 6.03)	0.26 (0.03, 2.26)	1.17 (0.14, 9.73)	1.88 (0.42, 8.61)	0.33 (0.00, 12.31)		-	-
Trazodone	0.96 (0.00, 725.30)	0.40 (0.00, 322.50)	0.49 (0.00, 386.00)	0.52 (0.00, 486.10)	0.32 (0.00, 621.80)	0.09 (0.00, 92.95)	9.54 (0.00, 50970.00)	18.15 (0.01, 121500.00)	0.14 (0.00, 329.80)	1.01 (0.00, 941.80)	0.06 (0.00, 48.80)	0.17 (0.00, 143.80)	0.05 (0.00, 42.14)	0.21 (0.00, 186.60)	0.33 (0.00, 263.00)	0.05 (0.00, 81.58)	0.18 (0.00, 149.4 0)		-
Venlafaxine	0.96 (0.17, 5.48)	0.41 (0.05, 2.94)	0.49 (0.07, 3.29)	0.53 (0.04, 6.34)	0.31 (0.01, 19.60)	0.09 (0.00, 1.71)	7.86 (0.29, 3391.00)	15.60 (0.36, 8930.00)	0.16 (0.00, 10.80)	1.03 (0.09, 12.33)	0.06 (0.01, 0.55)	0.17 (0.02, 1.50)	0.05 (0.00, 0.54)	0.21 (0.02, 2.33)	0.33 (0.05, 2.25)	0.06 (0.00, 2.65)	0.18 (0.02, 1.50)	1.00 (0.00, 1248.0 0)	

Values given are odds ratios.

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

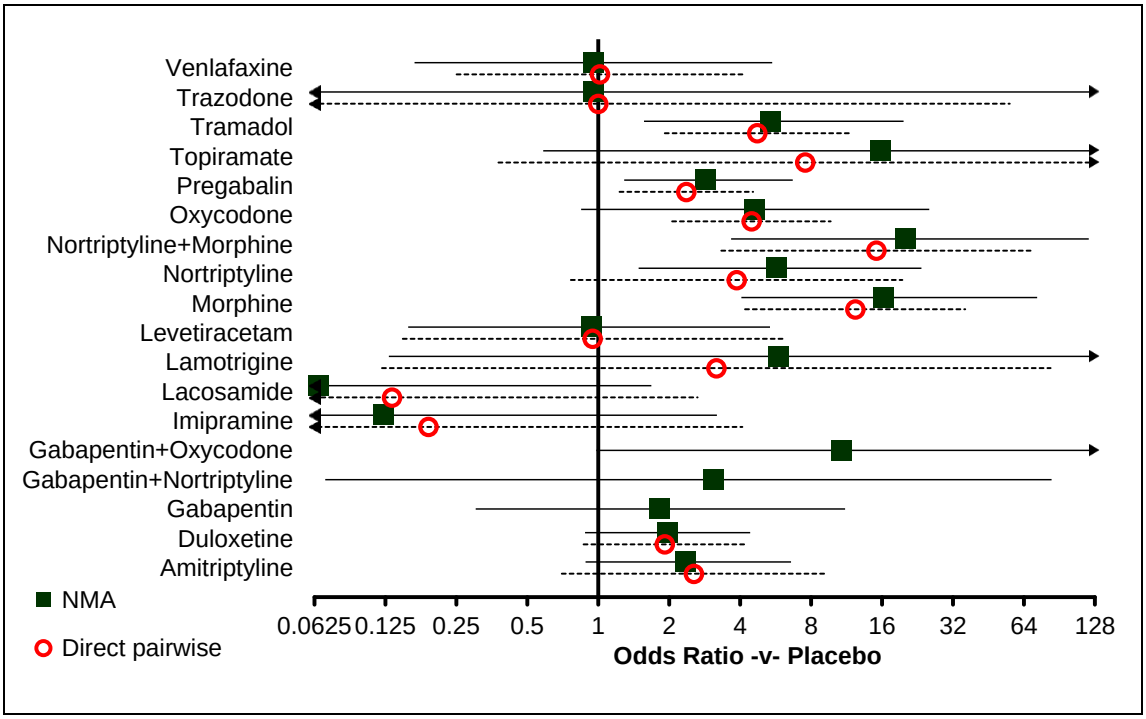

Figure 14 constipation - relative effect of all options compared with placebo

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

Table 23 constipation - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (3, 8)
Amitriptyline	0.000	9 (5, 14)
Duloxetine	0.000	8 (4, 13)
Gabapentin	0.002	8 (3, 15)
Gabapentin+Nortriptyline	0.019	11 (2, 19)
Gabapentin+Oxycodone	0.000	16 (6, 19)
Imipramine	0.333	2 (1, 11)
Lacosamide	0.478	2 (1, 7)
Lamotrigine	0.010	14 (2, 19)
Levetiracetam	0.012	5 (2, 13)
Morphine	0.000	17 (12, 19)
Nortriptyline	0.000	13 (8, 17)
Nortriptyline+Morphine	0.000	17 (12, 19)
Oxycodone	0.000	13 (5, 18)
Pregabalin	0.000	10 (6, 15)
Topiramate	0.001	17 (4, 19)
Tramadol	0.000	13 (7, 18)
Trazodone	0.136	5 (1, 19)
Venlafaxine	0.007	5 (2, 14)

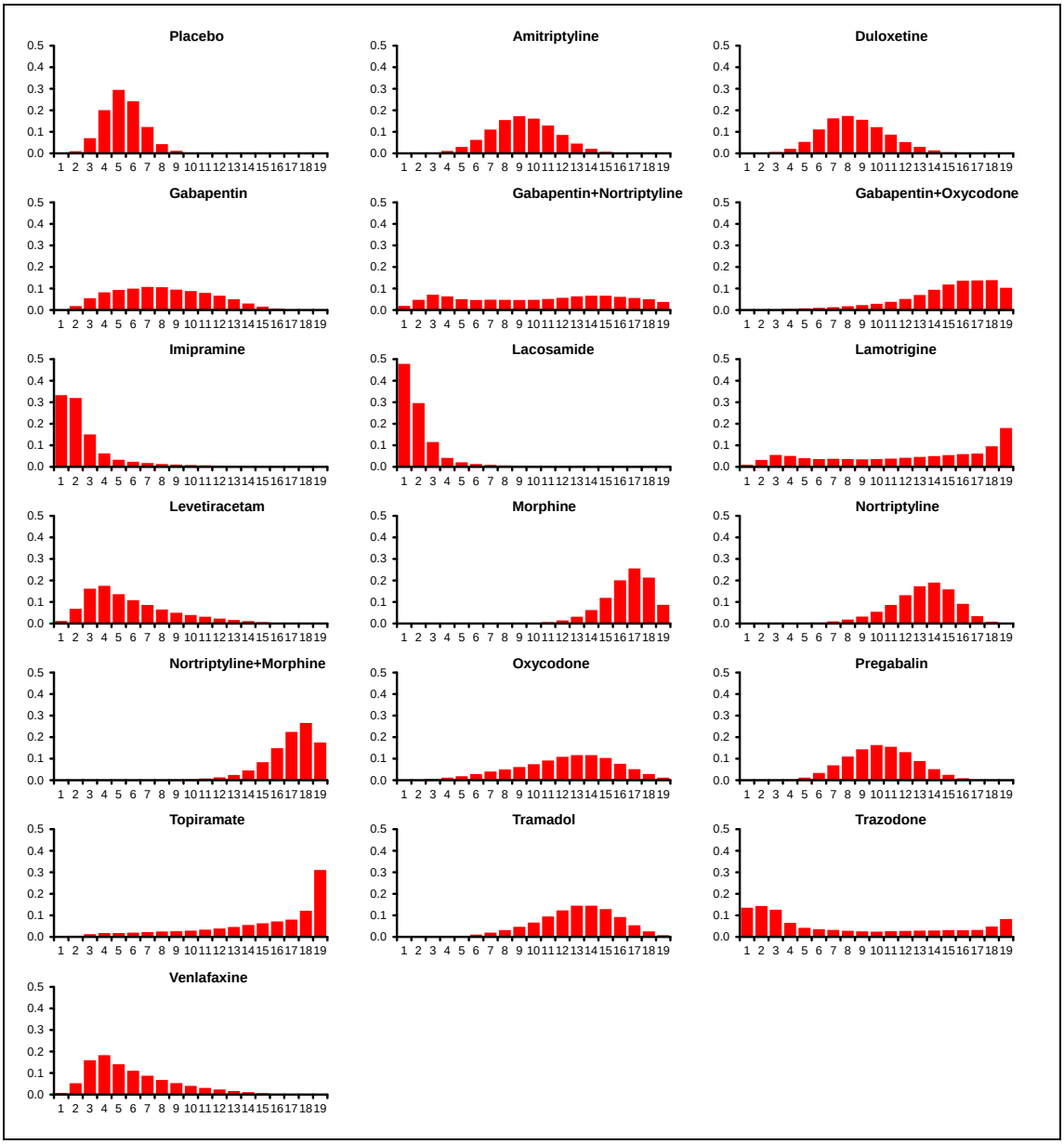

Figure 15 constipation - rank probability histograms

Table 24 constipation - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
86.02 (compared to 82 data-points)	335.552	271.288	64.264	399.815	0.337 (95%CrI: 0.110, 1.433)

Table 25 constipation - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- It was not possible to include the results from Huse (2001) in the synthesis because the study recorded the intensity of adverse events on a visual

analogue scale (from ‘not at all’ to extremely) rather than the proportion of patients who reported the event which the majority of the other studies reported.

- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- Model convergence: topiramate and trazodone have poor autocorrelation because there is only one study with low event rates for these interventions.

Summary GRADE profile 3f: nausea

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Nausea	56 RCTs[a] n=11769	Very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] allocation concealment was inadequate in 1 study and unclear in 30 studies; there is uncertainty about comparability at baseline between groups in 31 studies and there are differences between groups in 4 studies (particularly for use of concomitant drugs); during 23 studies, it was unclear if the same care was received by each group and in 6 studies the same care was not received (these were usually to do with concomitant drug and rescue medication use); average baseline severity ranged from 3.9 to 7.7 on a 11-point scale across the network; concomitant drugs permitted varies across the studies in the network; insufficient follow-up in 18 studies

[2] I^2 was 63%, 48%, 34%, and 27% for pregabalin vs placebo, duloxetine vs placebo, amitriptyline vs placebo, and capsaicin patch vs placebo, respectively. This may indicate that any heterogeneity in the first comparison may be moderate to substantial, in the second comparison may be moderate, and in the third and fourth might not be important; indirect and direct estimates appear relatively similar

[3] all aspects of PICO conform to review protocol

[4] few head-to-head trials; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=94): Kalso et al. (1995), Vrethem et al. (1997)

Cannabis Sativa Extract (n=191): Nurmikko et al. (2007), Rog et al. (2005)

Capsaicin Patch (n=1918): Backonja et al. (2008), Clifford et al. (2012), Irving et al. (2011), Simpson et al. (2008), Webster et al. (2010)

Duloxetine (n=1344): Gao et al. (2010), Goldstein et al. (2005), Wernicke et al. (2006), Yasuda et al. (2011)

Gabapentin (n=559): Backonja et al. (1998), Bone et al. (2002), Hahn et al. (2004), Levendoglu et al. (2004), Rao et al. (2007), Simpson (2001)

Imipramine (n=80): Sindrup et al. (2003)

Lacosamide (n=1314): Rauck et al. (2007), Shaibani et al. (2009), Wymer et al. (2009), Ziegler et al. (2010)

Lamotrigine (n=1125): Eisenberg et al. (2001), Rao et al. (2008), Simpson et al. (2003), Vinik et al. (2007), Vinik et al. (2007)

Levetiracetam (n=158): Falah et al. (2012), Holbech et al. (2011), Rossi et al. (2009)

Morphine (n=222): Khoromi et al. (2007), Wu et al. (2008)

Nortriptyline, Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxcarbazepine (n=634): Beydoun et al. (2006), Dogra et al. (2005), Grosskopf et al. (2006)

Oxycodone (n=159): Gimbel et al. (2003)

Pregabalin (n=892): Freynhagen et al. (2005), Rosenstock et al. (2004), van Seventer et al. (2006), Vranken et al. (2008)

Valproate (n=84): Agrawal et al. (2009), Kochar et al. (2004)

Topiramate (n=1592): Raskin et al. (2004), Thienel et al. (2004)

Tramadol (n=381): Boureau et al. (2003), Harati et al. (1998), Norrbrink & Lundeberg (2009), Sindrup et al. (1999)

Venlafaxine (n=355): Rowbotham et al. (2004), Sindrup et al. (2003), Tasmuth et al. (2002)

Capsaicin Cream (n=143): Watson et al. (1993)

Head-to-head trials:

Amitriptyline vs Gabapentin (n=50): Morello et al. (1999)

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

Gabapentin vs Gabapentin+Oxycodone (n=338): Hanna et al. (2008)

Imipramine vs Venlafaxine (n=80): Sindrup et al. (2003)

Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine, Nortriptyline vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

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

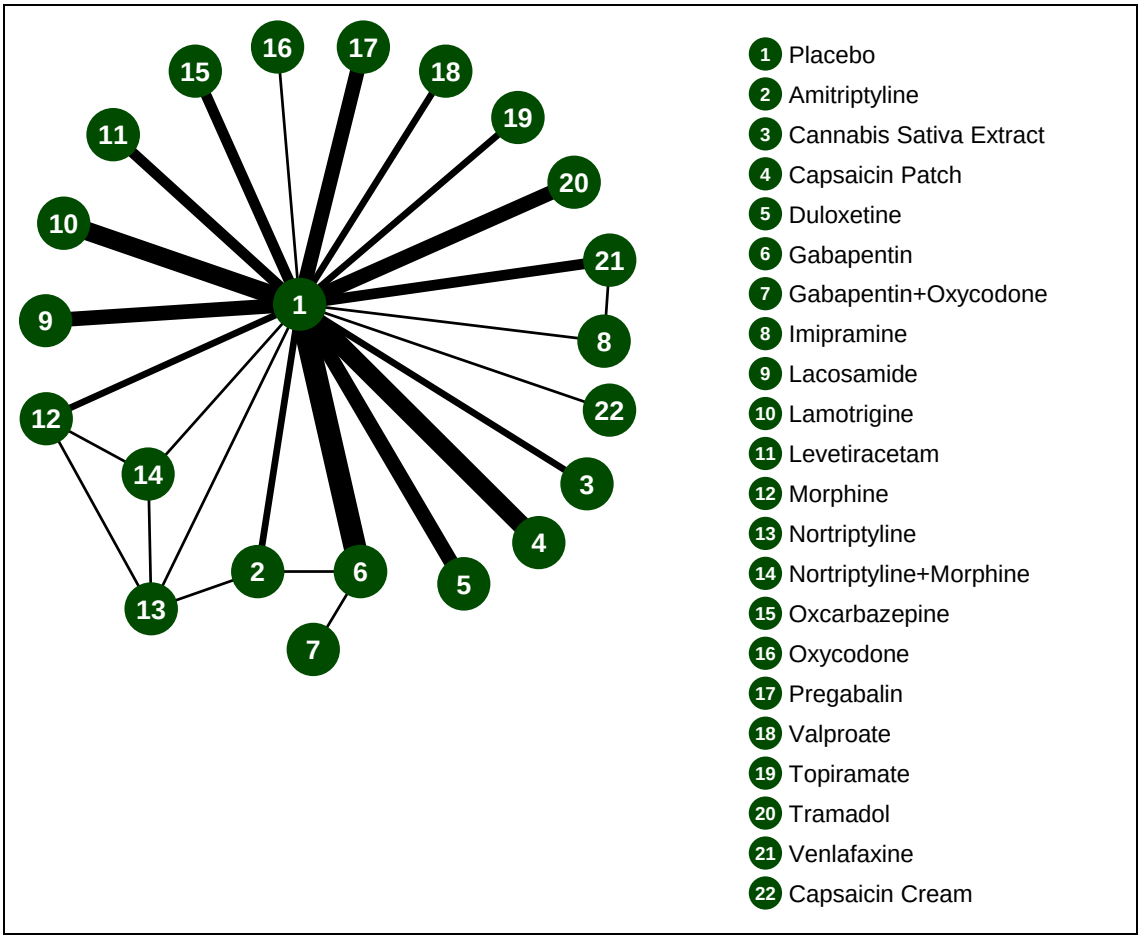

Figure 16 nausea - evidence network

Table 26 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[21,48] total n=94																				
Cannabis Sativa Extract	2 RCTs[27,32] total n=191	-																			
Capsaicin Patch	5 RCTs[3,7,20,39,51] total n=1918	-	-																		
Duloxetine	4 RCTs[12,14,52,55] total n=1344	-	-	-																	
Gabapentin	6 RCTs[2,5,16,24,28,37] total n=559	1 RCT[25] total n=50	-	-	-																
Gabapentin +Oxycodone	-	-	-	-	-	1 RCT[17] total n=338															
Imipramine	1 RCT[41] total n=80	-	-	-	-	-	-														
Lacosamide	4 RCTs[31,36,54,56] total n=1314	-	-	-	-	-	-	-													
Lamotrigine	5 RCTs[9,29,38,45,46] total n=1125	-	-	-	-	-	-	-	-												
Levetiracetam	3 RCTs[10,19,34] total n=158	-	-	-	-	-	-	-	-	-											
Morphine	2 RCTs[22,53] total n=222	-	-	-	-	-	-	-	-	-	-										

	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
Nortriptyline	1 RCT[22] total n=110	1 RCT[50] total n=66	-	-	-	-	-	-	-	-	-	1 RCT[22] total n=110									
Nortriptyline +Morphine	1 RCT[22] total n=110	-	-	-	-	-	-	-	-	-	-	1 RCT[22] total n=110	1 RCT[22] total n=110								
Oxcarbazepine	3 RCTs[4,8,15] total n=634	-	-	-	-	-	-	-	-	-	-	-	-	-							
Oxycodone	1 RCT[13] total n=159	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Pregabalin	4 RCTs[11,33,44,47] total n=892	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
Valproate	2 RCTs[1,23] total n=84	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Topiramate	2 RCTs[30,43] total n=1592	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	4 RCTs[6,18,26,40] total n=381	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Venlafaxine	3 RCTs[35,41,42] 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.

	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
(2011); (21) Kalso et al. (1995); (22) Khoromi et al. (2007); (23) Kochar et al. (2004); (24) Levendoglu et al. (2004); (25) Morello et al. (1999); (26) Norrbrink & Lundeberg (2009); (27) Nurmikko et al. (2007); (28) Rao et al. (2007); (29) Rao et al. (2008); (30) Raskin et al. (2004); (31) Rauck et al. (2007); (32) Rog et al. (2005); (33) Rosenstock et al. (2004); (34) Rossi et al. (2009); (35) Rowbotham et al. (2004); (36) Shaibani et al. (2009); (37) Simpson (2001); (38) Simpson et al. (2003); (39) Simpson et al. (2008); (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)																				

Table 27 nausea - relative effectiveness of all pairwise combinations

	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	0.64 (0.13, 2.97)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	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	1.94 (0.64, 5.82)	3.06 (0.47, 20.37)		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	1.48 (0.77, 2.96)	2.38 (0.43, 12.86)	0.77 (0.21, 2.77)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duloxetine	3.71 (2.18, 6.58)	5.81 (1.16, 31.63)	1.91 (0.57, 6.65)	2.49 (1.05, 5.96)		N/A	N/A	N/A	N/A	N/A	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	1.15 (0.51, 2.61)	1.82 (0.36, 9.28)	0.59 (0.15, 2.36)	0.76 (0.27, 2.24)	0.31 (0.11, 0.83)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gabapentin +Oxycodone	3.02 (0.80, 11.29)	4.77 (0.71, 33.40)	1.56 (0.28, 8.80)	2.02 (0.47, 8.76)	0.82 (0.19, 3.41)	2.63 (0.94, 7.54)		N/A	N/A	N/A	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	2.82 (0.58, 14.01)	4.44 (0.51, 42.59)	1.46 (0.21, 9.86)	1.90 (0.33, 10.73)	0.76 (0.14, 4.20)	2.46 (0.41, 15.20)	0.93 (0.12, 7.57)		N/A	N/A	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	1.76 (0.94, 3.44)	2.80 (0.53, 15.43)	0.91 (0.26, 3.31)	1.19 (0.46, 2.99)	0.47 (0.20, 1.12)	1.54 (0.56, 4.44)	0.58 (0.14, 2.58)	0.63 (0.11, 3.47)		N/A	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	Gabapentin	Gabapentin +Oxycodone	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Oxycodone	Pregabalin	Valproate	Topiramate	Tramadol	Venlafaxine	Capsaicin Cream
Lamotrigine	1.08 (0.60, 1.96)	1.71 (0.32, 9.26)	0.56 (0.16, 1.92)	0.73 (0.29, 1.77)	0.29 (0.13, 0.65)	0.95 (0.34, 2.55)	0.36 (0.08, 1.52)	0.38 (0.07, 2.09)	0.61 (0.25, 1.47)		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	2.00 (0.55, 8.83)	3.19 (0.42, 29.22)	1.05 (0.19, 6.56)	1.35 (0.31, 6.70)	0.54 (0.13, 2.57)	1.75 (0.38, 9.08)	0.67 (0.11, 4.62)	0.72 (0.09, 6.14)	1.14 (0.27, 5.74)	1.84 (0.45, 9.53)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morphine	4.67 (0.84, 38.87)	7.65 (0.74, 91.42)	2.48 (0.31, 25.89)	3.16 (0.49, 27.69)	1.27 (0.21, 10.95)	4.13 (0.59, 37.94)	1.58 (0.17, 18.31)	1.71 (0.16, 22.33)	2.68 (0.42, 23.92)	4.34 (0.70, 38.14)	2.30 (0.25, 28.29)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline	0.27 (0.01, 3.73)	0.43 (0.01, 5.76)	0.14 (0.00, 2.32)	0.18 (0.00, 2.77)	0.07 (0.00, 1.04)	0.23 (0.01, 3.63)	0.09 (0.00, 1.68)	0.09 (0.00, 2.06)	0.15 (0.00, 2.37)	0.25 (0.01, 3.66)	0.13 (0.00, 2.56)	0.06 (0.00, 0.88)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nortriptyline +Morphine	2.36 (0.12, 38.78)	3.90 (0.13, 82.31)	1.23 (0.05, 23.85)	1.58 (0.07, 27.61)	0.64 (0.03, 10.69)	2.07 (0.09, 36.70)	0.79 (0.03, 16.35)	0.83 (0.03, 20.25)	1.33 (0.06, 23.80)	2.17 (0.10, 39.17)	1.13 (0.05, 26.81)	0.52 (0.03, 4.50)	8.93 (0.27, 600.80)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxcarbazepine	2.32 (0.87, 6.62)	3.71 (0.61, 23.31)	1.20 (0.28, 5.39)	1.56 (0.47, 5.45)	0.63 (0.20, 2.04)	2.03 (0.58, 7.64)	0.77 (0.15, 4.15)	0.82 (0.13, 5.58)	1.32 (0.40, 4.43)	2.15 (0.69, 7.08)	1.16 (0.19, 6.23)	0.49 (0.05, 3.69)	8.75 (0.50, 361.80)	1.00 (0.05, 24.37)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Oxycodone	5.89 (1.73, 22.18)	9.43 (1.30, 70.37)	3.06 (0.59, 16.89)	3.98 (0.97, 17.15)	1.60 (0.41, 6.64)	5.16 (1.19, 24.28)	1.95 (0.32, 12.84)	2.10 (0.27, 16.73)	3.35 (0.84, 14.68)	5.45 (1.38, 23.60)	2.93 (0.45, 19.03)	1.24 (0.11, 11.09)	22.51 (1.17, 1043.00)	2.52 (0.12, 64.31)	2.53 (0.51, 13.25)		N/A	N/A	N/A	N/A	N/A	N/A
Pregabalin	1.08 (0.51, 2.29)	1.71 (0.31, 9.65)	0.56 (0.15, 2.10)	0.72 (0.26, 1.94)	0.29 (0.11, 0.73)	0.94 (0.31, 2.84)	0.36 (0.08, 1.61)	0.38 (0.07, 2.19)	0.61 (0.22, 1.66)	1.00 (0.39, 2.54)	0.53 (0.10, 2.42)	0.23 (0.02, 1.53)	4.08 (0.25, 162.30)	0.46 (0.03, 9.88)	0.46 (0.13, 1.59)	0.18 (0.04, 0.77)		N/A	N/A	N/A	N/A	N/A
Valproate	3.63 (0.53, 40.95)	5.86 (0.48, 101.70)	1.92 (0.20, 26.39)	2.47 (0.31, 28.92)	0.98 (0.13, 11.83)	3.20 (0.39, 38.95)	1.22 (0.12, 17.77)	1.31 (0.10, 21.89)	2.05 (0.27, 25.95)	3.40 (0.43, 41.31)	1.82 (0.16, 26.33)	0.78 (0.04, 14.76)	14.42 (0.47, 912.90)	1.59 (0.05, 69.11)	1.56 (0.17, 21.76)	0.62 (0.06, 9.33)	3.42 (0.41, 43.19)		N/A	N/A	N/A	N/A
Topiramate	1.75	2.76	0.91	1.18	0.47	1.53	0.58	0.62	0.99	1.62	0.87	0.37	6.59	0.75	0.75	0.30	1.62	0.48		N/A	N/A	N/

	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
	(0.88, 3.52)	(0.51, 15.56)	(0.24, 3.36)	(0.44, 3.06)	(0.19, 1.14)	(0.51, 4.45)	(0.13, 2.63)	(0.11, 3.39)	(0.38, 2.55)	(0.66, 4.04)	(0.17, 3.84)	(0.04, 2.48)	(0.43, 255.50)	(0.04, 16.34)	(0.22, 2.52)	(0.07, 1.22)	(0.59, 4.53)	(0.04, 3.84)				A
Tramadol	4.17 (1.94, 9.54)	6.67 (1.17, 37.32)	2.16 (0.57, 8.71)	2.80 (1.00, 8.08)	1.13 (0.43, 3.02)	3.67 (1.17, 11.37)	1.39 (0.29, 6.67)	1.48 (0.25, 8.85)	2.37 (0.85, 6.66)	3.87 (1.44, 10.69)	2.08 (0.39, 9.85)	0.89 (0.09, 6.07)	15.97 (0.99, 620.10)	1.78 (0.10, 42.09)	1.79 (0.49, 6.52)	0.70 (0.15, 3.12)	3.87 (1.31, 11.87)	1.15 (0.09, 9.71)	2.38 (0.86, 7.02)		N/A	N/A
Venlafaxine	2.79 (1.12, 7.45)	4.43 (0.76, 28.88)	1.46 (0.35, 6.16)	1.88 (0.61, 6.09)	0.75 (0.26, 2.33)	2.45 (0.72, 8.59)	0.93 (0.19, 4.76)	0.99 (0.23, 4.48)	1.60 (0.51, 5.07)	2.58 (0.87, 8.12)	1.40 (0.24, 7.05)	0.59 (0.06, 4.23)	10.53 (0.65, 420.00)	1.20 (0.07, 27.27)	1.22 (0.31, 4.64)	0.47 (0.10, 2.35)	2.60 (0.81, 8.82)	0.76 (0.06, 6.91)	1.61 (0.51, 5.27)	0.67 (0.20, 2.29)		N/A
Capsaicin Cream	9.25 (0.43, 6354.00)	15.02 (0.46, 13370.00)	4.83 (0.18, 3828.00)	6.23 (0.27, 4544.00)	2.50 (0.11, 1724.00)	8.18 (0.32, 6076.00)	3.15 (0.11, 2597.00)	3.40 (0.10, 2990.00)	5.22 (0.22, 3671.00)	8.68 (0.37, 5765.00)	4.69 (0.14, 3135.00)	1.97 (0.04, 1688.00)	38.11 (0.56, 69710.00)	4.23 (0.06, 4826.00)	4.05 (0.15, 2851.00)	1.63 (0.05, 1228.00)	8.70 (0.36, 6231.00)	2.58 (0.05, 2926.00)	5.36 (0.22, 3936.00)	2.25 (0.09, 1519.00)	3.36 (0.12, 2505.00)	

Values given are hazard ratios.

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

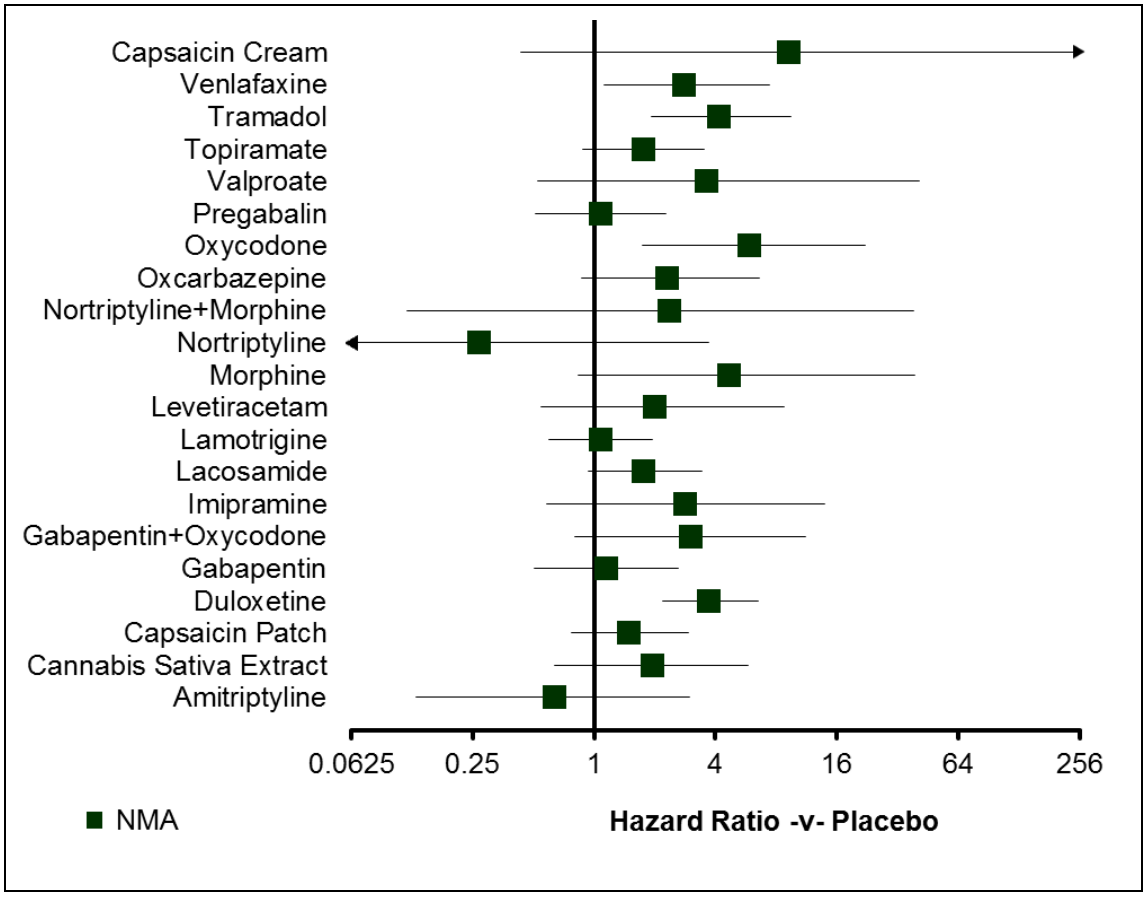

Figure 17 nausea - relative effect of all options compared with placebo

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

Table 28 nausea - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.006	5 (2, 8)
Amitriptyline	0.154	2 (1, 15)
Cannabis Sativa Extract	0.008	11 (2, 20)
Capsaicin Patch	0.005	9 (3, 16)
Duloxetine	0.000	17 (12, 21)
Gabapentin	0.020	6 (2, 14)
Gabapentin+Oxycodone	0.002	15 (4, 22)
Imipramine	0.009	15 (2, 22)
Lacosamide	0.001	10 (4, 17)
Lamotrigine	0.021	6 (2, 12)
Levetiracetam	0.013	12 (2, 21)
Morphine	0.001	18 (4, 22)
Nortriptyline	0.631	1 (1, 16)
Nortriptyline+Morphine	0.064	13 (1, 22)
Oxcarbazepine	0.002	13 (4, 20)
Oxycodone	0.000	20 (10, 22)
Pregabalin	0.032	6 (1, 13)
Valproate	0.014	17 (2, 22)
Topiramate	0.002	10 (4, 17)
Tramadol	0.000	18 (11, 22)
Venlafaxine	0.000	15 (6, 21)
Capsaicin Cream	0.017	21 (2, 22)

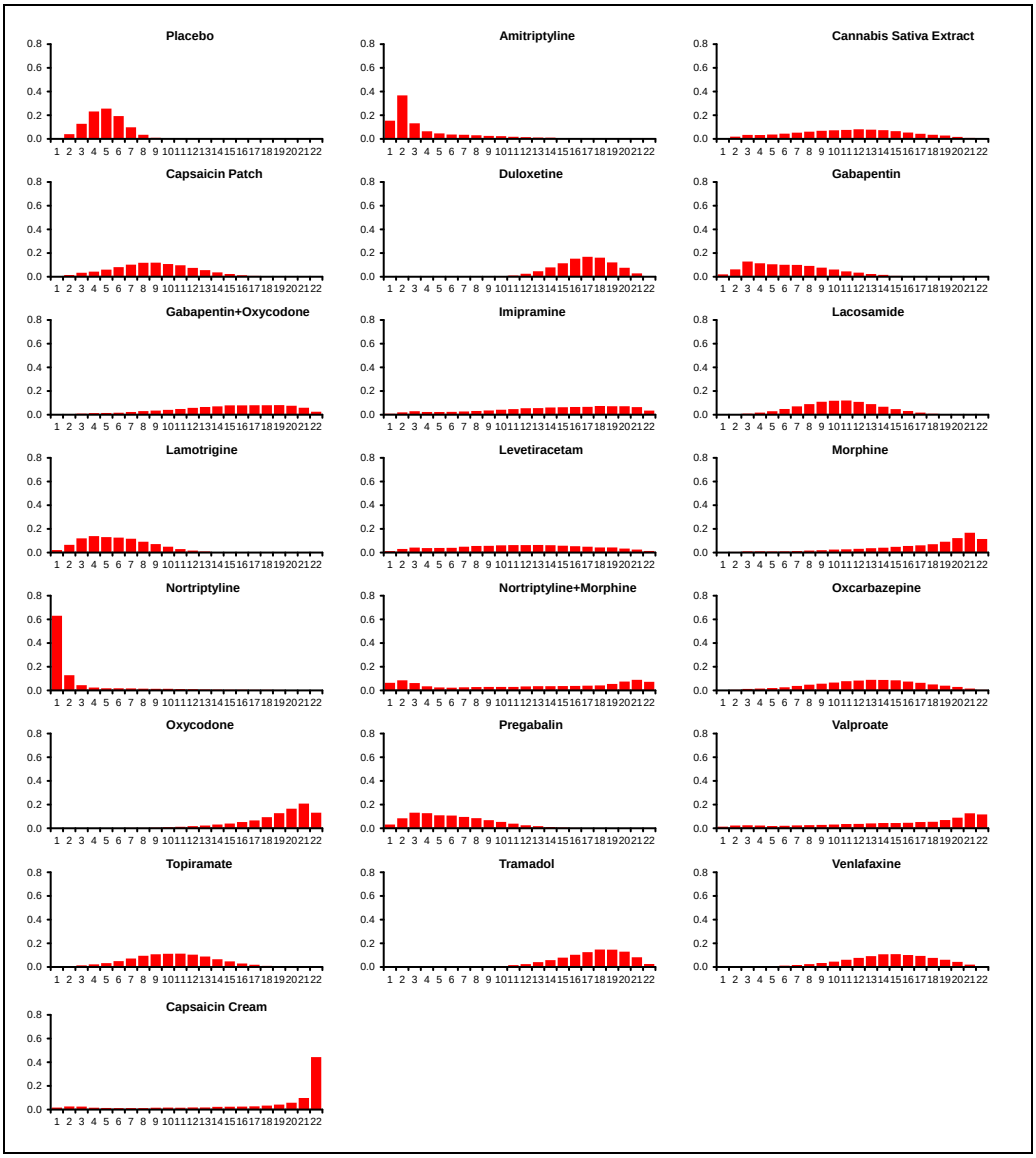

Figure 18 nausea - rank probability histograms

Table 29 nausea - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
138.5 (compared to 140 data-points)	594.372	498.29	96.082	690.453	0.148 (95%CI: 0.054, 0.436)

Table 30 nausea - notes

- Log–log ('cloglog') model used as the results from this analysis were used in the health economic model (this is explained in Appendix K).
- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.

- It was not possible to include the results from Huse (2001) in the synthesis because the study recorded the intensity of adverse events on a visual analogue scale (from ‘not at all’ to extremely) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- Model convergence: there was poor autocorrelation for capsaicin cream since there was one study with small event rates and for nortriptyline, morphine and nortriptyline+morphine because the data for these interventions came mostly from one 3-armed trial with low event rates.

Summary GRADE profile 3g: vomiting

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Vomiting	19 RCTs[a] n=4553	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] allocation concealment was unclear in 9 studies and inadequate 1 study; there is uncertainty about comparability at baseline between groups in 9 studies and in 4 there were differences in groups at baseline (particularly for use of concomitant drugs); during 11 studies, it was unclear if the same care was received by each group and in 2 studies different care was received in each group (these were usually to do with concomitant drug and rescue medication use); mean baseline severity ranged from 3.95 to 8.8 on a normalised 11-point scale across the studies in the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 40% for duloxetine vs placebo which may indicate that any heterogeneity between the studies that make this comparison might not be important; appeared to be consistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] only one head-to-head trial; most links have one study; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Cannabis Sativa Extract (n=191): Nurmikko et al. (2007), Rog et al. (2005)

Capsaicin Patch (n=1424): Backonja et al. (2008), Irving et al. (2011), Simpson et al. (2008), Webster et al. (2010)

Duloxetine (n=553): Gao et al. (2010), Yasuda et al. (2011)

Gabapentin (n=270): Levendoglu et al. (2004), Rao et al. (2007)

Lacosamide (n=825): Shaibani et al. (2009), Ziegler et al. (2010)

Lamotrigine (n=125): Rao et al. (2008)

Oxcarbazepine (n=146): Dogra et al. (2005)

Oxycodone (n=159): Gimbel et al. (2003)

Pregabalin (n=146): Rosenstock et al. (2004)

Tramadol (n=131): Harati et al. (1998)

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

Head-to-head trials:

Gabapentin vs Gabapentin+Oxycodone (n=338): Hanna et al. (2008)

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

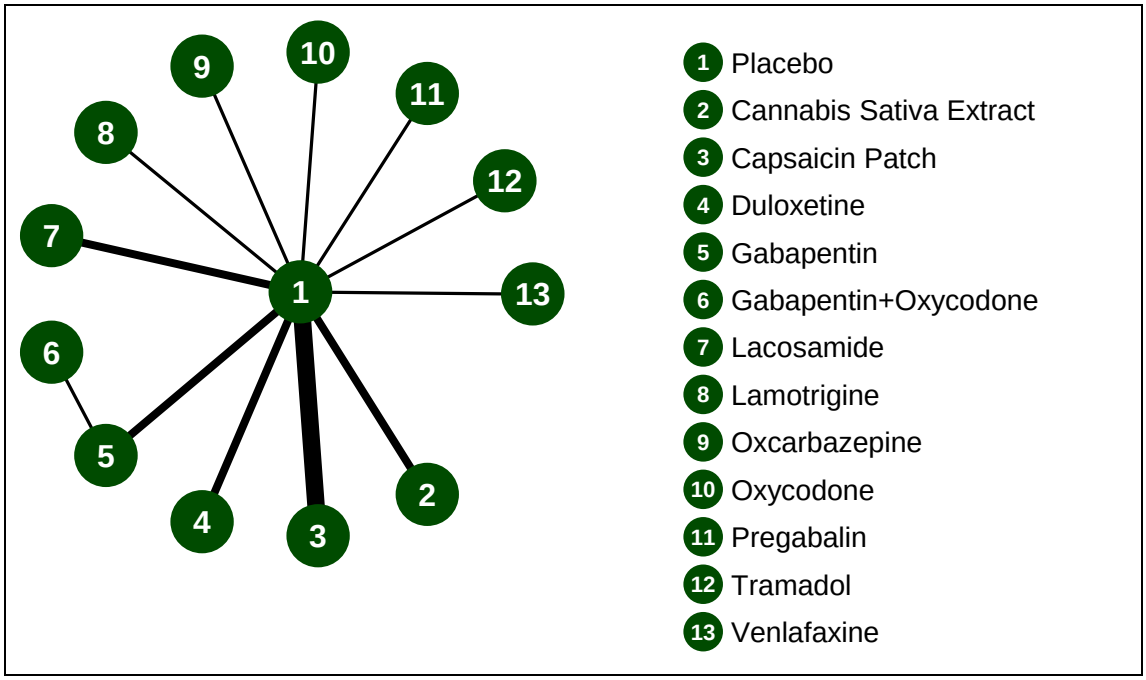

Figure 19 vomiting - evidence network

Table 31 vomiting - trials included in analysis

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Oxcarbazepine	Oxycodone	Pregabalin	Tramadol
Cannabis Sativa Extract	2 RCTs[9,12] total n=191											
Capsaicin Patch	4 RCTs[1,7,16,17] total n=1424	-										
Duloxetine	2 RCTs[3,18] total n=553	-	-									
Gabapentin	2 RCTs[8,10] total n=270	-	-	-								
Gabapentin +Oxycodone	-	-	-	-	1 RCT[5] total n=338							
Lacosamide	2 RCTs[15,19] total n=825	-	-	-	-	-						
Lamotrigine	1 RCT[11] total n=125	-	-	-	-	-	-					
Oxcarbazepine	1 RCT[2] total n=146	-	-	-	-	-	-	-				
Oxycodone	1 RCT[4] total n=159	-	-	-	-	-	-	-	-			
Pregabalin	1 RCT[13] total n=146	-	-	-	-	-	-	-	-	-		
Tramadol	1 RCT[6] total n=131	-	-	-	-	-	-	-	-	-	-	
Venlafaxine	1 RCT[14] total n=245	-	-	-	-	-	-	-	-	-	-	-

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Oxcarbazepine	Oxycodone	Pregabalin	Tramadol
(1) Backonja et al. (2008); (2) Dogra et al. (2005); (3) Gao et al. (2010); (4) Gimbel et al. (2003); (5) Hanna et al. (2008); (6) Harati et al. (1998); (7) Irving et al. (2011); (8) Levendoglu et al. (2004); (9) Nurmikko et al. (2007); (10) Rao et al. (2007); (11) Rao et al. (2008); (12) Rog et al. (2005); (13) Rosenstock et al. (2004); (14) Rowbotham et al. (2004); (15) Shaibani et al. (2009); (16) Simpson et al. (2008); (17) Webster et al. (2010); (18) Yasuda et al. (2011); (19) Ziegler et al. (2010)												

Table 32 vomiting - relative effectiveness of all pairwise combinations

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Oxcarbazepine	Oxycodone	Pregabalin	Tramadol	Venlafaxine
Placebo		2.87 (0.81, 10.18)	1.83 (0.43, 7.72)	2.18 (0.62, 7.71)	0.56 (0.11, 2.70)	-	5.53 (0.74, 41.21)	0.64 (0.10, 4.00)	2.27 (0.20, 25.59)	9.81 (2.18, 44.06)	2.84 (0.29, 27.92)	7.45 (0.38, 147.11)	9.96 (0.57, 173.26)
Cannabis Sativa Extract	3.26 (0.57, 22.41)		-	-	-	-	-	-	-	-	-	-	-
Capsaicin Patch	2.35 (0.70, 8.33)	0.73 (0.08, 6.07)		-	-	-	-	-	-	-	-	-	-
Duloxetine	2.43 (0.63, 10.69)	0.74 (0.07, 7.31)	1.03 (0.17, 7.02)		-	-	-	-	-	-	-	-	-
Gabapentin	0.47 (0.05, 3.62)	0.14 (0.01, 2.07)	0.20 (0.02, 2.15)	0.19 (0.01, 2.18)		2.42 (0.97, 6.04)	-	-	-	-	-	-	-
Gabapentin	1.21	0.37	0.51	0.49	2.54		-	-	-	-	-	-	-

	Placebo	Cannabis Sativa Extract	Capsaicin Patch	Duloxetine	Gabapentin	Gabapentin +Oxycodone	Lacosamide	Lamotrigine	Oxcarbazepine	Oxycodone	Pregabalin	Tramadol	Venlafaxine
+Oxycodone	(0.07, 17.72)	(0.01, 8.93)	(0.02, 9.91)	(0.02, 9.70)	(0.41, 15.61)								
Lacosamide	8.32 (1.14, 571.00)	2.68 (0.15, 234.00)	3.65 (0.34, 283.70)	3.50 (0.29, 271.60)	19.07 (1.01, 1866.00)	7.72 (0.24, 1113.00)		-	-	-	-	-	-
Lamotrigine	0.59 (0.04, 6.84)	0.18 (0.01, 3.67)	0.25 (0.01, 3.87)	0.24 (0.01, 4.03)	1.26 (0.05, 33.89)	0.49 (0.01, 20.60)	0.06 (0.00, 1.62)		-	-	-	-	-
Oxcarbazepine	2.82 (0.14, 146.10)	0.87 (0.02, 66.62)	1.21 (0.05, 78.07)	1.17 (0.04, 70.84)	6.16 (0.17, 528.50)	2.41 (0.04, 300.20)	0.32 (0.00, 26.88)	5.01 (0.10, 577.40)		-	-	-	-
Oxycodone	12.25 (1.52, 146.80)	3.83 (0.22, 77.10)	5.24 (0.45, 81.63)	5.07 (0.39, 83.42)	26.37 (1.49, 701.60)	10.38 (0.35, 451.80)	1.42 (0.01, 34.46)	21.49 (0.81, 750.50)	4.43 (0.05, 197.30)		-	-	-
Pregabalin	3.71 (0.23, 152.20)	1.16 (0.04, 71.50)	1.59 (0.07, 77.70)	1.55 (0.07, 81.61)	8.22 (0.26, 584.70)	3.26 (0.07, 331.60)	0.43 (0.00, 29.95)	6.64 (0.16, 613.90)	1.32 (0.01, 154.10)	0.30 (0.01, 22.71)		-	-
Tramadol	16.02 (0.62, 6010.00)	5.22 (0.10, 2403.00)	7.07 (0.21, 2840.00)	6.78 (0.19, 2901.00)	38.07 (0.70, 16650.00)	15.44 (0.18, 7934.00)	1.83 (0.01, 1040.00)	30.79 (0.42, 16670.00)	6.04 (0.04, 4040.00)	1.37 (0.02, 686.00)	4.53 (0.03, 2607.00)		-
Venlafaxine	22.81 (1.26, 8102.00)	7.18 (0.21, 3018.00)	9.90 (0.41, 3551.00)	9.71 (0.36, 3842.00)	51.31 (1.32, 22700.00)	20.73 (0.35, 11340.00)	2.62 (0.02, 1307.00)	42.42 (0.87, 22510.00)	8.92 (0.06, 5944.00)	1.91 (0.04, 973.60)	6.45 (0.06, 3872.00)	1.48 (0.00, 975.10)	

Values given are odds ratios.

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

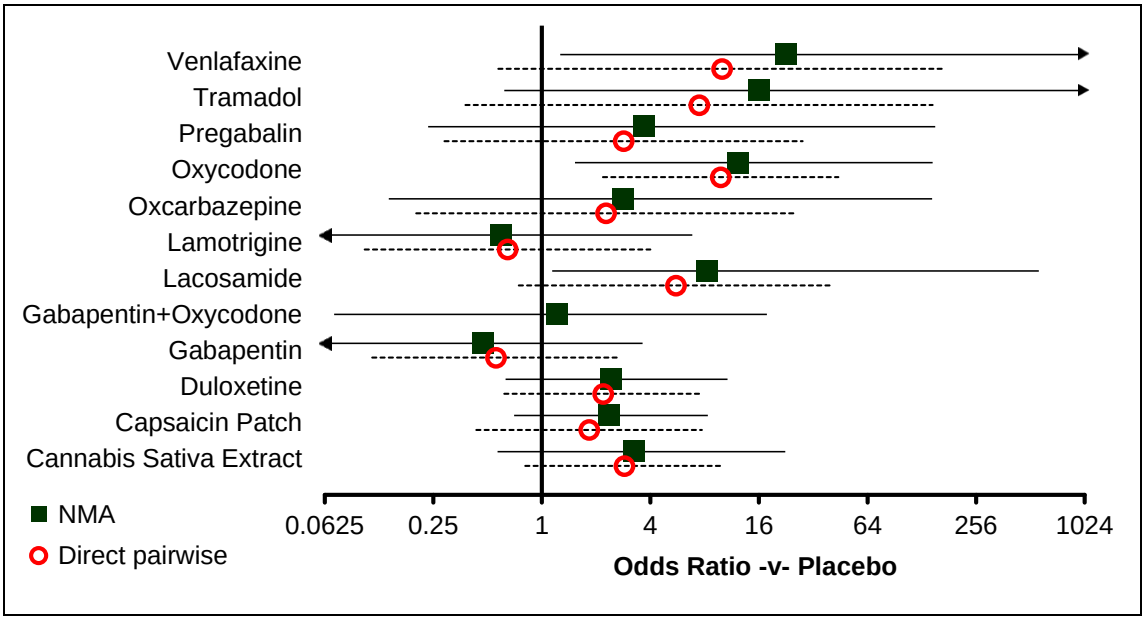

Figure 20 vomiting - relative effect of all options compared with placebo

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

Table 33 vomiting - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.033	4 (1, 6)
Cannabis Sativa Extract	0.011	8 (2, 12)
Capsaicin Patch	0.006	7 (2, 10)
Duloxetine	0.008	7 (2, 11)
Gabapentin	0.392	2 (1, 7)
Gabapentin+Oxycodone	0.066	4 (1, 11)
Lacosamide	0.002	10 (4, 13)
Lamotrigine	0.350	2 (1, 10)
Oxcarbazepine	0.075	7 (1, 13)
Oxycodone	0.002	11 (5, 13)
Pregabalin	0.043	8 (1, 13)
Tramadol	0.009	11 (3, 13)
Venlafaxine	0.002	12 (5, 13)

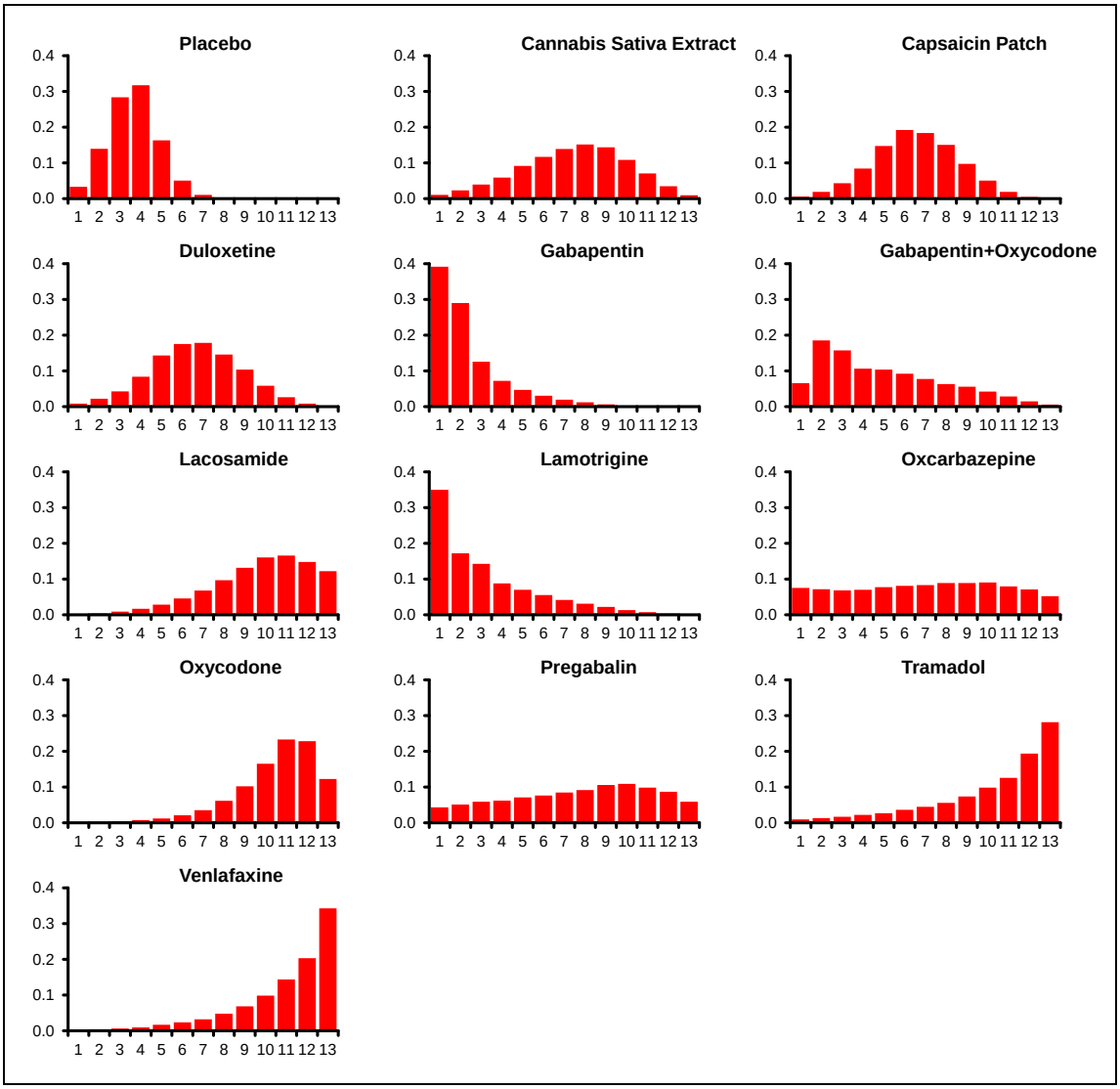

Figure 21 vomiting - rank probability histograms

Table 34 vomiting - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
45.09 (compared to 43 data-points)	166.659	132.781	33.878	200.537	0.001 (95%CI: 0.001, 2.606)

Table 35 vomiting - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times)

rather than the proportion of patients who reported the event which the majority of the other studies reported.

- Poor autocorrelation for lacosamide, tramadol, venlafaxine because small numbers of events in the single studies with each intervention.

Summary GRADE profile 3h: pruritus

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Pruritus	11 RCTs[a] n=3127	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear about randomisation method in 7 studies; there is uncertainty about comparability at baseline between groups in 6 studies and there are differences between groups at baseline in 2 studies (particularly for use of concomitant drugs); during 6 studies, it was unclear if the same care was received by each group and in 2 studies different care was received (these were usually to do with concomitant drug and rescue medication use); concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for capsaicin patch vs placebo which may indicate no heterogeneity between the studies that form this comparison (heterogeneity not possible for comparisons with only one trial); no loops so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] no head-to-head trials; most links have one study; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] Capsaicin Patch (n=2074): Backonja et al. (2008), Clifford et al. (2012), Irving et al. (2011), Simpson et al. (2008), Webster et al. (2010), Webster et al. (2010)

Duloxetine (n=215): Gao et al. (2010)

Lacosamide (n=468): Shaibani et al. (2009)

Oxycodone (n=159): Gimbel et al. (2003)

Tramadol (n=131): Harati et al. (1998)

Capsaicin Cream (n=80): Low et al. (1995)

[all compared to placebo]

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

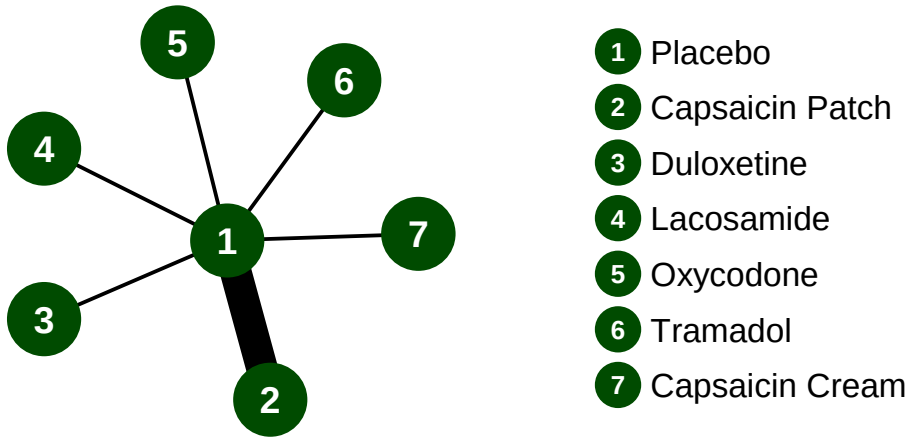

Figure 22 pruritus - evidence network

Table 36 pruritus - trials included in analysis

	Placebo	Capsaicin Patch	Duloxetine	Lacosamide	Oxycodone	Tramadol
Capsaicin Patch	6 RCTs[1,2,6,9,10,11] total n=2074					
Duloxetine	1 RCT[3] total n=215	-				
Lacosamide	1 RCT[8] total n=468	-	-			
Oxycodone	1 RCT[4] total n=159	-	-	-		
Tramadol	1 RCT[5] total n=131	-	-	-	-	
Capsaicin Cream	1 RCT[7] total n=80	-	-	-	-	-

(1) Backonja et al. (2008); (2) Clifford et al. (2012); (3) Gao et al. (2010); (4) Gimbel et al. (2003); (5) Harati et al. (1998); (6) Irving et al. (2011); (7) Low et al. (1995); (8) Shaibani et al. (2009); (9) Simpson et al. (2008); (10) Webster et al. (2010); (11) Webster et al. (2010)

Table 37 pruritus - relative effectiveness of all pairwise combinations

	Placebo	Capsaicin Patch	Duloxetine	Lacosamide	Oxycodone	Tramadol	Capsaicin Cream
Placebo		1.61 (0.94, 2.76	0.37 (0.09, 1.43)	3.70 (0.49, 27.90)	3.82 (1.44, 10.11)	9.73 (0.51, 184.50)	2.11 (0.36, 12.24)
Capsaicin Patch	1.62 (0.96, 2.81)		-	-	-	-	-
Duloxetine	0.34 (0.06, 1.62)	0.20 (0.03, 1.09)		-	-	-	-
Lacosamide	5.03 (0.77, 126.90)	3.10 (0.44, 83.11)	16.07 (1.24, 579.90)		-	-	-
Oxycodone	4.04 (1.14, 15.88)	2.48 (0.62, 10.68)	12.27 (1.59, 110.80)	0.79 (0.02, 8.23)		-	-
Tramadol	18.45 (1.11, 6585.00)	11.48 (0.64, 4132.00)	60.05 (2.17, 26400.00)	3.70 (0.05, 1722.00)	4.71 (0.20, 1766.00)		-
Capsaicin Cream	2.33 (0.30, 23.15)	1.42 (0.17, 15.12)	7.08 (0.56, 120.70)	0.44 (0.01, 9.11)	0.58 (0.05, 7.70)	0.12 (0.00, 4.98)	

Values given are odds ratios.

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

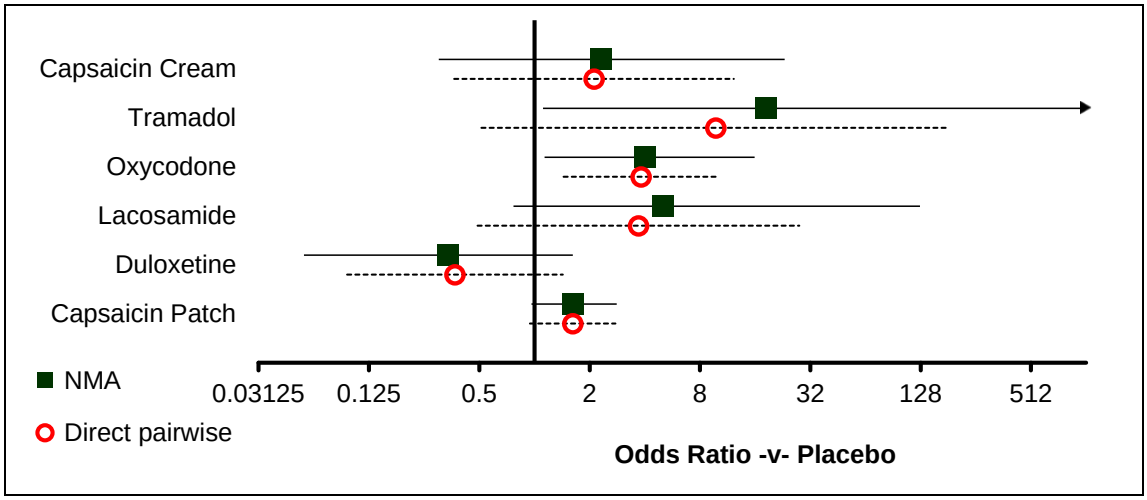

Figure 23 pruritus - relative effect of all options compared with placebo

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

Table 38 pruritus - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.059	2 (1, 4)
Capsaicin Patch	0.004	3 (2, 5)
Duloxetine	0.870	1 (1, 3)
Lacosamide	0.008	6 (2, 7)
Oxycodone	0.003	5 (3, 7)
Tramadol	0.004	7 (3, 7)
Capsaicin Cream	0.052	4 (1, 7)

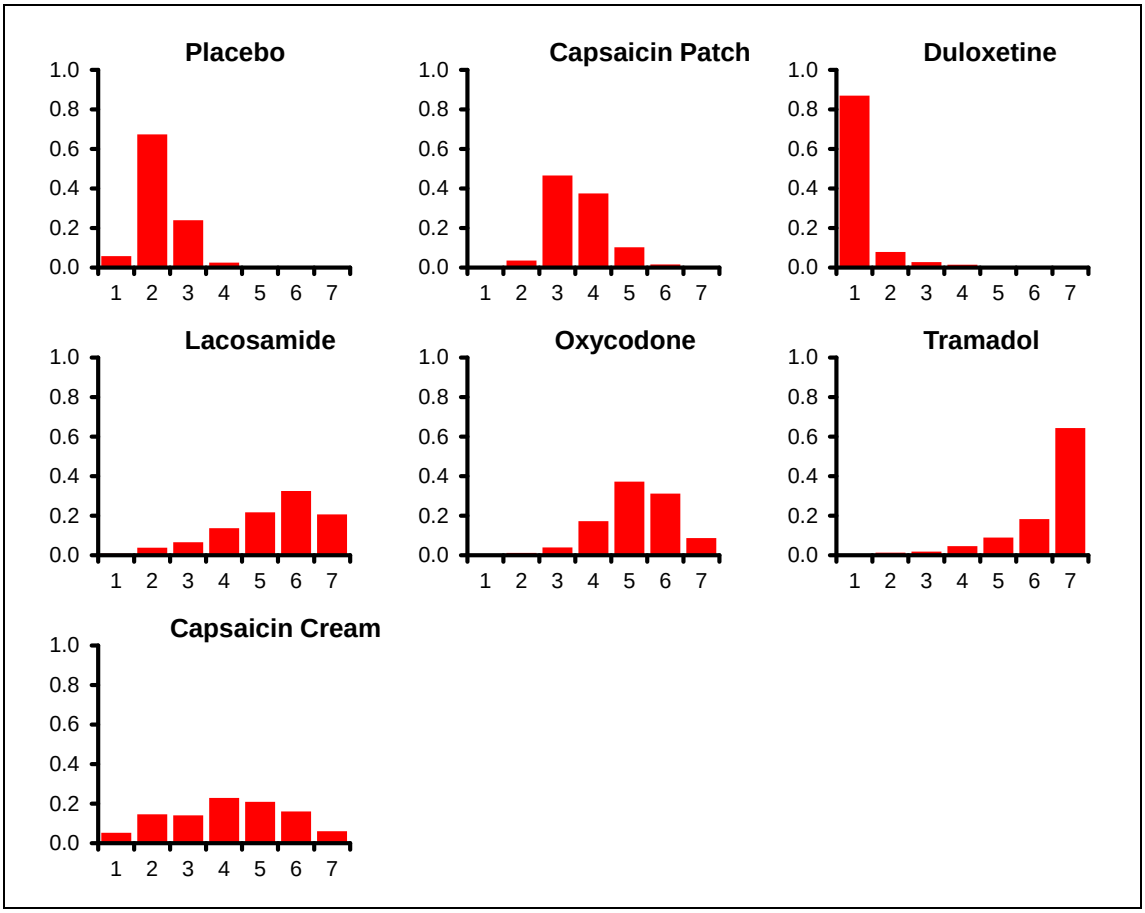

Figure 24 pruritus - rank probability histograms

Table 39 pruritus - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
27.31 (compared to 28 data-points)	123.145	103.492	19.653	142.798	0.000 (95%CI: 0.000, 0.880)

Table 40 pruritus - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- Not possible to include Gilron (2009) and Morello (1999) in the synthesis because they were not connected to the any interventions in the network.
- Model convergence: autocorrelation problems for lacosamide and tramadol because both interventions had only one study connecting them to the network and they had low event rates.

Summary GRADE profile 3i: burning pain

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Burning pain	12 RCTs[a] n=1470	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear about randomisation method in 6 studies and allocation concealment in 8 studies; there is uncertainty about comparability at baseline between groups in 6 studies and there are differences between groups at baseline in 2 studies (particularly for use of concomitant drugs); during 10 studies, it was unclear if the same care was received by each group (these were usually to do with concomitant drug and rescue medication use); mean baseline severity ranged from 3.95 to 8.4 on a normalised 11-point scale across the studies in the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 28% for capsaicin patch vs placebo which may indicate no heterogeneity between the studies that make this comparison; no loops so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] only one head-to-head trial; most links have one study; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Cannabis Sativa Extract (n=66): Rog et al. (2005)

Capsaicin Patch (n=462): Simpson et al. (2008), Webster et al. (2010)

Capsaicin Cream (n=707): Bernstein et al. (1989), Donofrio & Capsaicin study (1992), Low et al. (1995), McCleane (2000), Scheffler et al. (1991), Tandan et al. (1992), Watson & Evans (1992), Watson et al. (1993)

Head-to-head trials:

Amitriptyline vs Capsaicin Cream (n=235): Biesbroeck et al. (1995)

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

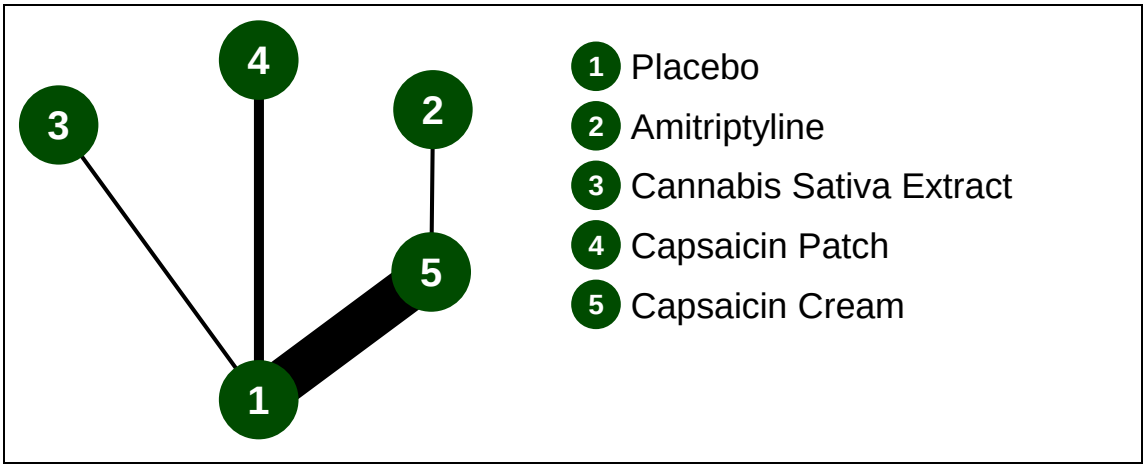

Figure 25 burning pain - evidence network

Table 41 burning pain - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Capsaicin Cream
Placebo		-	0.30 (0.01, 7.75)	3.53 (0.94, 13.33)	5.25 (3.37, 8.19)
Amitriptyline	0.06 (0.01, 0.43)		-	-	78.20 (18.44, 331.65)
Cannabis Sativa Extract	0.18 (0.00, 7.10)	2.97 (0.00, 237.60)		-	-
Capsaicin Patch	4.12 (0.89, 29.94)	73.45 (5.68, 1504.00)	24.61 (0.43, 18920.00)		-
Capsaicin Cream	5.76 (3.25, 11.23)	95.64 (15.52, 973.60)	32.46 (0.78, 21770.00)	1.40 (0.18, 7.51)	

(1) Bernstein et al. (1989); (2) Biesbroeck et al. (1995); (3) Donofrio & Capsaicin study (1992); (4) Low et al. (1995); (5) McCleane (2000); (6) Rog et al. (2005); (7) Scheffler et al. (1991); (8) Simpson et al. (2008); (9) Tandan et al. (1992); (10) Watson & Evans (1992); (11) Watson et al. (1993); (12) Webster et al. (2010)

Table 42 burning pain - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Capsaicin Cream
Placebo		-	0.30 (0.01, 7.75)	3.53 (0.94, 13.33)	5.25 (3.37, 8.19)
Amitriptyline	0.06 (0.01, 0.43)		-	-	78.20 (18.44, 331.65)
Cannabis Sativa Extract	0.18 (0.00, 7.10)	2.97 (0.00, 237.60)		-	-
Capsaicin Patch	4.12 (0.89, 29.94)	73.45 (5.68, 1504.00)	24.61 (0.43, 18920.00)		-
Capsaicin Cream	5.76 (3.25, 11.23)	95.64 (15.52, 973.60)	32.46 (0.78, 21770.00)	1.40 (0.18, 7.51)	

Values given are odds ratios.

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

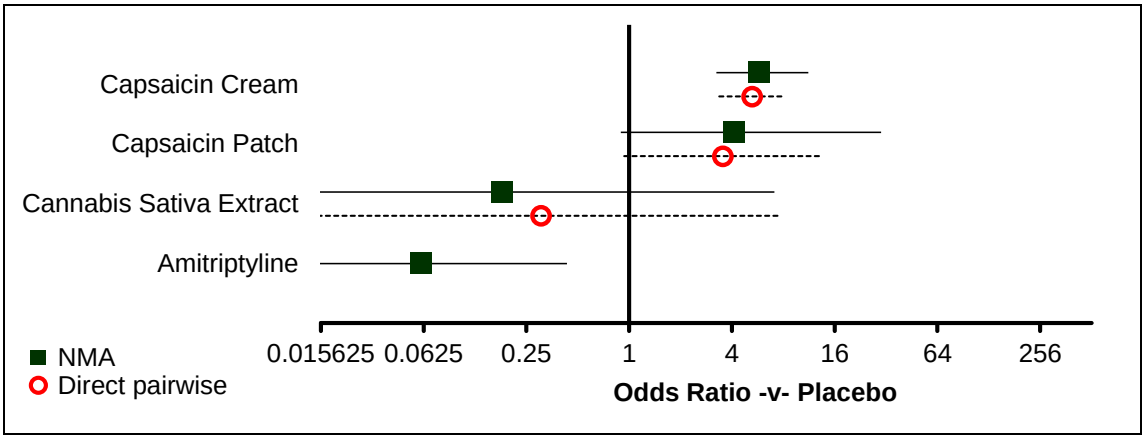

Figure 26 burning pain - relative effect of all options compared with placebo

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

Table 43 burning pain - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.001	3 (2, 4)
Amitriptyline	0.666	1 (1, 2)
Cannabis Sativa Extract	0.332	2 (1, 5)
Capsaicin Patch	0.001	4 (3, 5)
Capsaicin Cream	0.000	5 (4, 5)

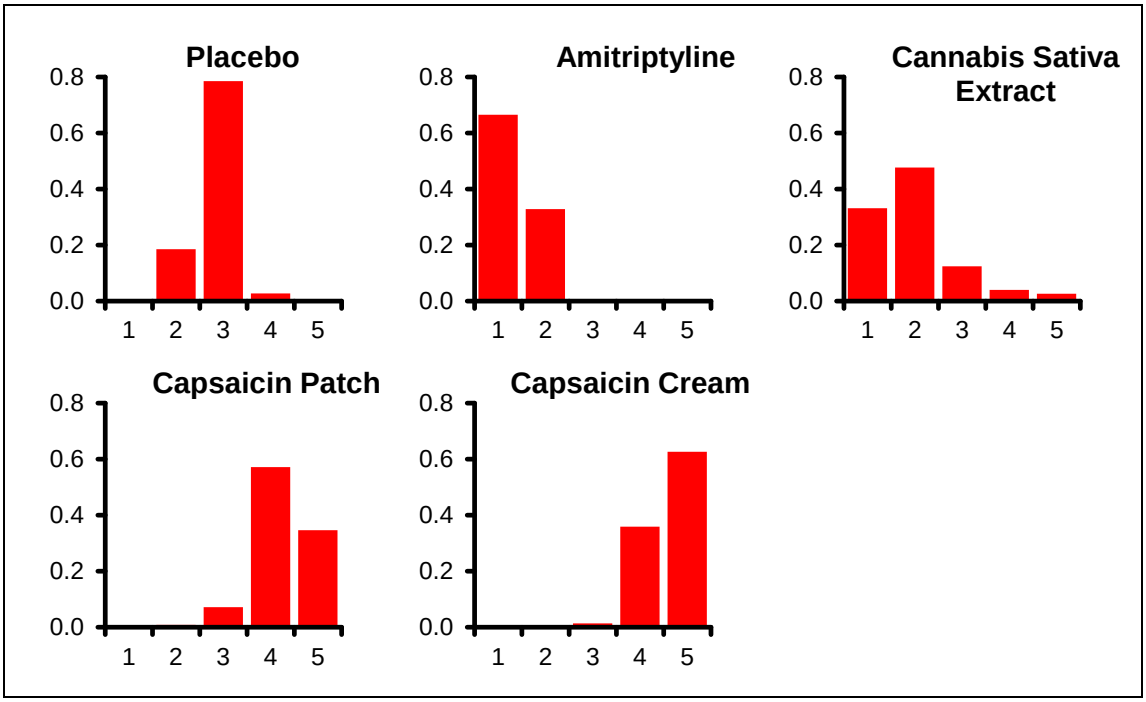

Figure 27 burning pain - rank probability histograms

Table 44 burning pain - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
24.29 (compared to 24 data-points)	104.988	85.961	19.028	124.016	0.000 (95%CI: 0.001, 2.107)

Table 45 burning pain - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- Model convergence: poor autocorrelation for lacosamide and tramadol due to one study with low event rates for both interventions.

Summary GRADE profile 3j: Rash/urticarial/overall erythema (not restricted to site)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Rash/urticarial/overall erythema (not restricted to site)	16 RCTs[a] n=3360	Very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear about randomisation method in 8 studies and allocation concealment in 10 studies; during 9 studies, it was unclear if the same care was received by each group and in 1 study different care was received (these were usually to do with concomitant drug and rescue medication use); mean baseline severity ranged from 4.5 to 8.4 on a normalised 11-point scale across the studies in the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 90% for pregabalin vs placebo which may indicate substantial heterogeneity between the studies that make this comparison; no loops so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] no head-to-head trials; half of the links had only one trial; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] Amitriptyline (n=68): Vrethem et al. (1997)

Capsaicin Patch (n=1373): Clifford et al. (2012), Irving et al. (2011), Simpson et al. (2008), Webster et al. (2010)

Gabapentin (n=230): Rao et al. (2007)

Lamotrigine (n=1201): Breuer et al. (2007), Eisenberg et al. (2001), Luria et al. (2000), Rao et al. (2008), Simpson et al. (2003), Vinik et al. (2007), Vinik et al. (2007)

Tramadol (n=131): Harati et al. (1998)

Capsaicin Cream (n=357): Donofrio & Capsaicin study (1992), Low et al. (1995)

(all compared to placebo)

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

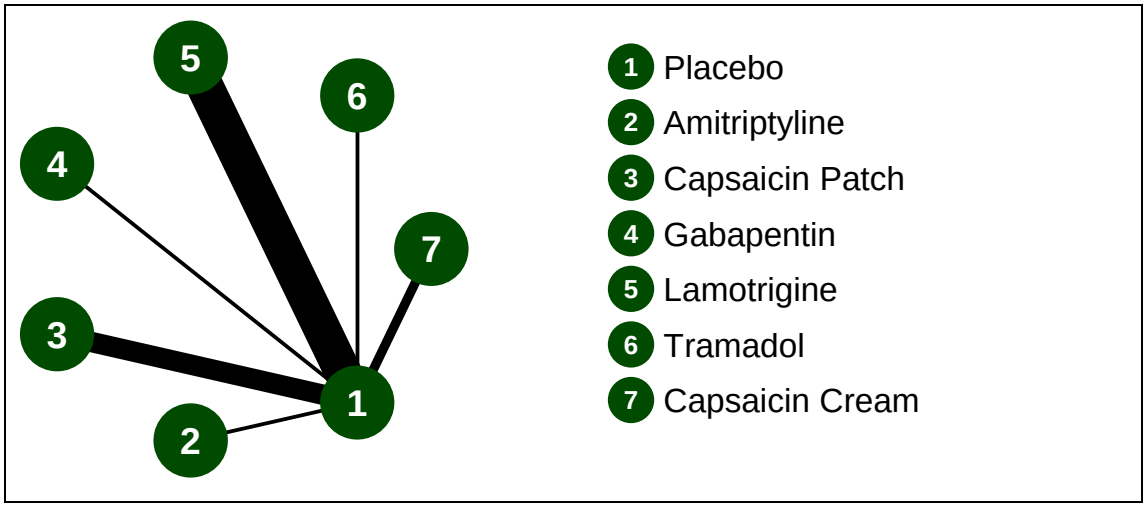

Figure 28 Rash, urticaria, erythema - evidence network

Table 46 Rash, urticaria, erythema - trials included in analysis

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Lamotrigine	Tramadol
Amitriptyline	1 RCT[15] total n=68					
Capsaicin Patch	4 RCTs[2,6,12,16] total n=1373	-				
Gabapentin	1 RCT[9] total n=230	-	-			
Lamotrigine	7 RCTs[1,4,8,10,11,13,14] total n=1201	-	-	-		
Tramadol	1 RCT[5] total n=131	-	-	-	-	
Capsaicin Cream	2 RCTs[3,7] total n=357	-	-	-	-	-

(1) Breuer et al. (2007); (2) Clifford et al. (2012); (3) Donofrio & Capsaicin study (1992); (4) Eisenberg et al. (2001); (5) Harati et al. (1998); (6) Irving et al. (2011); (7) Low et al. (1995); (8) Luria et al. (2000); (9) Rao et al. (2007); (10) Rao et al. (2008); (11) Simpson et al. (2003); (12) Simpson et al. (2008); (13) Vinik et al. (2007); (14) Vinik et al. (2007); (15) Vrethem et al. (1997); (16) Webster et al. (2010)

Table 47 Rash, urticaria, erythema - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Lamotrigine	Tramadol	Capsaicin Cream
Placebo		0.94 (0.02, 48.92)	1.59 (0.26, 9.91)	7.19 (0.37, 140.72)	1.48 (0.94, 2.33)	9.73 (0.51, 184.50)	2.69 (0.88, 8.17)
Amitriptyline	0.98 (0.00, 684.10)		-	-	-	-	-
Capsaicin Patch	1.50 (0.52, 3.70)	1.53 (0.00, 913.40)		-	-	-	-
Gabapentin	16.52 (0.62, 9249.00)	21.42 (0.01, 99360.00)	11.32 (0.38, 6660.00)		-	-	-
Lamotrigine	1.79 (0.88, 4.19)	1.86 (0.00, 1076.00)	1.19 (0.38, 4.92)	0.11 (0.00, 3.35)		-	-
Tramadol	19.53 (0.86, 9062.00)	24.46 (0.02, 121700.00)	13.18 (0.52, 6683.00)	1.19 (0.00, 1090.00)	10.85 (0.42, 5149.00)		-
Capsaicin Cream	2.98 (0.57, 17.64)	3.10 (0.00, 2110.00)	1.97 (0.32, 16.44)	0.17 (0.00, 7.76)	1.66 (0.25, 10.92)	0.15 (0.00, 5.64)	

Values given are odds ratios.

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

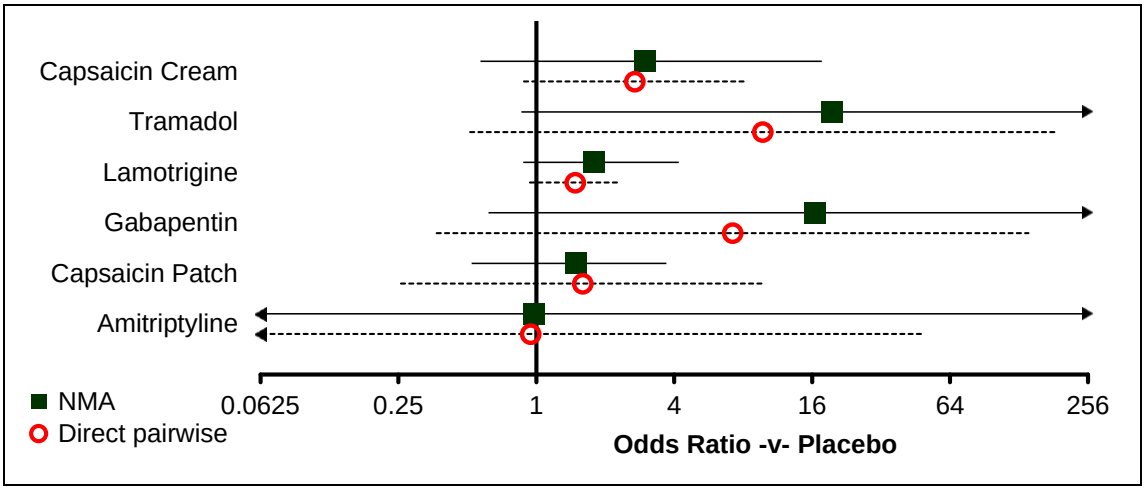

Figure 29 Rash, urticaria, erythema - relative effect of all options compared with placebo

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

Table 48 Rash, urticaria, erythema - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.312	2 (1, 4)
Amitriptyline	0.482	2 (1, 7)
Capsaicin Patch	0.099	3 (1, 5)
Gabapentin	0.027	6 (1, 7)
Lamotrigine	0.021	4 (2, 6)
Tramadol	0.016	6 (2, 7)
Capsaicin Cream	0.043	5 (1, 7)

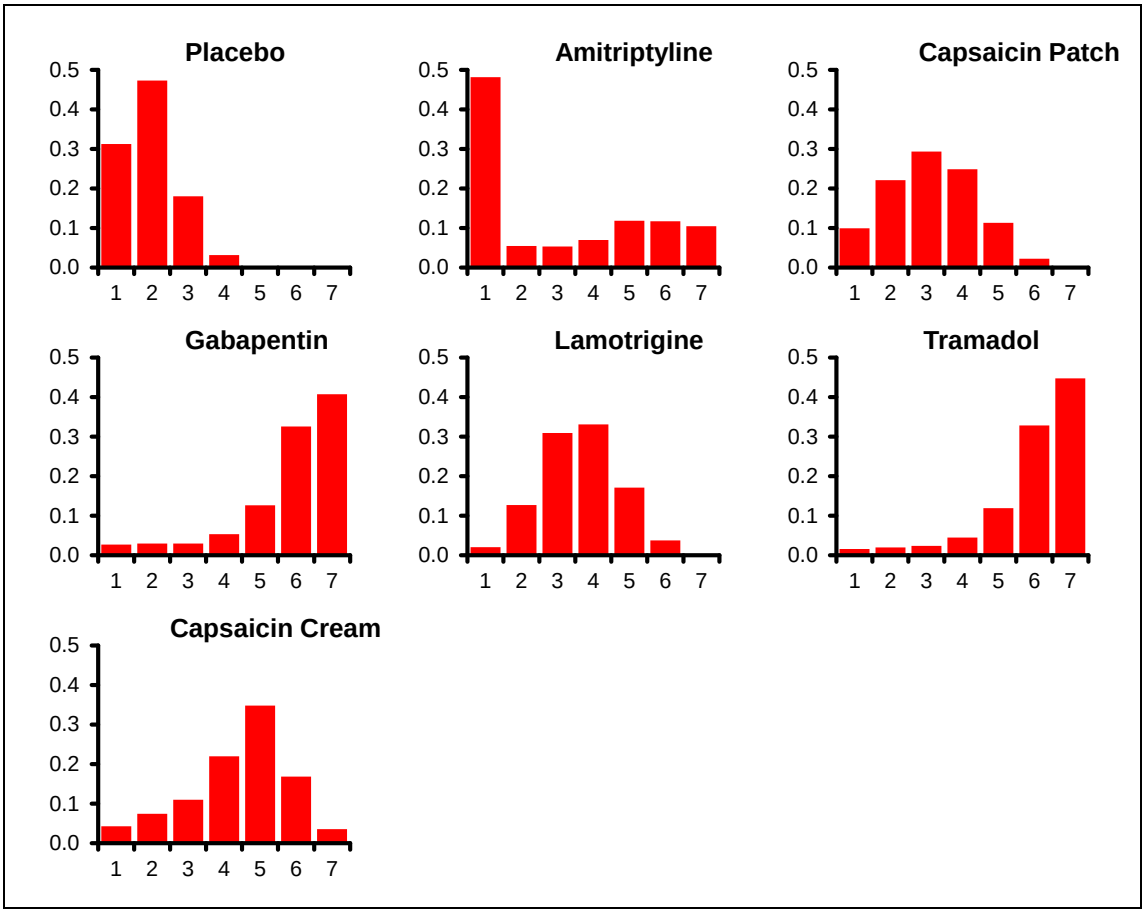

Figure 30 Rash, urticaria, erythema - rank probability histograms

Table 49 Rash, urticaria, erythema - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
37.97 (compared to 38 data-points)	150.689	122.659	28.029	178.718	0.000 (95%CI: 0.030, 1.700)

Table 50 Rash, urticaria, erythema - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.

Summary GRADE profile 3k: Network meta-analysis for blurred vision

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Blurred vision	16 RCTs[a] n=2365	Very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] more than half of studies are crossover studies; unclear about allocation concealment in 9 studies; there is uncertainty about comparability at baseline between groups in 13 studies and in 2 there were differences in groups at baseline (particularly for use of concomitant drugs); during 7 studies, it was unclear if the same care was received by each group and in 2 studies, different care was received in each group (these were usually to do with concomitant drug and rescue medication use); mean baseline severity ranged from 3.4 to 8.8 on a normalised 11-point scale across the studies in the network; concomitant drugs permitted varies across the studies in the network; insufficient follow-up in 9 studies

[2] I^2 was 75% for pregabalin vs placebo which may indicate substantial heterogeneity between the studies that make this comparison; appeared to be consistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] small proportion of head-to-head trials; most links have one study; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=123): Cardenas et al. (2002), Robinson et al. (2004)

Gabapentin (n=40): Levendoglu et al. (2004)

Imipramine (n=80): Sindrup et al. (2003)

Lacosamide (n=468): Shaibani et al. (2009)

Lamotrigine (n=36): Breuer et al. (2007)

Levetiracetam (n=138): Falah et al. (2012), Holbech et al. (2011)

Morphine (n=110): Khoromi et al. (2007)

Nortriptyline (n=110): Khoromi et al. (2007)

Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxcarbazepine (n=146): Dogra et al. (2005)

Pregabalin (n=774): Siddall et al. (2006), Stacey et al. (2008), van Seventer et al. (2006)

Topiramate (n=82): Khoromi et al. (2005)

Venlafaxine (n=80): Sindrup et al. (2003)

Head-to-head trials:

Amitriptyline vs Gabapentin (n=50): Morello et al. (1999)

Gabapentin vs Gabapentin+Nortriptyline, Gabapentin vs Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012)

Imipramine vs Venlafaxine (n=80): Sindrup et al. (2003)

Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

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

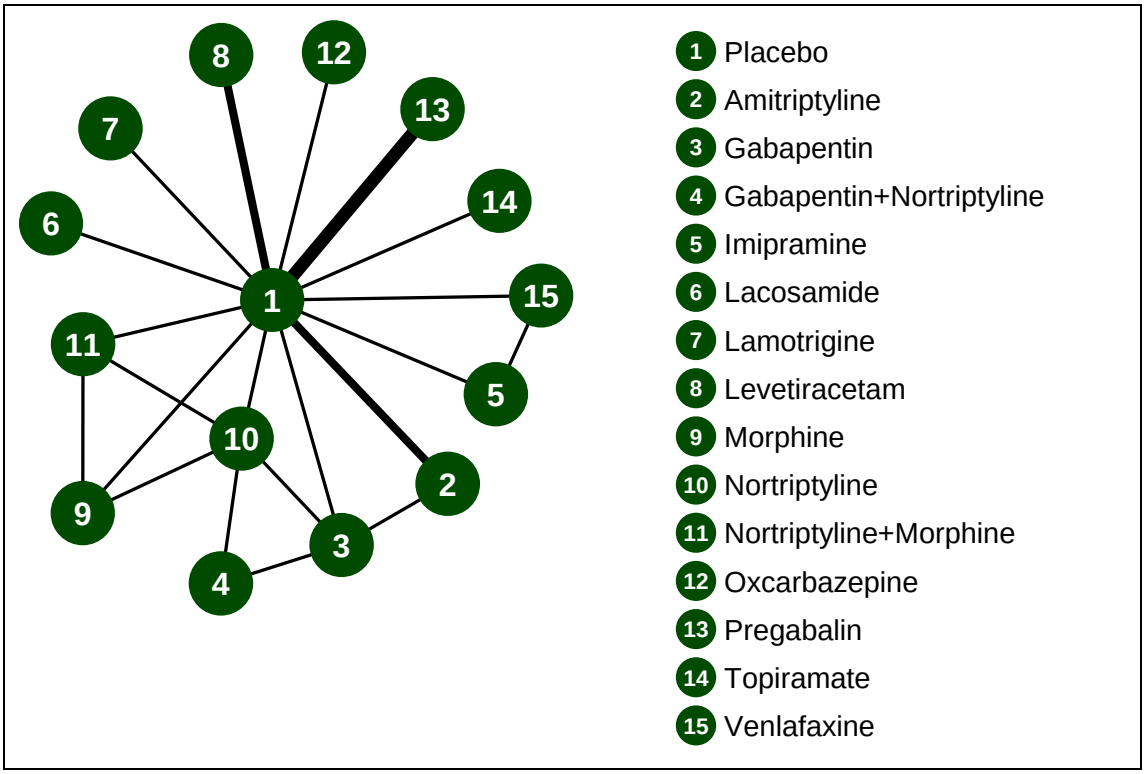

Figure 31 blurred vision - evidence network

Table 51 blurred vision - trials included in analysis

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate
Amitriptyline	2 RCTs[2,11] total n=123													
Gabapentin	1 RCT[9] total n=40	1 RCT[10] total n=50												
Gabapentin +Nortriptyline	-	-	1 RCT[5] total n=112											
Imipramine	1 RCT[14] total n=80	-	-	-										
Lacosamide	1 RCT[12] total n=468	-	-	-	-									
Lamotrigine	1 RCT[1] total n=36	-	-	-	-	-								
Levetiracetam	2 RCTs[4,6] total n=138	-	-	-	-	-	-							
Morphine	1 RCT[8] total n=110	-	-	-	-	-	-	-						
Nortriptyline	1 RCT[8] total n=110	-	1 RCT[5] total n=112	1 RCT[5] total n=112	-	-	-	-	1 RCT[8] total n=110					
Nortriptyline +Morphine	1 RCT[8] total n=110	-	-	-	-	-	-	-	1 RCT[8] total n=110	1 RCT[8] total n=110				
Oxcarbazepine	1 RCT[3] total n=146	-	-	-	-	-	-	-	-	-	-			
Pregabalin	3 RCTs[13,15,16]	-	-	-	-	-	-	-	-	-	-	-		

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate
	total n=774													
Topiramate	1 RCT[7] total n=82	-	-	-	-	-	-	-	-	-	-	-	-	
Venlafaxine	1 RCT[14] total n=80	-	-	-	1 RCT[14] total n=80	-	-	-	-	-	-	-	-	-

(1) Breuer et al. (2007); (2) Cardenas et al. (2002); (3) Dogra et al. (2005); (4) Falah et al. (2012); (5) Gilron et al. (2012); (6) Holbech et al. (2011); (7) Khoromi et al. (2005); (8) Khoromi et al. (2007); (9) Levendoglu et al. (2004); (10) Morello et al. (1999); (11) Robinson et al. (2004); (12) Shaibani et al. (2009); (13) Siddall et al. (2006); (14) Sindrup et al. (2003); (15) Stacey et al. (2008); (16) van Seventer et al. (2006)

Table 52 blurred vision - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate	Venlafaxine
Placebo		0.88 (0.02, 37.42)	1.00 (0.02, 52.85)	-	3.08 (0.12, 77.80)	4.18 (0.24, 71.50)	1.00 (0.02, 53.12)	3.09 (0.31, 30.45)	0.65 (0.10, 4.08)	0.14 (0.01, 2.68)	0.32 (0.03, 3.19)	1.12 (0.07, 18.22)	3.57 (0.99, 12.84)	3.07 (0.12, 77.69)	3.08 (0.12, 77.80)
Amitriptyline	0.88 (0.10, 8.86)		0.48 (0.04, 5.65)	-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	0.45 (0.02, 9.47)	0.52 (0.02, 9.09)		1.00 (0.06, 16.39)	-	-	-	-	-	0.33 (0.01, 8.21)	-	-	-	-	-
Gabapentin +Nortriptyline	0.42 (0.01, 32.52)	0.48 (0.01, 35.45)	0.93 (0.02, 33.72)		-	-	-	-	-	0.33 (0.01, 8.21)	-	-	-	-	-
Imipramine	5.54 (0.07, 4882.00)	6.55 (0.04, 7575.00)	13.36 (0.06, 19550.00)	15.02 (0.03, 39800.00)		-	-	-	-	-	-	-	-	-	1.00 (0.06, 16.56)
Lacosamide	8.25 (0.31, 3967.00)	9.82 (0.16, 6185.00)	19.54 (0.20, 16810.00)	23.09 (0.09, 34530.00)	1.58 (0.00, 2894.00)		-	-	-	-	-	-	-	-	-
Lamotrigine	1.01 (0.00, 788.70)	1.14 (0.00, 1197.00)	2.19 (0.00, 3291.00)	2.42 (0.00, 6431.00)	0.15 (0.00, 463.10)	0.10 (0.00, 205.40)		-	-	-	-	-	-	-	-
Levetiracetam	4.39 (0.23, 195.60)	5.08 (0.12, 383.40)	10.10 (0.14, 1214.00)	11.24 (0.06, 3372.00)	0.78 (0.00, 267.90)	0.49 (0.00, 82.17)	4.78 (0.00, 11480.00)		-	-	-	-	-	-	-
Morphine	0.69 (0.03, 14.49)	0.78 (0.02, 27.99)	1.52 (0.02, 84.19)	1.63 (0.01, 243.50)	0.11 (0.00, 24.62)	0.08 (0.00, 7.26)	0.67 (0.00, 1358.00)	0.15 (0.00, 10.43)		0.19 (0.01, 4.11)	0.49 (0.04, 5.58)	-	-	-	-

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Lacosamide	Lamotrigine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxcarbazepine	Pregabalin	Topiramate	Venlafaxine
Nortriptyline	0.09 (0.00, 1.91)	0.10 (0.00, 3.01)	0.19 (0.00, 5.05)	0.20 (0.00, 10.78)	0.01 (0.00, 3.46)	0.01 (0.00, 1.03)	0.08 (0.00, 155.20)	0.02 (0.00, 1.44)	0.12 (0.00, 4.92)		3.06 (0.12, 76.64)	-	-	-	-
Nortriptyline +Morphine	0.36 (0.01, 8.54)	0.41 (0.01, 16.32)	0.78 (0.01, 48.68)	0.85 (0.00, 140.30)	0.06 (0.00, 15.30)	0.04 (0.00, 4.22)	0.35 (0.00, 728.50)	0.08 (0.00, 6.02)	0.52 (0.01, 16.11)	4.16 (0.08, 439.60)		-	-	-	-
Oxcarbazepine	1.08 (0.01, 102.10)	1.23 (0.01, 178.10)	2.39 (0.01, 537.50)	2.58 (0.01, 1398.00)	0.17 (0.00, 108.30)	0.11 (0.00, 36.56)	1.10 (0.00, 3744.00)	0.23 (0.00, 53.91)	1.58 (0.01, 404.70)	13.93 (0.06, 5422.00)	3.11 (0.01, 895.80)		-	-	-
Pregabalin	4.62 (0.75, 42.77)	5.37 (0.28, 111.30)	10.54 (0.30, 445.50)	11.64 (0.10, 1557.00)	0.84 (0.00, 113.70)	0.55 (0.00, 30.12)	4.79 (0.00, 6981.00)	1.07 (0.02, 41.19)	6.93 (0.20, 337.40)	57.85 (1.52, 6082.00)	13.32 (0.35, 843.50)	4.39 (0.03, 623.40)		-	-
Topiramate	5.42 (0.07, 4935.00)	6.45 (0.04, 7467.00)	12.93 (0.06, 19300.00)	14.72 (0.03, 36600.00)	0.96 (0.00, 2861.00)	0.61 (0.00, 1072.00)	6.51 (0.00, 82330.00)	1.27 (0.00, 1749.00)	8.66 (0.04, 13500.00)	76.30 (0.30, 161800.00)	16.89 (0.07, 29990.00)	5.88 (0.01, 13770.00)	1.17 (0.01, 1247.00)		-
Venlafaxine	5.62 (0.07, 4955.00)	6.47 (0.04, 7334.00)	13.12 (0.06, 19580.00)	14.97 (0.03, 36180.00)	1.01 (0.02, 44.71)	0.62 (0.00, 1347.00)	6.66 (0.00, 65360.00)	1.29 (0.00, 1794.00)	8.84 (0.04, 13440.00)	76.27 (0.32, 179300.00)	17.49 (0.07, 30000.00)	5.84 (0.01, 15700.00)	1.20 (0.01, 1249.00)	1.04 (0.00, 2714.00)	

Values given are odds ratios.

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

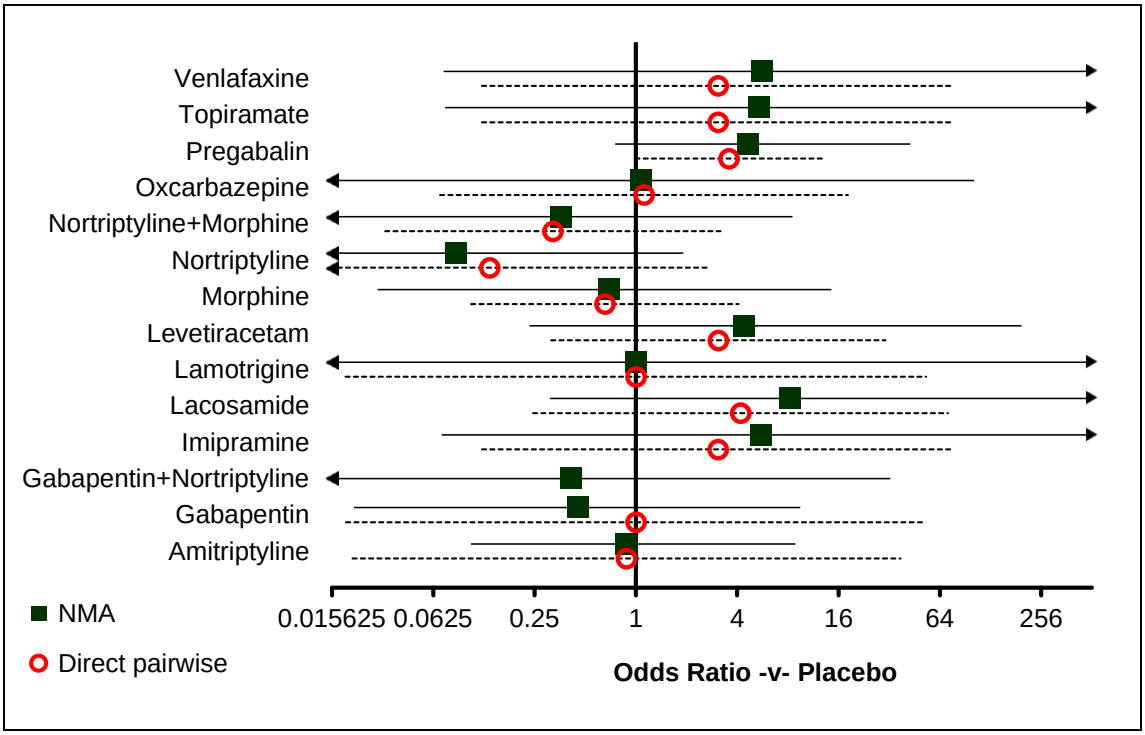

Figure 32 blurred vision - relative effect of all options compared with placebo

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

Table 53 blurred vision - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.001	7 (4, 11)
Amitriptyline	0.012	7 (2, 13)
Gabapentin	0.040	5 (1, 12)
Gabapentin+Nortriptyline	0.108	5 (1, 14)
Imipramine	0.017	12 (2, 15)
Lacosamide	0.003	13 (4, 15)
Lamotrigine	0.161	7 (1, 15)
Levetiracetam	0.005	11 (3, 15)
Morphine	0.033	6 (1, 13)
Nortriptyline	0.400	2 (1, 8)
Nortriptyline+Morphine	0.104	4 (1, 12)
Oxcarbazepine	0.079	8 (1, 15)
Pregabalin	0.000	11 (6, 15)
Topiramate	0.020	12 (2, 15)
Venlafaxine	0.017	12 (2, 15)

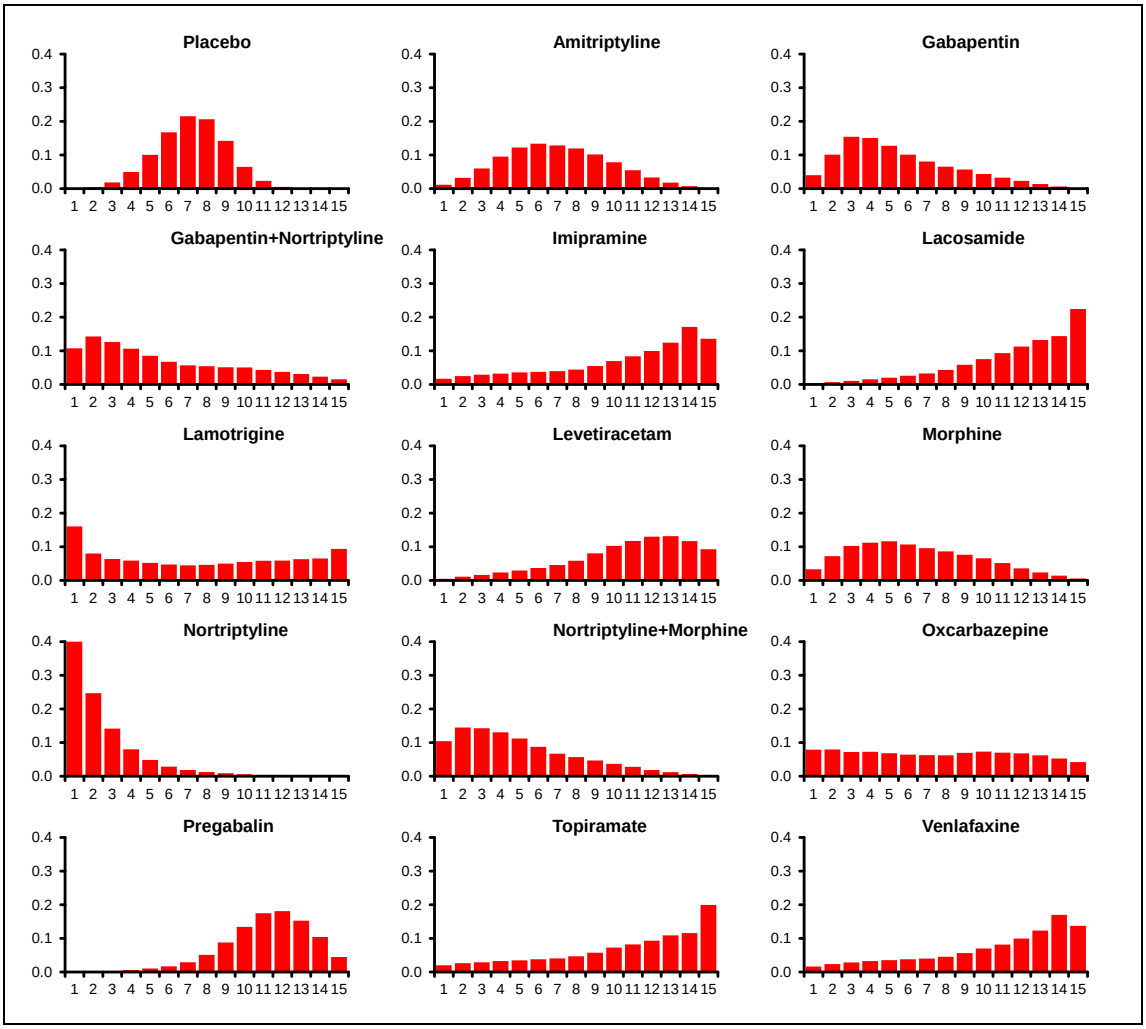

Figure 33 blurred vision - rank probability histograms

Table 54 blurred vision - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
43.04 (compared to 41 data-points)	132.434	100.281	32.153	164.587	0.023 (95%CrI: 0.016, 6.605)

Table 55 blurred vision - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- Model convergence: poor autocorrelation for lacosamide due to one study with zero events in the placebo arm.

Summary GRADE profile 3l: Network meta-analysis for peripheral oedema

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Peripheral oedema	19 RCTs[a] n=5179	very serious[1]	not serious[2]	not serious[3]	serious[4]	low	Important

[1] unclear about allocation concealment in 11 studies; there is uncertainty about comparability at baseline between groups in 13 studies (particularly for use of concomitant drugs); during 9 studies, it was unclear if the same care was received by each group and in 2 study, different care was received in each group (these were usually to do with concomitant drug and rescue medication use); concomitant drugs permitted varies across the studies in the network

[2] I^2 was 37% for pregabalin vs placebo and 32% for gabapentin vs placebo which may indicate moderate or no heterogeneity between the studies that make this comparison; appears to be consistent direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] only one head-to-head trial; most links have one study; wide confidence intervals for overall rankings within the network

[a] placebo-controlled trials:

Capsaicin Patch (n=494): Clifford et al. (2012)

Gabapentin (n=563): Rice & Maton (2001), Rowbotham et al. (1998)

Lacosamide (n=468): Shaibani et al. (2009)

Pregabalin (n=3552): Arezzo et al. (2008), Dworkin et al. (2003), Freynhagen et al. (2005), Kim et al. (2011), Lesser et al. (2004), Richter et al. (2005), Rosenstock et al. (2004), Sabatowski et al. (2004), Satoh et al. (2011), Simpson et al. (2010), Stacey et al. (2008), Tolle et al. (2008), van Seventer et al. (2006), Vranken et al. (2008)

Head-to-head trials:

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

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

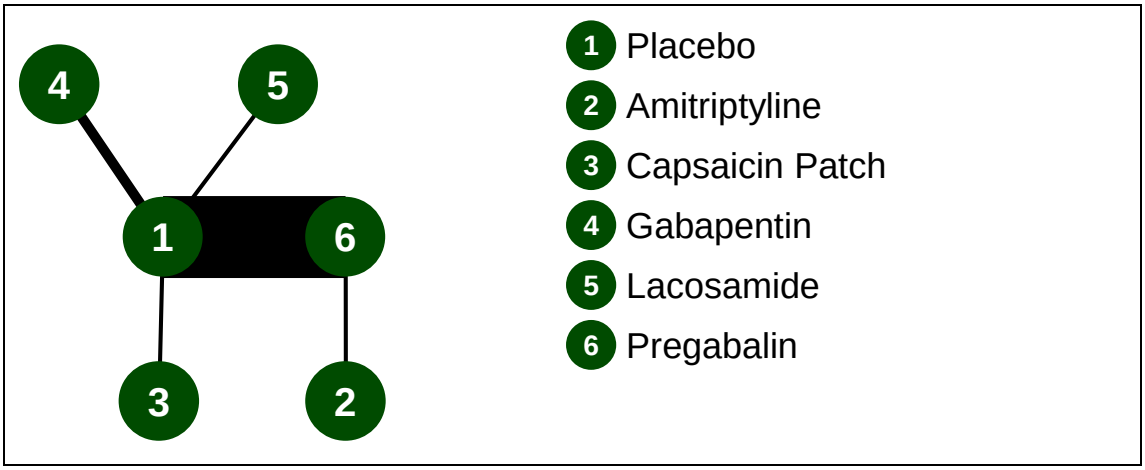

Figure 34 peripheral oedema - evidence network

Table 56 peripheral oedema - trials included in analysis

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Lacosamide
Amitriptyline	-				
Capsaicin Patch	1 RCT[3] total n=494	-			
Gabapentin	2 RCTs[8,11] total n=563	-	-		
Lacosamide	1 RCT[14] total n=468	-	-	-	
Pregabalin	14 RCTs[1,4,5,6,7,9,10,12,13,15,16,17,18,19] total n=3552	1 RCT[2] total n=102	-	-	-

(1) Arezzo et al. (2008); (2) Bansal et al. (2009); (3) Clifford et al. (2012); (4) Dworkin et al. (2003); (5) Freynhagen et al. (2005); (6) Kim et al. (2011); (7) Lesser et al. (2004); (8) Rice & Maton (2001); (9) Richter et al. (2005); (10) Rosenstock et al. (2004); (11) Rowbotham et al. (1998); (12) Sabatowski et al. (2004); (13) Satoh et al. (2011); (14) Shaibani et al. (2009); (15) Simpson et al. (2010); (16) Stacey et al. (2008); (17) Tolle et al. (2008); (18) van Seventer et al. (2006); (19) Vranken et al. (2008)

Table 57 peripheral oedema - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Lacosamide	Pregabalin
Placebo		-	0.38 (0.10, 1.45)	4.96 (0.97, 25.38)	0.53 (0.14, 1.96)	2.47 (1.61, 3.79)
Amitriptyline	0.26 (0.00, 7.64)		-	-	-	5.20 (0.24, 111.09)
Capsaicin Patch	0.36 (0.06, 1.98)	1.45 (0.03, 858.10)		-	-	-
Gabapentin	6.45 (1.70, 31.12)	25.60 (0.63, 14920.00)	17.95 (2.08, 184.80)		-	-
Lacosamide	0.54 (0.10, 3.55)	2.19 (0.05, 1361.00)	1.51 (0.13, 18.75)	0.08 (0.01, 0.82)		-
Pregabalin	2.72 (1.73, 4.50)	10.30 (0.37, 5187.00)	7.47 (1.31, 46.73)	0.42 (0.08, 1.76)	5.04 (0.74, 30.01)	

Values given are odds ratios.

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

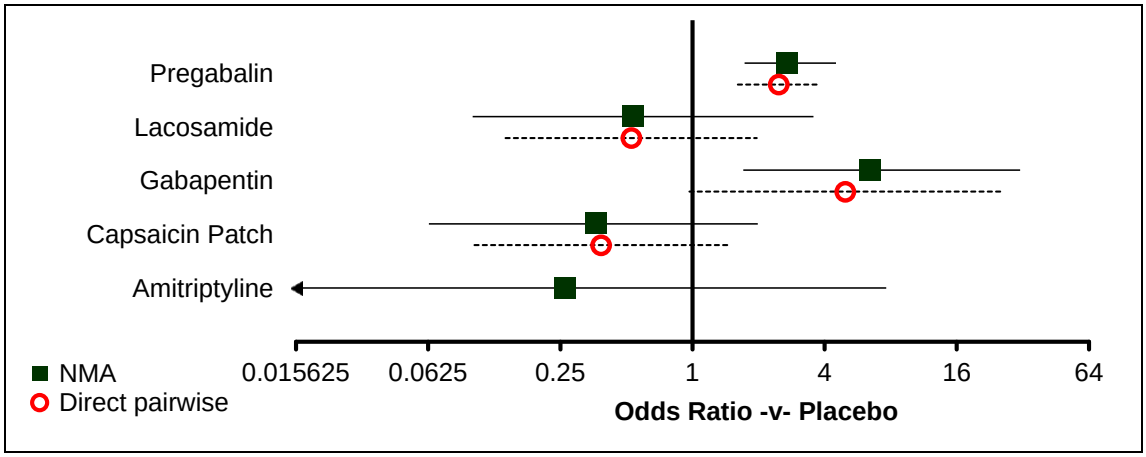

Figure 35 peripheral oedema - relative effect of all options compared with placebo

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

Table 58 peripheral oedema - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.007	4 (2, 4)
Amitriptyline	0.508	1 (1, 6)
Capsaicin Patch	0.310	2 (1, 4)
Gabapentin	0.000	6 (4, 6)
Lacosamide	0.175	2 (1, 5)
Pregabalin	0.000	5 (4, 6)

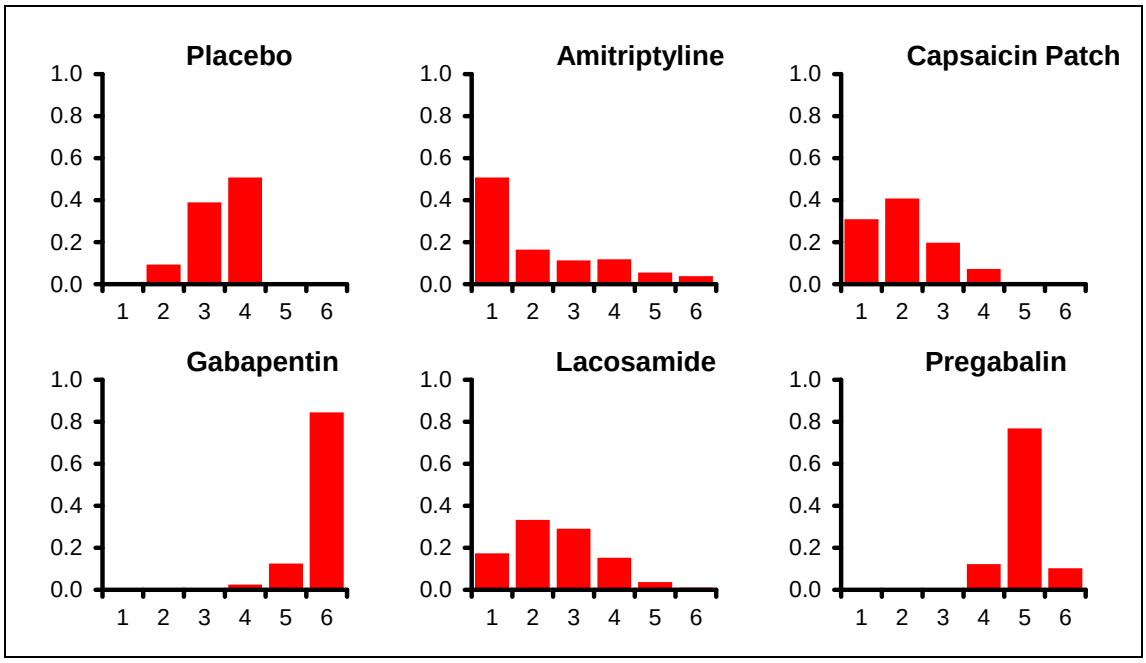

Figure 36 peripheral oedema - rank probability histograms

Table 59 peripheral oedema - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
54.46 (compared to 54 data-points)	233.937	195.325	38.612	272.55	0.284 (95%CrI: 0.097, 1.129)

Table 60 peripheral oedema - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- Model convergence: autocorrelation poor for lacosamide and gabapentin due to one study for each intervention with low event rates.

Summary GRADE profile 3m: Network meta-analysis for oedema

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Oedema	15 RCTs[a] n=3237	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear about allocation concealment in 8 studies; there is uncertainty about comparability at baseline between groups in 10 studies and in 2 there were differences in groups at baseline (particularly for use of concomitant drugs); during 10 studies, it was unclear if the same care was received by each group and in 1 study, different care was received in each group (these were usually to do with concomitant drug and rescue medication use); mean baseline severity ranged from 4 to 8.8 on a normalised 11-point scale across the studies in the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 39% for pregabalin vs placebo which may indicate moderate or no heterogeneity between the studies that make this comparison; the network is not susceptible to inconsistency because the only loop is from a multi-armed trial

[3] all aspects of PICO conform to review protocol

[4] only two head-to-head trials; most links have one study; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Capsaicin Patch (n=818): Backonja et al. (2008), Irving et al. (2011)

Gabapentin (n=40): Levendoglu et al. (2004)

Lacosamide (n=370): Wymer et al. (2009)

Lamotrigine (n=36): Breuer et al. (2007)

Levetiracetam (n=78): Holbech et al. (2011)

Pregabalin (n=1595): Arezzo et al. (2008), Guan et al. (2011), Kim et al. (2011), Siddall et al. (2006), Tolle et al. (2008), van Seventer et al. (2006)

Topiramate (n=82): Khoromi et al. (2005)

Head-to-head trials:

Amitriptyline vs Gabapentin (n=50): Morello et al. (1999)

Gabapentin vs Gabapentin+Nortriptyline vs nortriptyline (n=112): Gilron et al. (2012)

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

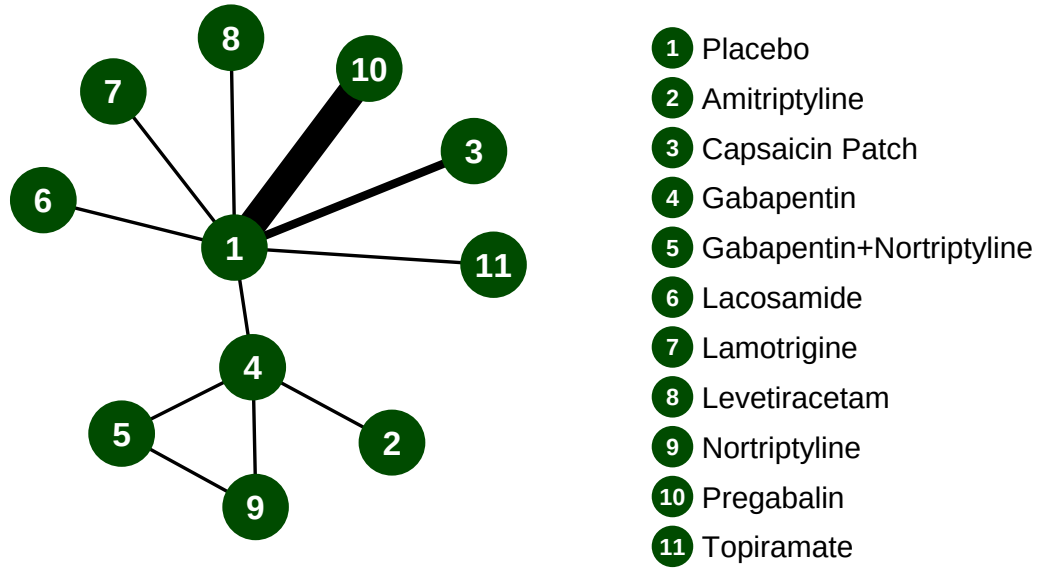

Figure 37 oedema - evidence network

Table 61 oedema - trials included in analysis

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Gabapentin +Nortriptyline	Lacosamide	Lamotrigine	Levetiracetam	Nortriptyline	Pregabalin
Amitriptyline	-									
Capsaicin Patch	2 RCTs[2,7] total n=818	-								
Gabapentin	1 RCT[10] total n=40	1 RCT[11] total n=50	-							
Gabapentin +Nortriptyline	-	-	-	1 RCT[4] total n=112						
Lacosamide	1 RCT[15] total n=370	-	-	-	-					
Lamotrigine	1 RCT[3] total n=36	-	-	-	-	-				
Levetiracetam	1 RCT[6] total n=78	-	-	-	-	-	-			
Nortriptyline	-	-	-	1 RCT[4] total n=112	1 RCT[4] total n=112	-	-	-		
Pregabalin	6 RCTs[1,5,9,12,13,14] total n=1595	-	-	-	-	-	-	-	-	
Topiramate	1 RCT[8] total n=82	-	-	-	-	-	-	-	-	-

(1) Arezzo et al. (2008); (2) Backonja et al. (2008); (3) Breuer et al. (2007); (4) Gilron et al. (2012); (5) Guan et al. (2011); (6) Holbech et al. (2011); (7) Irving et al. (2011); (8) Khoromi et al. (2005); (9) Kim et al. (2011); (10) Levendoglu et al. (2004); (11) Morello et al. (1999); (12) Siddall et al. (2006); (13) Tolle et al. (2008); (14) van Seventer et al. (2006); (15) Wymer et al. (2009)

Table 62 oedema - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Gabapentin +Nortriptyline	Lacosamide	Lamotrigine	Levetiracetam	Nortriptyline	Pregabalin	Topiramate
Placebo		-	8.49 (2.24, 32.17)	8.20 (0.40, 169.90)	-	0.75 (0.22, 2.49)	0.29 (0.03, 3.14)	1.00 (0.06, 16.58)	-	2.81 (1.08, 7.34)	3.07 (0.12, 77.69)
Amitriptyline	10.79 (0.08, 14860)		-	1.57 (0.24, 10.30)	-	-	-	-	-	-	-
Capsaicin Patch	13.87 (1.96, 159.00)	1.31 (0.00, 332.70)		-	-	-	-	-	-	-	-
Gabapentin	16.70 (0.41, 13570)	1.68 (0.08, 38.75)	1.24 (0.01, 1192)		1.00 (0.24, 4.21)	-	-	-	0.48 (0.08, 2.74)	-	-
Gabapentin +Nortriptyline	17.85 (0.16, 21750)	1.64 (0.03, 100.80)	1.28 (0.01, 1848)	0.98 (0.06, 14.74)		-	-	-	0.48 (0.08, 2.74)	-	-
Lacosamide	0.79 (0.06, 10.66)	0.07 (0.00, 18.86)	0.06 (0.00, 1.43)	0.04 (0.00, 4.28)	0.04 (0.00, 9.33)		-	-	-	-	-
Lamotrigine	0.22 (0.00, 5.66)	0.02 (0.00, 7.85)	0.01 (0.00, 0.67)	0.01 (0.00, 1.90)	0.01 (0.00, 3.93)	0.26 (0.00, 17.09)		-	-	-	-
Levetiracetam	1.02 (0.01, 74.67)	0.09 (0.00, 63.84)	0.07 (0.00, 7.77)	0.05 (0.00, 16.83)	0.05 (0.00, 32.37)	1.29 (0.01, 188.60)	5.07 (0.02, 1737)		-	-	-
Nortriptyline	7.62 (0.06, 9749)	0.71 (0.01, 48.60)	0.55 (0.00, 841.10)	0.42 (0.02, 7.19)	0.43 (0.02, 7.54)	9.92 (0.04, 18350)	40.60 (0.10, 130600)	8.09 (0.01, 26410)		-	-
Pregabalin	3.08 (1.04, 9.50)	0.29 (0.00, 45.51)	0.22 (0.02, 2.11)	0.18 (0.00, 8.69)	0.17 (0.00, 21.63)	3.91 (0.23, 63.54)	14.57 (0.45, 988.40)	3.03 (0.04, 236.10)	0.41 (0.00, 59.01)		-
Topiramate	5.44	0.53	0.39	0.31	0.32	7.18	29.40	6.02	0.75	1.77	

	Placebo	Amitriptyline	Capsaicin Patch	Gabapentin	Gabapentin +Nortriptyline	Lacosamide	Lamotrigine	Levetiracetam	Nortriptyline	Pregabalin	Topiramate
	(0.08, 3601)	(0.00, 1644)	(0.00, 334.70)	(0.00, 498.60)	(0.00, 799.00)	(0.05, 6997)	(0.13, 49640)	(0.01, 10700)	(0.00, 2066)	(0.02, 1263)	

Values given are odds ratios.

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

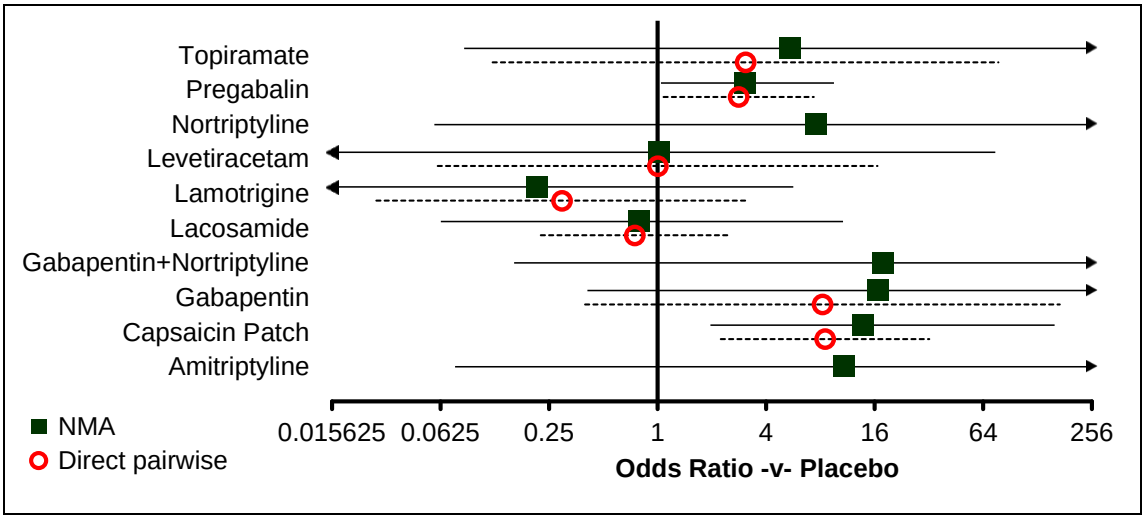

Figure 38 oedema - relative effect of all options compared with placebo

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

Table 63 oedema - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.018	4 (2, 7)
Amitriptyline	0.035	8 (1, 11)
Capsaicin Patch	0.000	8 (5, 11)
Gabapentin	0.001	9 (4, 11)
Gabapentin+Nortriptyline	0.011	9 (2, 11)
Lacosamide	0.125	3 (1, 9)
Lamotrigine	0.532	1 (1, 8)
Levetiracetam	0.183	4 (1, 11)
Nortriptyline	0.045	7 (1, 11)
Pregabalin	0.001	6 (3, 10)
Topiramate	0.050	7 (1, 11)

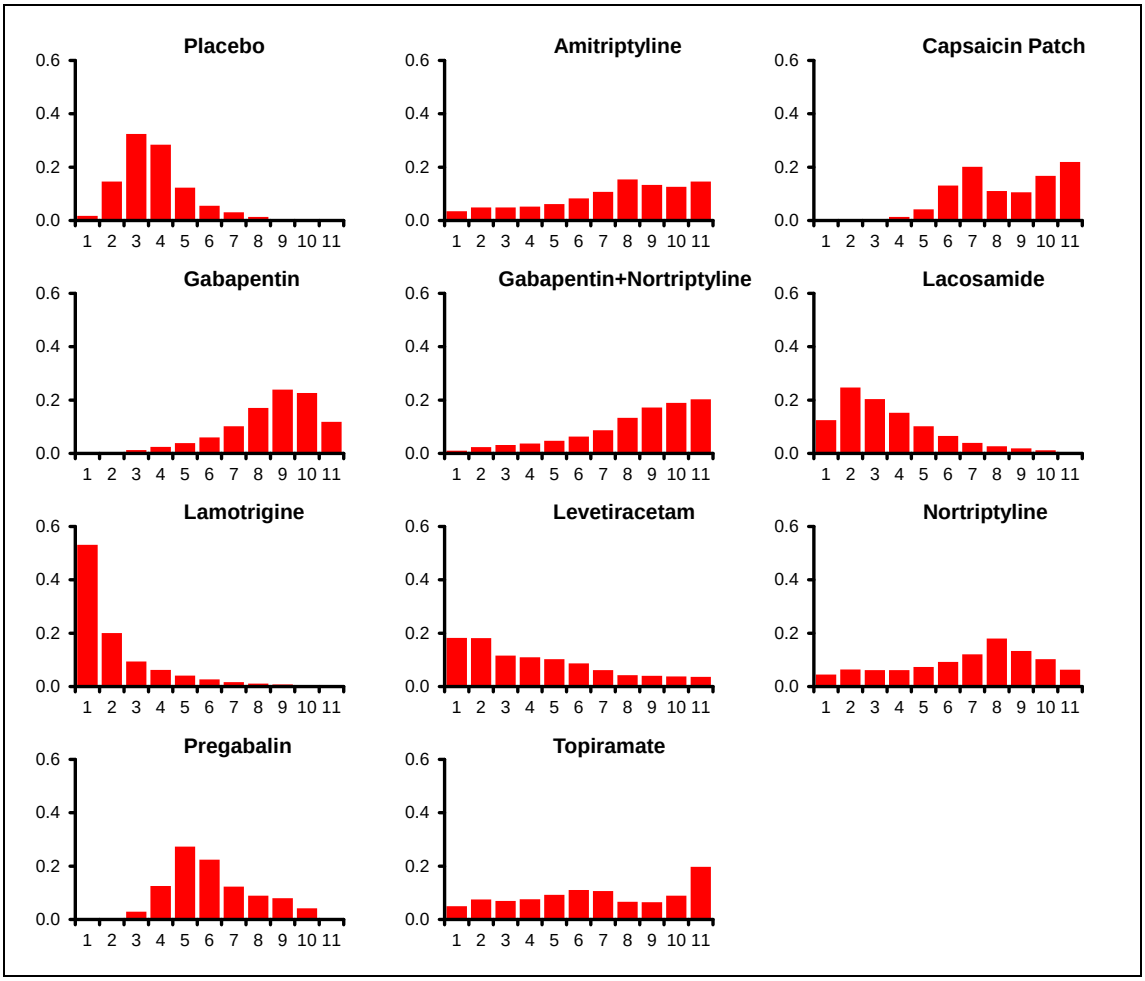

Figure 39 oedema - rank probability histograms

Table 64 oedema - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
38.06 (compared to 35 data-points)	128.09	108.211	29.879	167.969	0.017 (95%CrI: 0.019, 4.97)

Table 65 oedema - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 30000 burn-ins and 50000 iterations.
- Model convergence: poor autocorrelation for amitriptyline, gabapentin, nortriptyline and gabapentin+nortriptyline. This is likely to do with low event rates and because much of the data for 3 of these interventions came from the same 3-armed trial.

Summary GRADE profile 3n: Network meta-analysis for confusion

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Confusion	11 RCTs[a] n=3070	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] unclear about allocation concealment in 8 studies; there is uncertainty about comparability at baseline between groups in 6 studies (particularly for use of concomitant drugs); concomitant drugs permitted varies across the studies in the network

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

[3] all aspects of PICO conform to review protocol

[4] only one head-to-head trial; most links have one study; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Duloxetine (n=48): Vranken et al. (2011)

Gabapentin (n=465): Backonja et al. (1998), Gordh et al. (2008), Simpson (2001)

Pregabalin (n=1186): Dworkin et al. (2003), Lesser et al. (2004), Stacey et al. (2008), van Seventer et al. (2006), Vranken et al. (2008)

Topiramate (n=1269): Thienel et al. (2004)

Head-to-head trials:

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

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

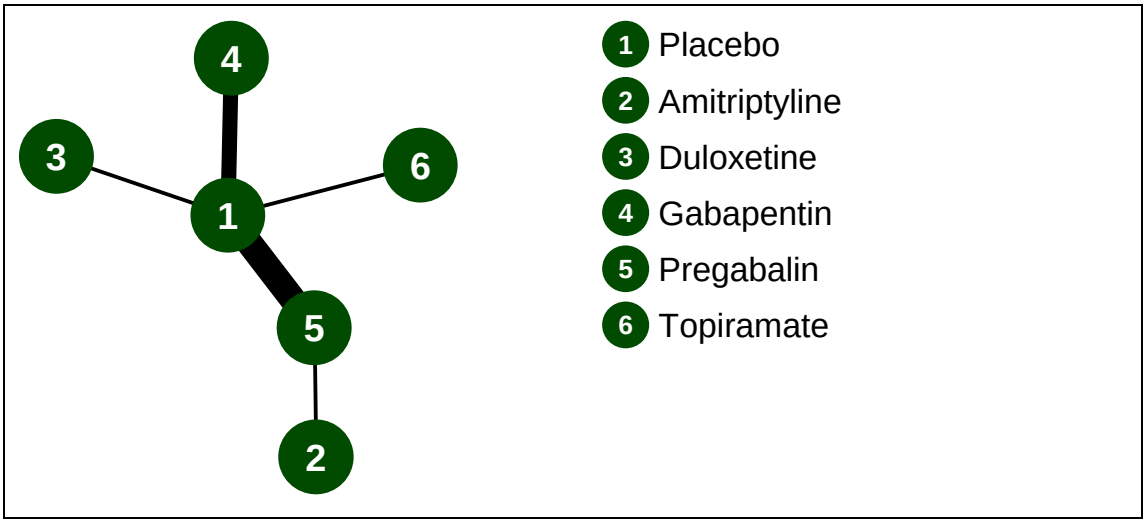

Figure 40 confusion - evidence network

Table 66 confusion - trials included in analysis

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Pregabalin
Amitriptyline	-				
Duloxetine	1 RCT[11] total n=48	-			
Gabapentin	3 RCTs[1,4,6] total n=465	-	-		
Pregabalin	5 RCTs[3,5,7,9,10] total n=1186	1 RCT[2] total n=102	-	-	
Topiramate	1 RCT[8] total n=1269	-	-	-	-

(1) Backonja et al. (1998); (2) Bansal et al. (2009); (3) Dworkin et al. (2003); (4) Gordh et al. (2008); (5) Lesser et al. (2004); (6) Simpson (2001); (7) Stacey et al. (2008); (8) Thienel et al. (2004); (9) van Seventer et al. (2006); (10) Vranken et al. (2008); (11) Vranken et al. (2011)

Table 67 confusion - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Duloxetine	Gabapentin	Pregabalin	Topiramate
Placebo		-	7.98 (0.39, 163.33)	7.93 (2.55, 24.66)	2.95 (1.26, 6.90)	4.15 (1.47, 11.71)
Amitriptyline	0.66 (0.00, 30.05)		-	-	3.06 (0.12, 76.88)	-
Duloxetine	16.90 (0.69, 5799.00)	33.37 (0.16, 112600.00)		-	-	-
Gabapentin	9.11 (2.34, 44.58)	14.54 (0.25, 6995.00)	0.53 (0.00, 19.71)		-	-
Pregabalin	3.53 (1.39, 10.13)	5.29 (0.14, 2321.00)	0.21 (0.00, 6.05)	0.39 (0.06, 2.18)		-
Topiramate	4.48 (1.04, 22.68)	7.04 (0.11, 3371.00)	0.26 (0.00, 9.72)	0.49 (0.06, 4.01)	1.27 (0.20, 8.12)	

Values given are odds ratios.

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

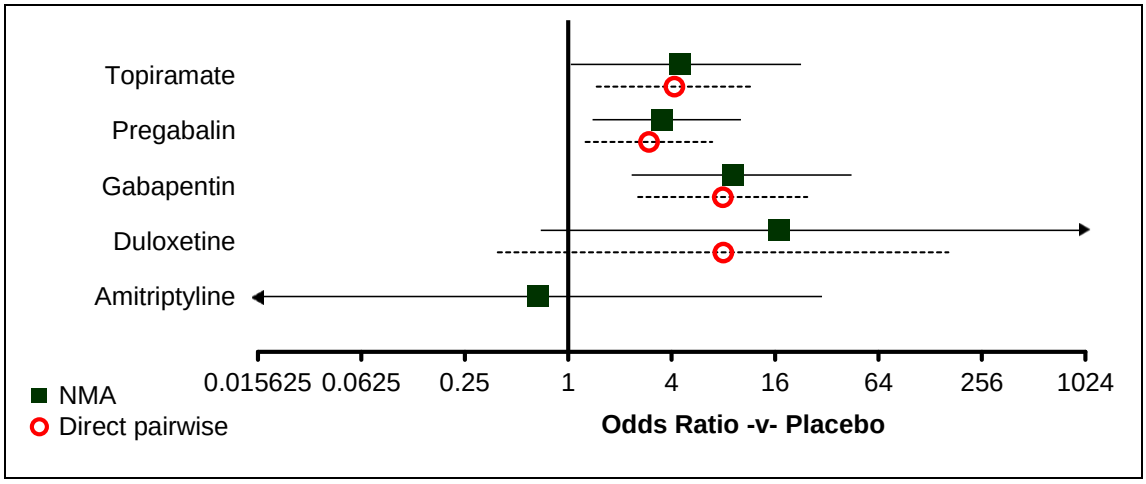

Figure 41 confusion - relative effect of all options compared with placebo

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

Table 68 confusion - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.394	2 (1, 3)
Amitriptyline	0.571	1 (1, 6)
Duloxetine	0.022	6 (2, 6)
Gabapentin	0.001	5 (3, 6)
Pregabalin	0.001	3 (2, 5)
Topiramate	0.011	4 (2, 6)

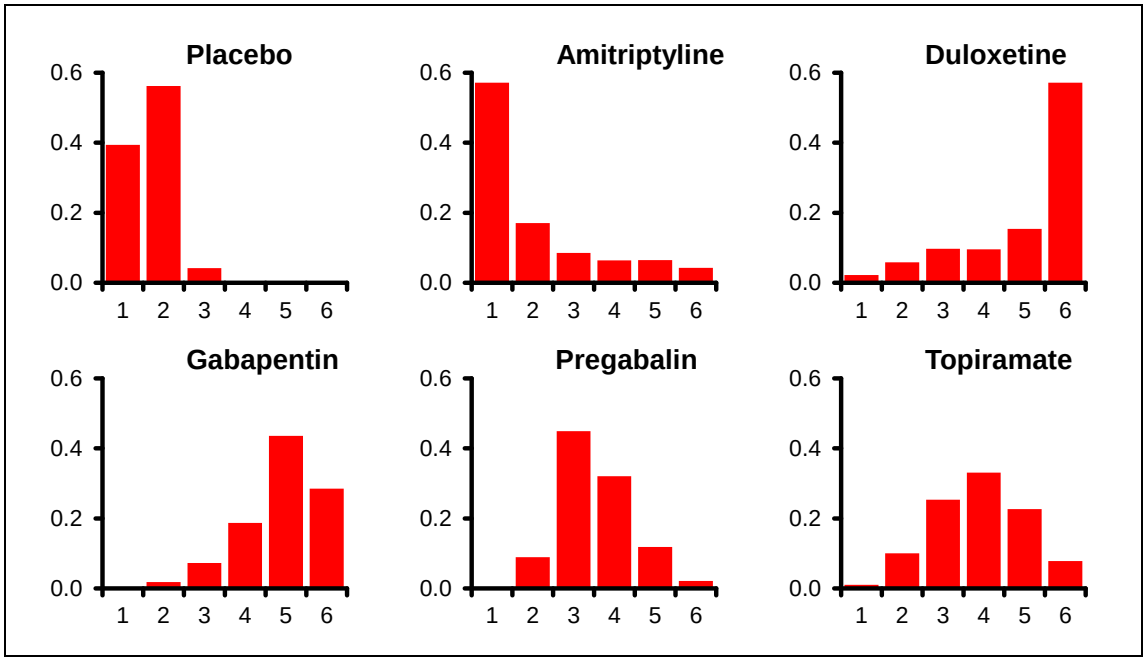

Figure 42 confusion - rank probability histograms

Table 69 confusion - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
28.53 (compared to 29 data-points)	110.634	90.819	19.815	130.449	0.003 (95%CrI: 0.003, 1.720)

Table 70 confusion - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 40000 burn-ins and 50000 iterations.
- Model convergence: poor autocorrelation for duloxetine because only one study with no event in the placebo arm.

Summary GRADE profile 3o: Network meta-analysis for cognitive impairment (including impaired attention)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
cognitive impairment (including impaired attention)	5 RCTs[a] n=1636	Very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] there is uncertainty about comparability at baseline between groups in 2 studies and there are differences between groups at baseline in 1 group (particularly for use of concomitant drugs); during 3 studies, it was unclear if the same care was received by each group (these were usually to do with concomitant drug and rescue medication use); insufficient follow-up 2 studies and unclear in one; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 68% for pregabalin vs placebo which may indicate moderate to substantial heterogeneity between the studies that make this comparison; there were some differences between direct and indirect comparisons for amitriptyline compared to pregabalin and nortriptyline, but comparison of a consistency and inconsistency models showed general consistency

[3] all aspects of PICO conform to review protocol

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

[a] Amitriptyline (n=124): Max et al. (1988)

Cannabis Sativa Extract (n=66): Rog et al. (2005)

Pregabalin (n=177): Siddall et al. (2006), Vranken et al. (2008)

Topiramate (n=1269): Thienel et al. (2004)

(all compared to placebo)

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

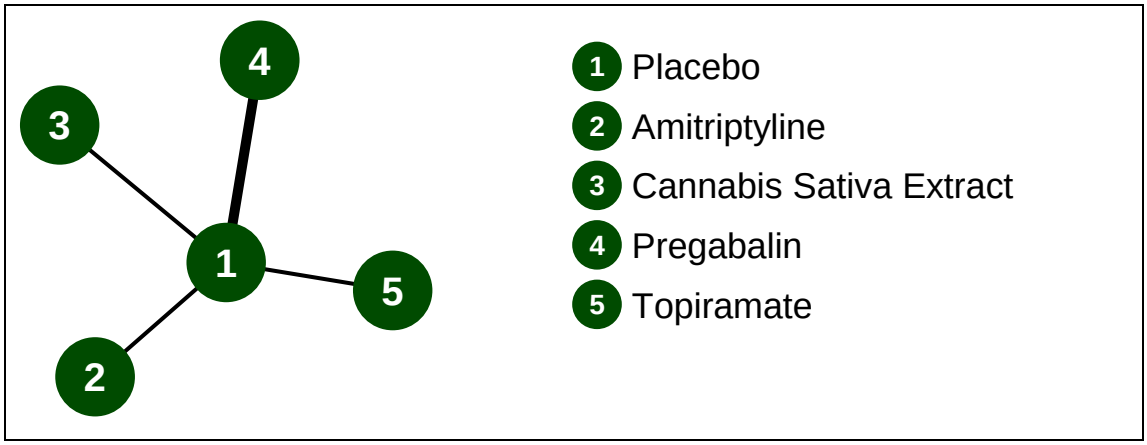

Figure 43 cognitive impairment - evidence network

Table 71 cognitive impairment - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Pregabalin
Amitriptyline	1 RCT[1] total n=124			
Cannabis Sativa Extract	1 RCT[2] total n=66	-		
Pregabalin	2 RCTs[3,5] total n=177	-	-	
Topiramate	1 RCT[4] total n=1269	-	-	-

(1) Max et al. (1988); (2) Rog et al. (2005); (3) Siddall et al. (2006); (4) Thienel et al. (2004); (5) Vranken et al. (2008)

Table 72 cognitive impairment - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Pregabalin	Topiramate
Placebo		9.62 (0.51, 182.51)	5.00 (0.23, 108.25)	1.69 (0.19, 15.17)	2.82 (1.26, 6.31)
Amitriptyline	20.24 (0.26, 15040.00)		-	-	-
Cannabis Sativa Extract	11.02 (0.11, 7790.00)	0.53 (0.00, 1314.00)		-	-
Pregabalin	1.71 (0.15, 34.68)	0.08 (0.00, 18.26)	0.15 (0.00, 40.48)		-
Topiramate	2.83 (0.14, 54.66)	0.14 (0.00, 24.90)	0.25 (0.00, 58.56)	1.67 (0.02, 73.16)	

Values given are odds ratios.

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

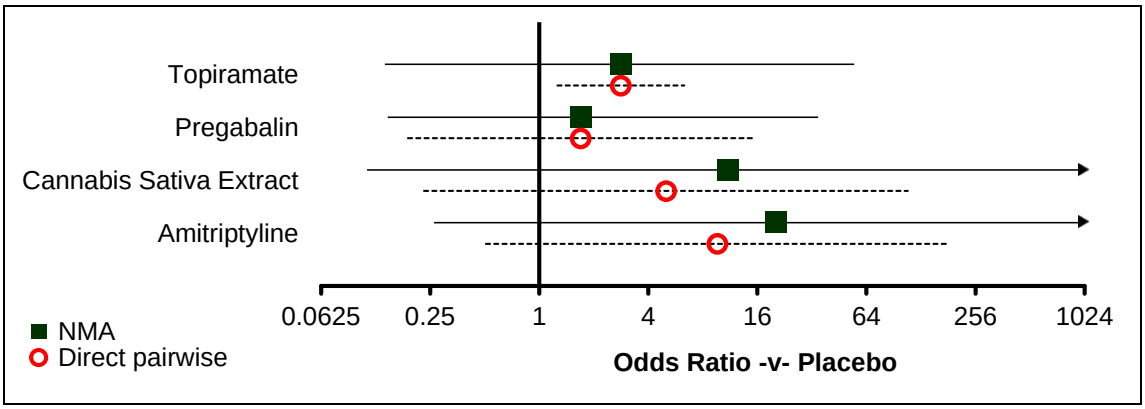

Figure 44 cognitive impairment - relative effect of all options compared with placebo

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

Table 73 cognitive impairment - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.501	1 (1, 3)
Amitriptyline	0.052	5 (1, 5)
Cannabis Sativa Extract	0.110	4 (1, 5)
Pregabalin	0.227	2 (1, 5)
Topiramate	0.110	3 (1, 5)

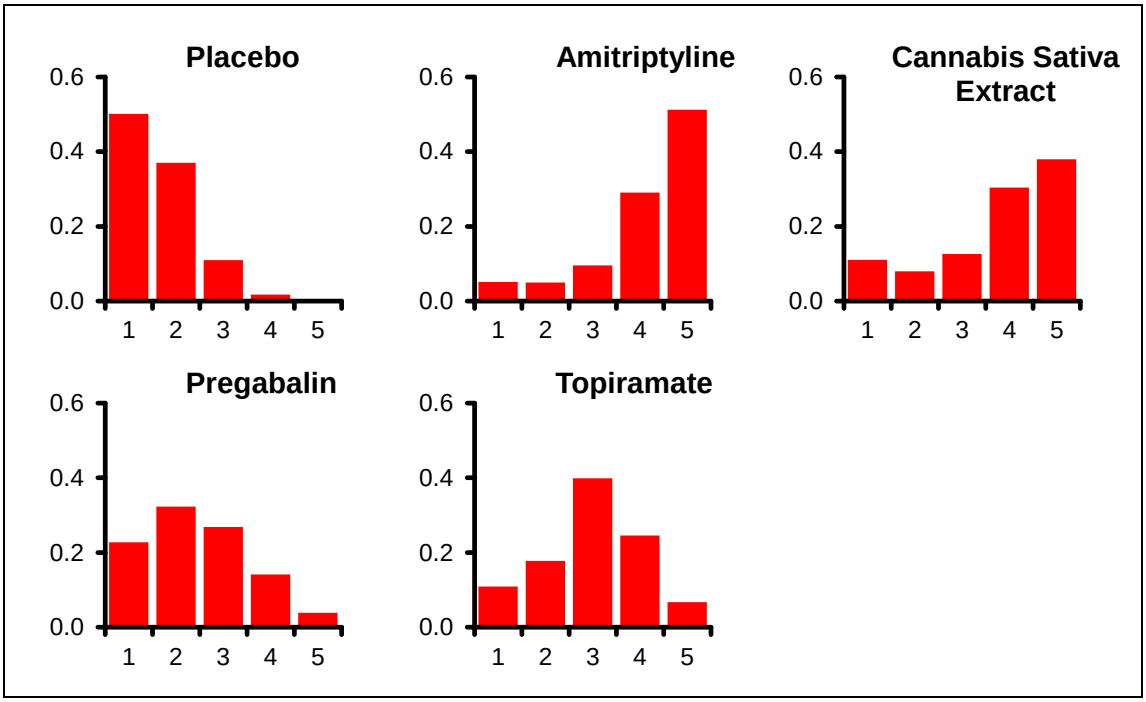

Figure 45 cognitive impairment - rank probability histograms

Table 74 cognitive impairment - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 20000 burn-ins and 50000 iterations.
- Removed Gilron (2009) because nortriptyline, gabapentin, nortriptyline+gabapentin were not connected to the network.

Summary GRADE profile 3p: Network meta-analysis for mood disturbance (including depression and euphoria)

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
mood disturbance (including depression and euphoria)	9 RCTs[a] n=1455	very serious[1]	serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] more than half of studies are crossover studies; there is uncertainty about comparability at baseline between groups in all but 2 studies (particularly for use of concomitant drugs); patients who completed the studies were not comparable between groups in 2 studies and it was unclear if they were comparable in another 2 studies; insufficient follow-up in all but 2 studies; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 70% for pregabalin vs placebo which indicates considerable heterogeneity between the studies that make this comparison; no loops so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

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

[a] Amitriptyline (n=124): Max et al. (1988)

Cannabis Sativa Extract (n=66): Rog et al. (2005)

Capsaicin Patch (n=307): Simpson et al. (2008)

Levetiracetam (n=138): Falah et al. (2012), Holbech et al. (2011)

Pregabalin (n=738): Arezzo et al. (2008), Simpson et al. (2010), Stacey et al. (2008)

Topiramate (n=82): Khoromi et al. (2005)

(all are compared to placebo)

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

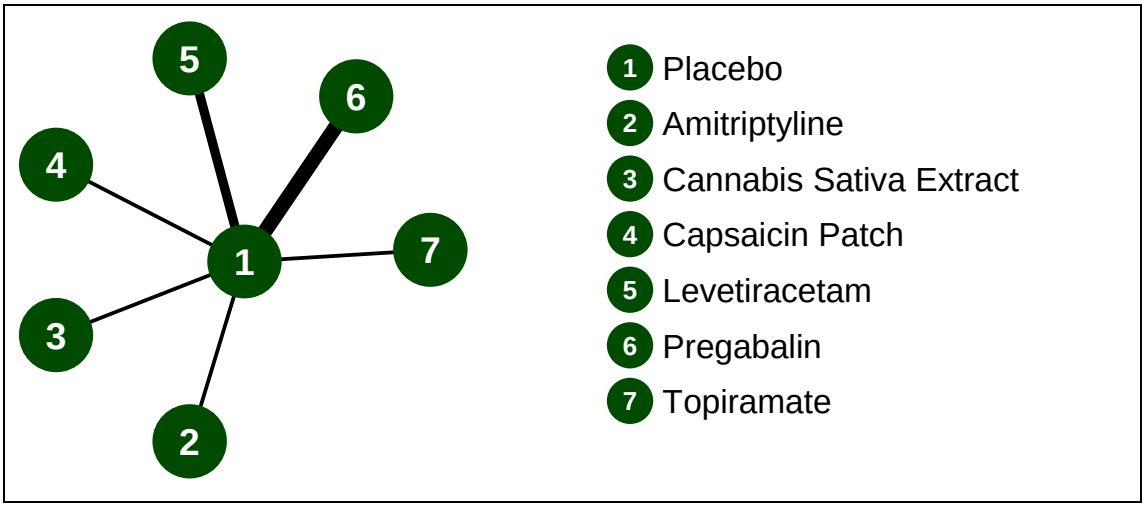

Figure 46 mood disturbance - evidence network

Table 75 mood disturbance - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Levetiracetam	Pregabalin
Amitriptyline	1 RCT[5] total n=124					
Cannabis Sativa Extract	1 RCT[6] total n=66	-				
Capsaicin Patch	1 RCT[7] total n=307	-	-			
Levetiracetam	2 RCTs[2,3] total n=138	-	-	-		
Pregabalin	3 RCTs[1,8,9] total n=738	-	-	-	-	
Topiramate	1 RCT[4] total n=82	-	-	-	-	-

(1) Arezzo et al. (2008); (2) Falah et al. (2012); (3) Holbech et al. (2011); (4) Khoromi et al. (2005); (5) Max et al. (1988); (6) Rog et al. (2005); (7) Simpson et al. (2008); (8) Simpson et al. (2010); (9) Stacey et al. (2008)

Table 76 mood disturbance - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Levetiracetam	Pregabalin	Topiramate
Placebo		9.62 (0.51, 182.51)	5.00 (0.23, 108.25)	2.60 (0.32, 21.47)	2.96 (0.52, 16.82)	2.57 (0.16, 41.27)	7.55 (0.38, 150.87)
Amitriptyline	22.88 (0.05, 59530.00)		-	-	-	-	-
Cannabis Sativa Extract	10.38 (0.02, 22460.00)	0.45 (0.00, 9131.00)		-	-	-	-
Capsaicin Patch	4.00 (0.01, 1964.00)	0.17 (0.00, 1048.00)	0.37 (0.00, 2498.00)		-	-	-
Levetiracetam	3.26 (0.04, 244.40)	0.13 (0.00, 264.80)	0.30 (0.00, 601.60)	0.80 (0.00, 1065.00)		-	-
Pregabalin	3.14 (0.11, 91.54)	0.13 (0.00, 152.60)	0.30 (0.00, 357.20)	0.77 (0.00, 640.90)	0.96 (0.00, 248.10)		-
Topiramate	17.16 (0.04, 45250.00)	0.76 (0.00, 15270.00)	1.66 (0.00, 37060.00)	4.42 (0.00, 67740.00)	5.52 (0.00, 42550.00)	5.58 (0.00, 27510.00)	

Values given are odds ratios.

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

	Placebo	Amitriptyline	Cannabis Sativa Extract	Capsaicin Patch	Levetiracetam	Pregabalin	Topiramate
The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.							

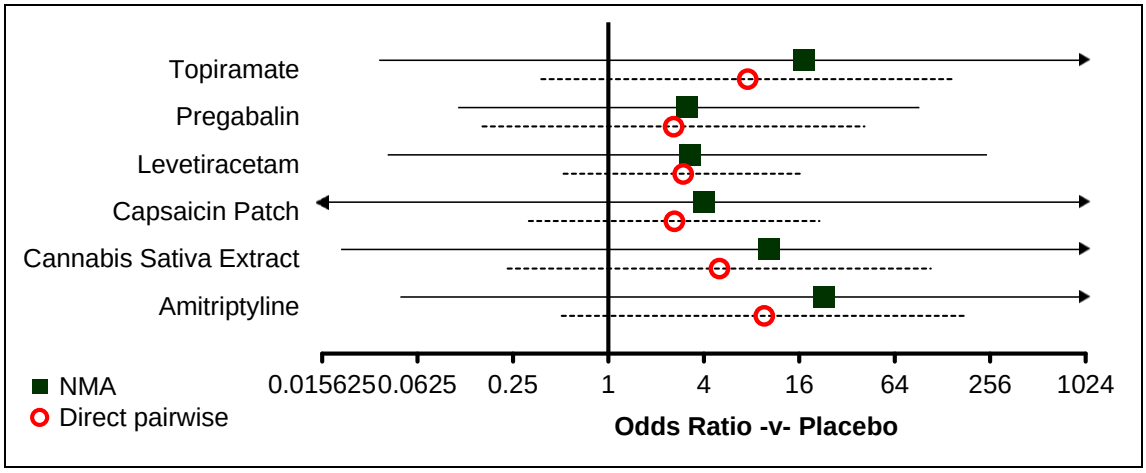

Figure 47 mood disturbance - relative effect of all options compared with placebo

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

Table 77 mood disturbance - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.369	2 (1, 4)
Amitriptyline	0.087	5 (1, 6)
Cannabis Sativa Extract	0.149	4 (1, 6)
Levetiracetam	0.169	3 (1, 6)
Pregabalin	0.120	3 (1, 6)
Topiramate	0.106	5 (1, 6)

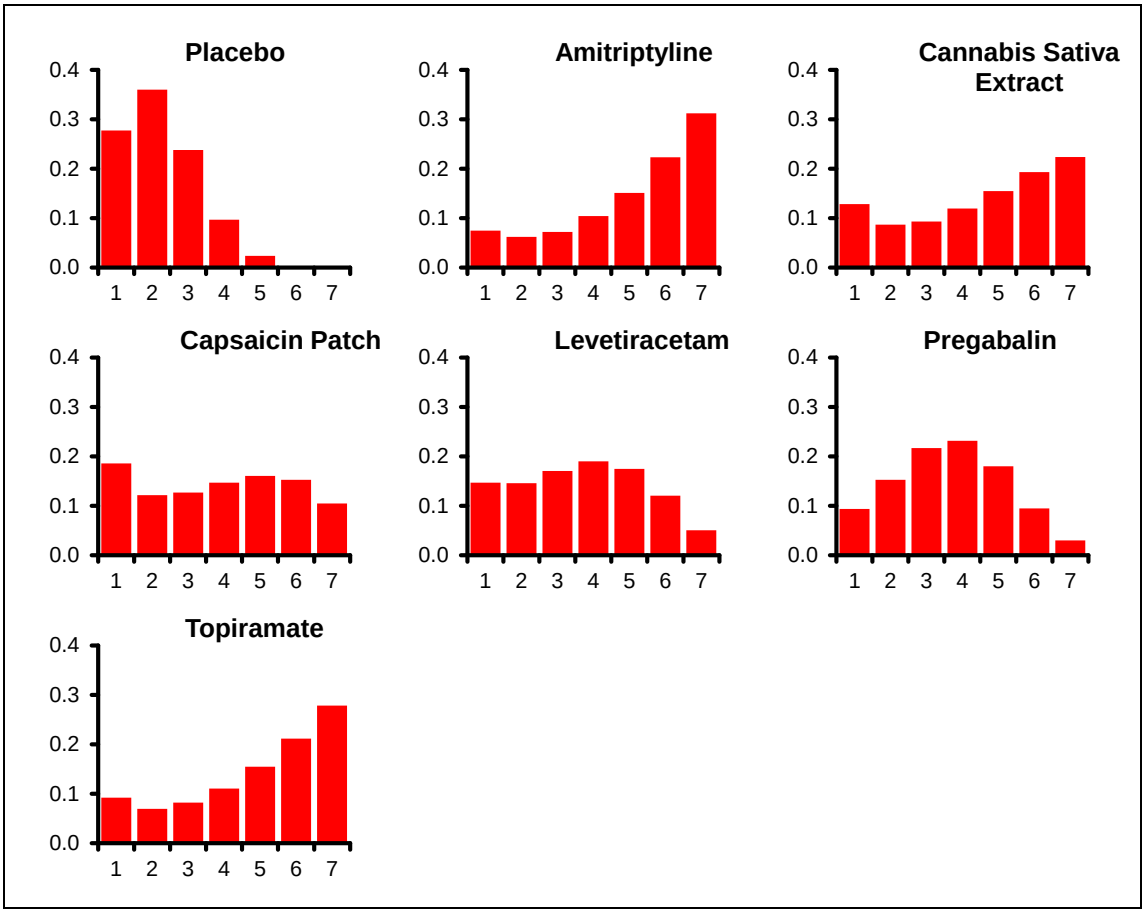

Figure 48 mood disturbance - rank probability histograms

Table 78 mood disturbance - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
20.33 (compared to 19 data-points)	66.75	49.943	16.808	83.558	0.008 (95%CI: 0.243, 21.867)

Table 79 mood disturbance - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 20000 burn-ins and 50000 iterations.
- Removed Gilron (2009) because nortriptyline, gabapentin, nortriptyline+gabapentin were not connected to the network.

Summary GRADE profile 3q: Network meta-analysis for dry mouth

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Dry mouth	34 RCTs[a] n=5512	very serious[1]	serious[2]	not serious[3]	very serious	Very low	Important

[1] there is uncertainty about comparability at baseline between groups in 23 studies and there are differences between groups in 4 studies (particularly for use of concomitant drugs); during 21 studies, it was unclear if the same care was received by each group and in 3 studies the same care was not received (these were usually to do with concomitant drug and rescue medication use); average baseline severity ranged from 3.4 to 7 on a 11-point scale across the network; concomitant drugs permitted varies across the studies in the network; insufficient follow-up in 22 studies

[2] was 60% for amitriptyline vs placebo which indicates moderate to substantial heterogeneity between the studies that make this comparison; I^2 was 0% for most other comparisons with more than one trial and 28% for pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons with only one trial); there were some differences between direct and indirect comparisons for amitriptyline compared to pregabalin and nortriptyline, but comparison of a consistency and inconsistency models showed general consistency

[3] all aspects of PICO conform to review protocol

[4] the majority of links in the network have only one trial; few head-to-head trials; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=341): Cardenas et al. (2002), Kalso et al. (1995), Max et al. (1988), Robinson et al. (2004), Vrethem et al. (1997)

Cannabis Sativa Extract (n=191): Nurmikko et al. (2007), Rog et al. (2005)

Duloxetine (n=720): Gao et al. (2010), Goldstein et al. (2005), Vranken et al. (2011)

Escitalopram (n=96): Otto et al. (2008)

Gabapentin (n=574): Gordh et al. (2008), Rice & Maton (2001)

Imipramine (n=80): Sindrup et al. (2003)

Levetiracetam (n=150): Finnerup et al. (2009), Holbech et al. (2011)

Morphine, Nortriptyline, Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

Oxycodone (n=159): Gimbel et al. (2003)

Pregabalin (n=2362): Arezzo et al. (2008), Dworkin et al. (2003), Lesser et al. (2004), Richter et al. (2005), Sabatowski et al. (2004), Siddall et al. (2006), Simpson et al. (2010), Tolle et al. (2008), van Seventer et al. (2006)

Tramadol (n=125): Norrbrink & Lundeberg (2009), Sindrup et al. (1999)

Trazodone (n=18): Davidoff et al. (1987)

Venlafaxine (n=110): Sindrup et al. (2003), Tasmuth et al. (2002)

Head-to-head trials:

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

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

Gabapentin vs Gabapentin+Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012)

Gabapentin vs Nortriptyline (n=182): Chandra et al. (2006), Gilron et al. (2012)

Imipramine vs Venlafaxine (n=80): Sindrup et al. (2003)

Morphine vs Nortriptyline, Morphine vs Nortriptyline+Morphine, Nortriptyline vs Nortriptyline+Morphine (n=110): Khoromi et al. (2007)

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

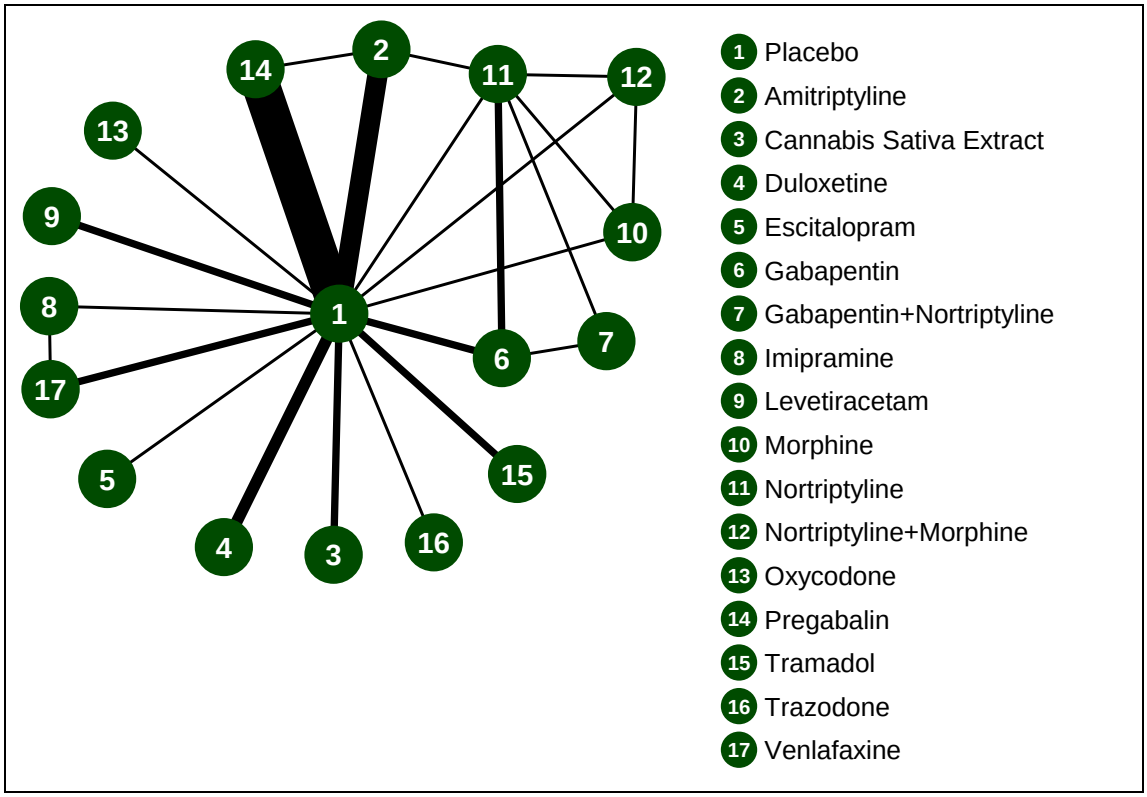

Figure 49 dry mouth - evidence network

Table 80 dry mouth - trials included in analysis

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Tramadol	Trazodone
Amitriptyline	5 RCTs[3,14,17,23,34] total n=341															
Cannabis Sativa Extract	2 RCTs[19,24] total n=191	-														
Duloxetine	3 RCTs[8,11,33] total n=720	-	-													
Escitalopram	1 RCT[20] total n=96	-	-	-												
Gabapentin	2 RCTs[12,21] total n=574	-	-	-	-											
Gabapentin +Nortriptyline	-	-	-	-	-	1 RCT[9] total n=112										
Imipramine	1 RCT[29] total n=80	-	-	-	-	-	-									
Levetiracetam	2 RCTs[7,13] total n=150	-	-	-	-	-	-	-								
Morphine	1 RCT[15] total n=110	-	-	-	-	-	-	-	-							
Nortriptyline	1 RCT[15] total n=110	1 RCT[35] total n=66	-	-	-	2 RCTs[4,9] total n=182	1 RCT[9] total n=112	-	-	1 RCT[15] total n=110						
Nortriptyline +Morphine	1 RCT[15] total n=110	-	-	-	-	-	-	-	-	1 RCT[15] total n=110	1 RCT[15] total n=110					

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Tramadol	Trazodone
Oxycodone	1 RCT[10] total n=159	-	-	-	-	-	-	-	-	-	-	-				
Pregabalin	9 RCTs[1,6,16,22,25,26,27,31,32] total n=2362	1 RCT[2] total n=102	-	-	-	-	-	-	-	-	-	-	-			
Tramadol	2 RCTs[18,28] total n=125	-	-	-	-	-	-	-	-	-	-	-	-	-		
Trazodone	1 RCT[5] total n=18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Venlafaxine	2 RCTs[29,30] total n=110	-	-	-	-	-	-	1 RCT[29] total n=80	-	-	-	-	-	-	-	-

(1) Arezzo et al. (2008); (2) Bansal et al. (2009); (3) Cardenas et al. (2002); (4) Chandra et al. (2006); (5) Davidoff et al. (1987); (6) Dworkin et al. (2003); (7) Finnerup et al. (2009); (8) Gao et al. (2010); (9) Gilron et al. (2012); (10) Gimbel et al. (2003); (11) Goldstein et al. (2005); (12) Gordh et al. (2008); (13) Holbech et al. (2011); (14) Kalso et al. (1995); (15) Khoromi et al. (2007); (16) Lesser et al. (2004); (17) Max et al. (1988); (18) Norrbrink & Lundeberg (2009); (19) Nurmikko et al. (2007); (20) Otto et al. (2008); (21) Rice & Maton (2001); (22) Richter et al. (2005); (23) Robinson et al. (2004); (24) Rog et al. (2005); (25) Sabatowski et al. (2004); (26) Siddall et al. (2006); (27) Simpson et al. (2010); (28) Sindrup et al. (1999); (29) Sindrup et al. (2003); (30) Tasmuth et al. (2002); (31) Tolle et al. (2008); (32) van Seventer et al. (2006); (33) Vranken et al. (2011); (34) Vrethem et al. (1997); (35) Watson et al. (1998)

Table 81 dry mouth - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Tramadol	Trazodone	Venlafaxine
Placebo		2.46 (1.05, 5.74)	4.79 (1.42, 16.10)	1.73 (0.85, 3.51)	1.00 (0.14, 7.40)	3.87 (1.27, 11.83)	-	5.29 (1.36, 20.53)	0.42 (0.06, 2.95)	1.00 (0.30, 3.32)	1.81 (0.61, 5.40)	1.39 (0.45, 4.31)	7.07 (1.54, 32.44)	3.97 (1.87, 8.41)	3.72 (1.56, 8.86)	6.33 (0.26, 152.86)	1.55 (0.53, 4.48)
Amitriptyline	3.89 (1.69, 9.84)		-	-	-	-	-	-	-	-	0.66 (0.19, 2.35)	-	-	0.19 (0.01, 4.11)	-	-	-
Cannabis Sativa Extract	6.32 (1.08, 47.16)	1.62 (0.22, 13.81)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duloxetine	1.86 (0.53, 6.84)	0.48 (0.10, 2.21)	0.29 (0.03, 2.65)		-	-	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	0.98 (0.06, 17.49)	0.25 (0.01, 5.00)	0.15 (0.00, 4.53)	0.53 (0.02, 12.14)		-	-	-	-	-	-	-	-	-	-	-	-
Gabapentin	1.37 (0.40, 5.08)	0.35 (0.08, 1.48)	0.22 (0.02, 1.94)	0.74 (0.12, 4.50)	1.40 (0.06, 32.72)		6.92 (2.77, 17.27)	-	-	-	14.07 (1.58, 124.90)	-	-	-	-	-	-
Gabapentin +Nortriptyline	8.15 (1.14, 63.64)	2.10 (0.25, 16.95)	1.28 (0.08, 19.54)	4.37 (0.41, 48.89)	8.30 (0.26, 284.50)	5.94 (1.00, 36.54)		-	-	-	0.93 (0.44, 1.95)	-	-	-	-	-	-
Imipramine	6.28 (0.83, 51.86)	1.61 (0.17, 15.25)	0.99 (0.06, 15.64)	3.36 (0.30, 39.46)	6.41 (0.19, 219.50)	4.58 (0.40, 51.67)	0.77 (0.04, 13.37)		-	-	-	-	-	-	-	-	0.26 (0.08, 0.89)
Levetiraceta	0.33 (0.02,	0.08 (0.00,	0.05 (0.00,	0.18 (0.01,	0.33 (0.01,	0.24 (0.01,	0.04 (0.00,	0.05 (0.00,		-	-	-	-	-	-	-	-

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Tramadol	Trazodone	Venlafaxine
m	3.48)	1.03)	1.02)	2.58)	13.89)	3.42)	0.87)	1.19)									
Morphine	1.97 (0.27, 14.21)	0.50 (0.06, 3.95)	0.31 (0.02, 4.42)	1.05 (0.10, 10.70)	2.01 (0.06, 64.01)	1.44 (0.16, 11.77)	0.24 (0.02, 2.98)	0.31 (0.02, 5.32)	6.01 (0.27, 177.90)		1.81 (0.61, 5.40)	1.39 (0.45, 4.31)	-	-	-	-	-
Nortriptyline	6.47 (1.90, 24.42)	1.67 (0.42, 6.57)	1.02 (0.10, 9.30)	3.47 (0.59, 21.62)	6.61 (0.29, 156.30)	4.71 (1.37, 16.89)	0.79 (0.13, 4.70)	1.03 (0.09, 11.85)	19.78 (1.38, 427.00)	3.30 (0.50, 24.14)		0.77 (0.28, 2.11)	-	-	-	-	-
Nortriptyline +Morphine	2.78 (0.41, 19.16)	0.72 (0.09, 5.37)	0.44 (0.03, 6.03)	1.49 (0.15, 14.78)	2.84 (0.09, 91.01)	2.03 (0.25, 15.94)	0.34 (0.03, 4.05)	0.44 (0.03, 7.34)	8.49 (0.40, 244.90)	1.41 (0.17, 11.76)	0.43 (0.06, 2.71)		-	-	-	-	-
Oxycodone	8.57 (0.87, 117.40)	2.21 (0.18, 33.13)	1.36 (0.06, 31.20)	4.63 (0.33, 82.69)	8.91 (0.22, 415.70)	6.32 (0.44, 111.40)	1.07 (0.05, 27.23)	1.38 (0.06, 36.74)	26.99 (0.96, 1169.00)	4.44 (0.21, 114.80)	1.33 (0.09, 23.26)	3.14 (0.15, 77.23)		-	-	-	-
Pregabalin	4.08 (1.96, 8.95)	1.05 (0.33, 3.14)	0.65 (0.08, 4.46)	2.20 (0.49, 9.57)	4.17 (0.21, 80.89)	2.99 (0.67, 12.65)	0.50 (0.06, 4.12)	0.65 (0.07, 5.74)	12.30 (1.06, 227.40)	2.08 (0.26, 17.41)	0.63 (0.14, 2.64)	1.47 (0.19, 11.56)	0.48 (0.03, 5.35)		-	-	-
Tramadol	3.90 (0.83, 18.49)	1.01 (0.16, 5.71)	0.61 (0.05, 6.47)	2.10 (0.28, 15.32)	3.98 (0.15, 101.70)	2.84 (0.38, 20.52)	0.48 (0.04, 5.79)	0.62 (0.04, 8.03)	11.84 (0.70, 287.00)	1.99 (0.16, 24.16)	0.60 (0.08, 4.36)	1.41 (0.12, 16.71)	0.45 (0.02, 7.20)	0.95 (0.17, 5.35)		-	-
Trazodone	13.20 (0.32, 6976.00)	3.41 (0.07, 1854.00)	2.15 (0.03, 1305.00)	7.25 (0.14, 4141.00)	14.65 (0.12, 11430.00)	9.74 (0.19, 5731.00)	1.68 (0.02, 1068.00)	2.20 (0.03, 1439.00)	44.68 (0.47, 34750.00)	7.14 (0.10, 4453.00)	2.08 (0.04, 1143.00)	5.00 (0.07, 3144.00)	1.59 (0.02, 1167.00)	3.24 (0.07, 1754.00)	3.49 (0.06, 2013.00)		-
Venlafaxine	1.59 (0.30, 8.59)	0.41 (0.06, 2.63)	0.25 (0.02, 2.93)	0.85 (0.10, 6.99)	1.63 (0.06, 44.16)	1.16 (0.14, 9.28)	0.19 (0.01, 2.59)	0.25 (0.03, 1.86)	4.84 (0.27, 125.10)	0.81 (0.06, 10.87)	0.24 (0.03, 1.96)	0.57 (0.05, 7.37)	0.18 (0.01, 3.18)	0.39 (0.06, 2.46)	0.41 (0.04, 4.03)	0.12 (0.00, 7.15)	

Values given are odds ratios.

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

	Placebo	Amitriptyline	Cannabis Sativa Extract	Duloxetine	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Imipramine	Levetiracetam	Morphine	Nortriptyline	Nortriptyline +Morphine	Oxycodone	Pregabalin	Tramadol	Trazodone	Venlafaxine
shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.																	

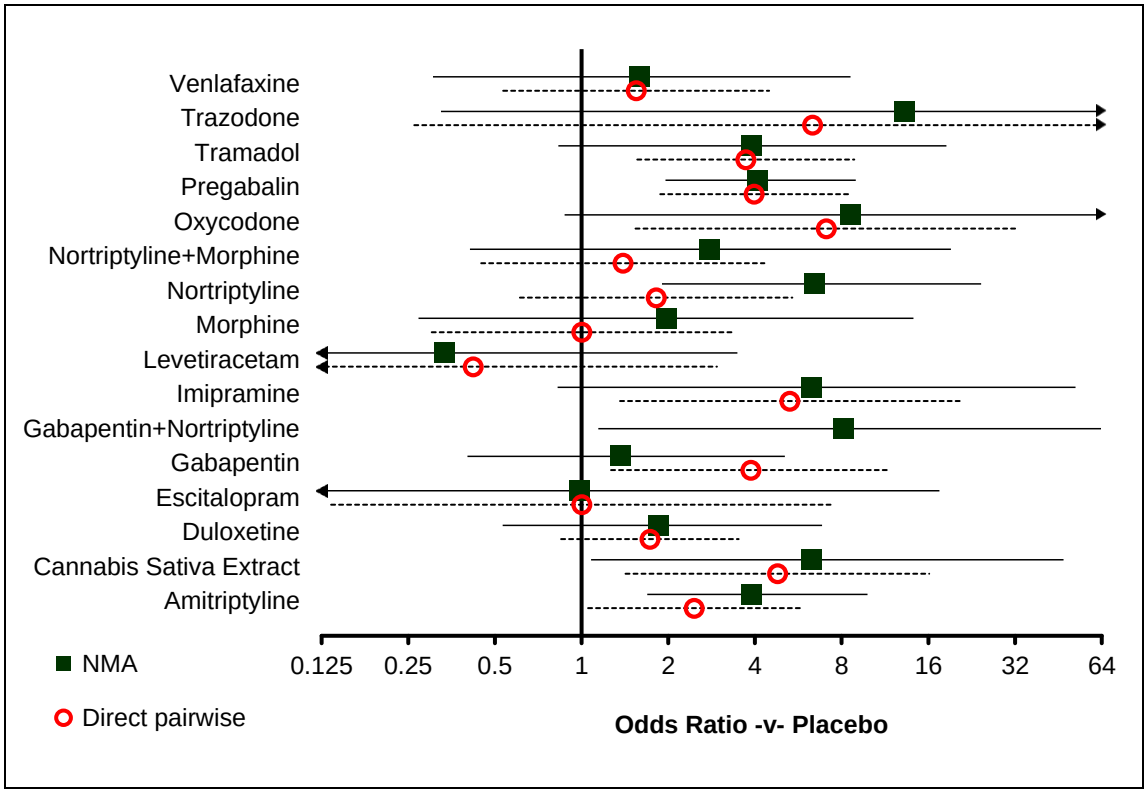

Figure 50 dry mouth - relative effect of all options compared with placebo

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

Table 82 dry mouth - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.022	4 (2, 7)
Amitriptyline	0.000	10 (6, 15)
Cannabis Sativa Extract	0.002	13 (4, 17)
Duloxetine	0.015	6 (2, 14)
Escitalopram	0.213	4 (1, 16)
Gabapentin	0.032	5 (1, 11)
Gabapentin+Nortriptyline	0.001	14 (5, 17)
Imipramine	0.003	13 (3, 17)
Levetiracetam	0.577	1 (1, 10)
Morphine	0.040	7 (1, 15)
Nortriptyline	0.000	13 (7, 17)
Nortriptyline+Morphine	0.017	8 (2, 16)
Oxycodone	0.004	14 (3, 17)
Pregabalin	0.000	11 (6, 15)
Tramadol	0.004	10 (3, 16)
Trazodone	0.024	16 (2, 17)
Venlafaxine	0.045	6 (1, 14)

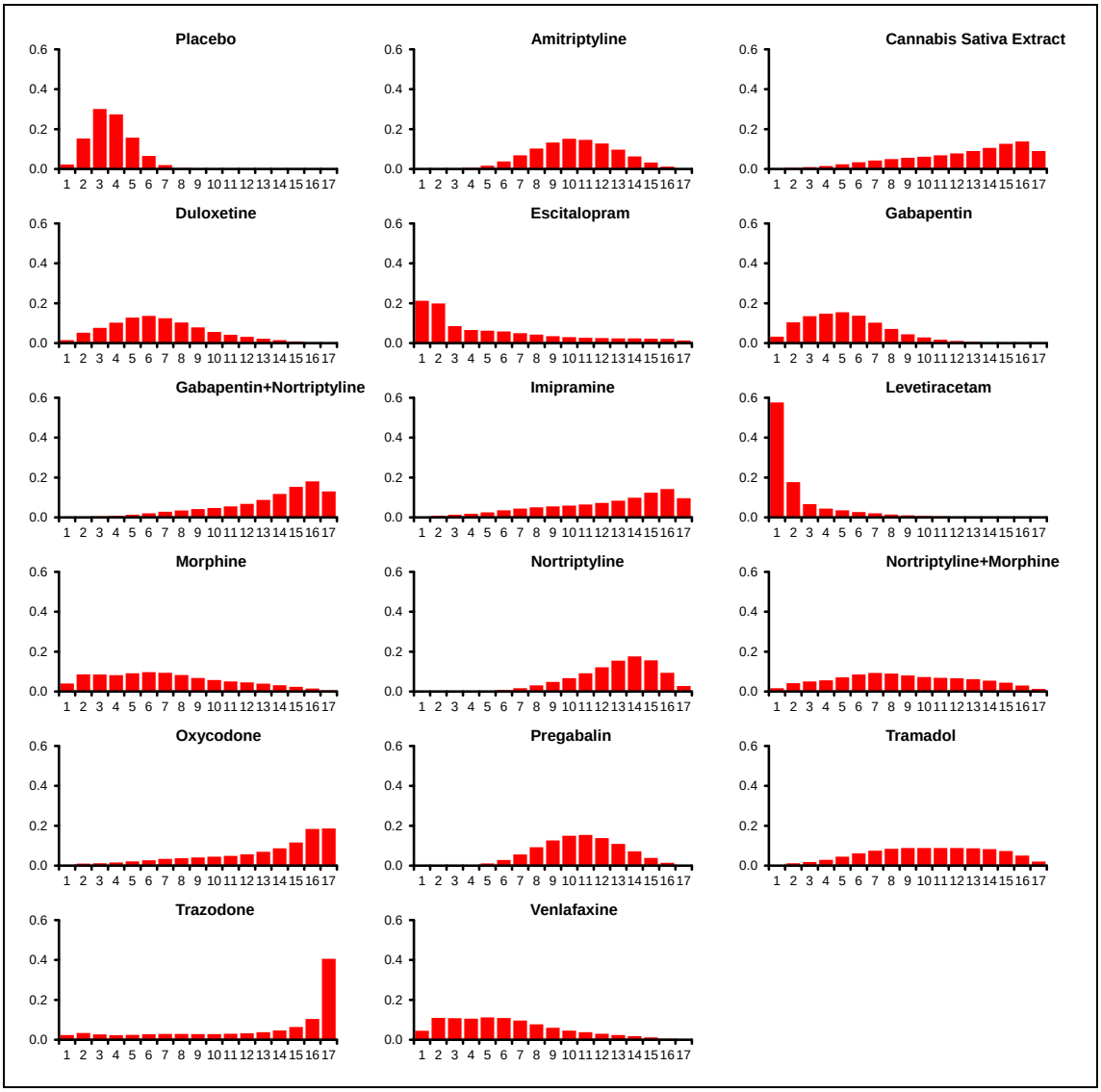

Figure 51 dry mouth - rank probability histograms

Table 83 dry mouth - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
87.35 (compared to 85 data-points)	354.093	285.117	68.976	423.069	0.591 (95%CrI: 0.224, 1.753)

Table 84 dry mouth - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 10000 burn-ins and 50000 iterations.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times)

rather than the proportion of patients who reported the event which the majority of the other studies reported.

- Model convergence: poor autocorrelation for tramadol because there is only one study with low event rates for this intervention.

Summary GRADE profile 3r: Network meta-analysis for urine retention

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Urine retention	10 RCTs[a] n=844	very serious[1]	not serious[2]	not serious[3]	very serious[4]	very low	Important

[1] half of studies are crossover studies; it was unclear if treatment groups were comparable at baseline in 7 studies, particularly for concomitant drug use and treatment groups were not comparable at baseline in 2 studies; all but one study had insufficient follow-up; during 5 studies, it was unclear if the same care was received by each group and during 2 studies the same care was not received in both groups (this was particularly with concomitant drug and rescue medication use); concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% for amitriptyline vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possible for comparisons which have only one trial); appears to be consistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] most links have only one trial; few head-to-head trials; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] placebo-controlled trials:

Amitriptyline (n=191): Cardenas et al. (2002), Robinson et al. (2004), Vrethem et al. (1997)

Escitalopram (n=96): Otto et al. (2008)

Levetiracetam (n=78): Holbech et al. (2011)

Tramadol (n=125): Boureau et al. (2003)

Trazodone (n=18): Davidoff et al. (1987)

Head-to-head trials:

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

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

Gabapentin vs Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012)

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

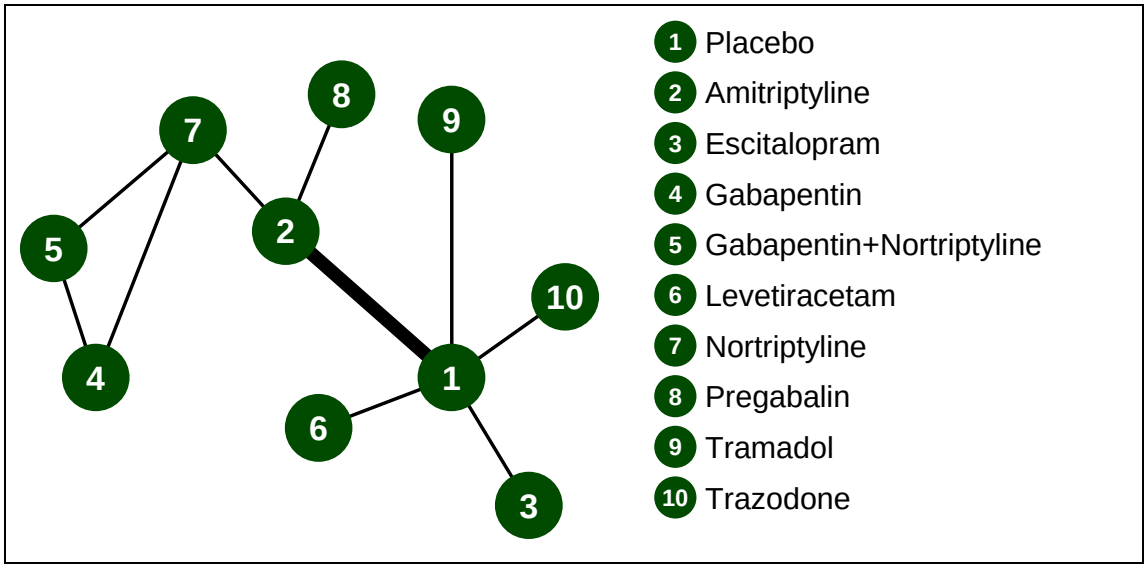

Figure 52 urine retention - evidence network

Table 85 urine retention - trials included in analysis

	Placebo	Amitriptyline	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Levetiracetam	Nortriptyline	Pregabalin	Tramadol
Amitriptyline	3 RCTs[3,8,9] total n=191								
Escitalopram	1 RCT[7] total n=96	-							
Gabapentin	-	-	-						
Gabapentin +Nortriptyline	-	-	-	1 RCT[5] total n=112					
Levetiracetam	1 RCT[6] total n=78	-	-	-	-				
Nortriptyline	-	1 RCT[10] total n=66	-	1 RCT[5] total n=112	1 RCT[5] total n=112	-			
Pregabalin	-	1 RCT[1] total n=102	-	-	-	-	-		
Tramadol	1 RCT[2] total n=125	-	-	-	-	-	-	-	
Trazodone	1 RCT[4] total n=18	-	-	-	-	-	-	-	-

(1) Bansal et al. (2009); (2) Boureau et al. (2003); (3) Cardenas et al. (2002); (4) Davidoff et al. (1987); (5) Gilron et al. (2012); (6) Holbech et al. (2011); (7) Otto et al. (2008); (8) Robinson et al. (2004); (9) Vrethem et al. (1997); (10) Watson et al. (1998)

Table 86 urine retention - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Escitalopram	Gabapentin	Gabapentin +Nortriptyline	Levetiracetam	Nortriptyline	Pregabalin	Tramadol	Trazodone
Placebo		1.04 (0.34, 3.21)	3.06 (0.12, 77.09)	-	-	3.08 (0.12, 77.91)	-	-	0.98 (0.06, 16.09)	3.35 (0.12, 93.83)
Amitriptyline	1.23 (0.09, 27.79)		-	-	-	-	0.32 (0.01, 8.23)	0.19 (0.01, 4.11)	-	-
Escitalopram	5.28 (0.02, 6831)	4.21 (0.01, 7331)		-	-	-	-	-	-	-
Gabapentin	0.04 (0.00, 138.00)	0.04 (0.00, 52.90)	0.01 (0.00, 123.70)		2.04 (0.18, 23.13)	-	3.11 (0.31, 30.88)	-	-	-
Gabapentin +Nortriptyline	0.12 (0.00, 347.90)	0.10 (0.00, 128.00)	0.02 (0.00, 335.20)	2.55 (0.02, 619.00)		-	1.53 (0.25, 9.52)	-	-	-
Levetiracetam	5.53 (0.02, 9690)	4.52 (0.01, 11690)	1.09 (0.00, 9885)	166.90 (0.01, 17330000)	59.87 (0.00, 4580000)		-	-	-	-
Nortriptyline	0.21 (0.00, 119.10)	0.17 (0.00, 37.95)	0.03 (0.00, 160.60)	4.24 (0.04, 931.50)	1.65 (0.02, 176.90)	0.03 (0.00, 146.50)		-	-	-
Pregabalin	0.11 (0.00, 51.01)	0.09 (0.00, 15.18)	0.02 (0.00, 69.89)	2.28 (0.00, 83560)	0.87 (0.00, 18820)	0.02 (0.00, 72.04)	0.52 (0.00, 3947)		-	-
Tramadol	1.02 (0.00, 245.00)	0.82 (0.00, 309.90)	0.18 (0.00, 394.00)	25.16 (0.00, 1197000)	9.38 (0.00, 292100)	0.16 (0.00, 376.30)	5.36 (0.00, 61660)	9.89 (0.00, 111200)		-
Trazodone	5.98 (0.03, 8392)	4.91 (0.01, 9762)	1.14 (0.00, 8618)	169.00 (0.01, 14310000)	64.02 (0.00, 3584000)	1.02 (0.00, 8784)	36.12 (0.01, 818300)	65.05 (0.02, 1977000)	6.42 (0.00, 47580)	

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

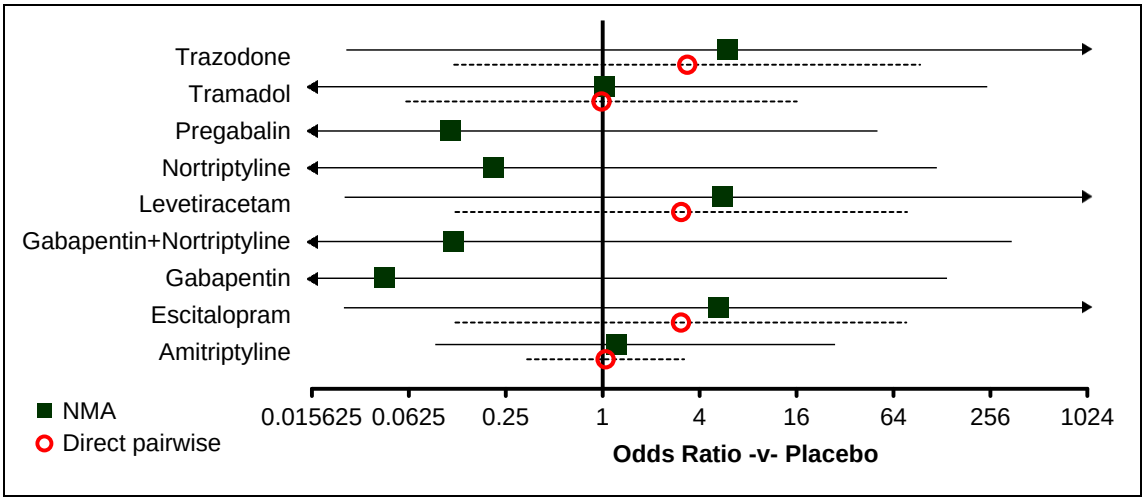

Figure 53 urine retention - relative effect of all options compared with placebo

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

Table 87 urine retention - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.007	6 (2, 8)
Amitriptyline	0.003	6 (3, 9)
Escitalopram	0.026	8 (1, 10)
Gabapentin	0.365	2 (1, 9)
Gabapentin+Nortriptyline	0.137	3 (1, 10)
Levetiracetam	0.024	8 (2, 10)
Nortriptyline	0.042	4 (1, 9)
Pregabalin	0.294	3 (1, 9)
Tramadol	0.078	6 (1, 10)
Trazodone	0.025	8 (2, 10)

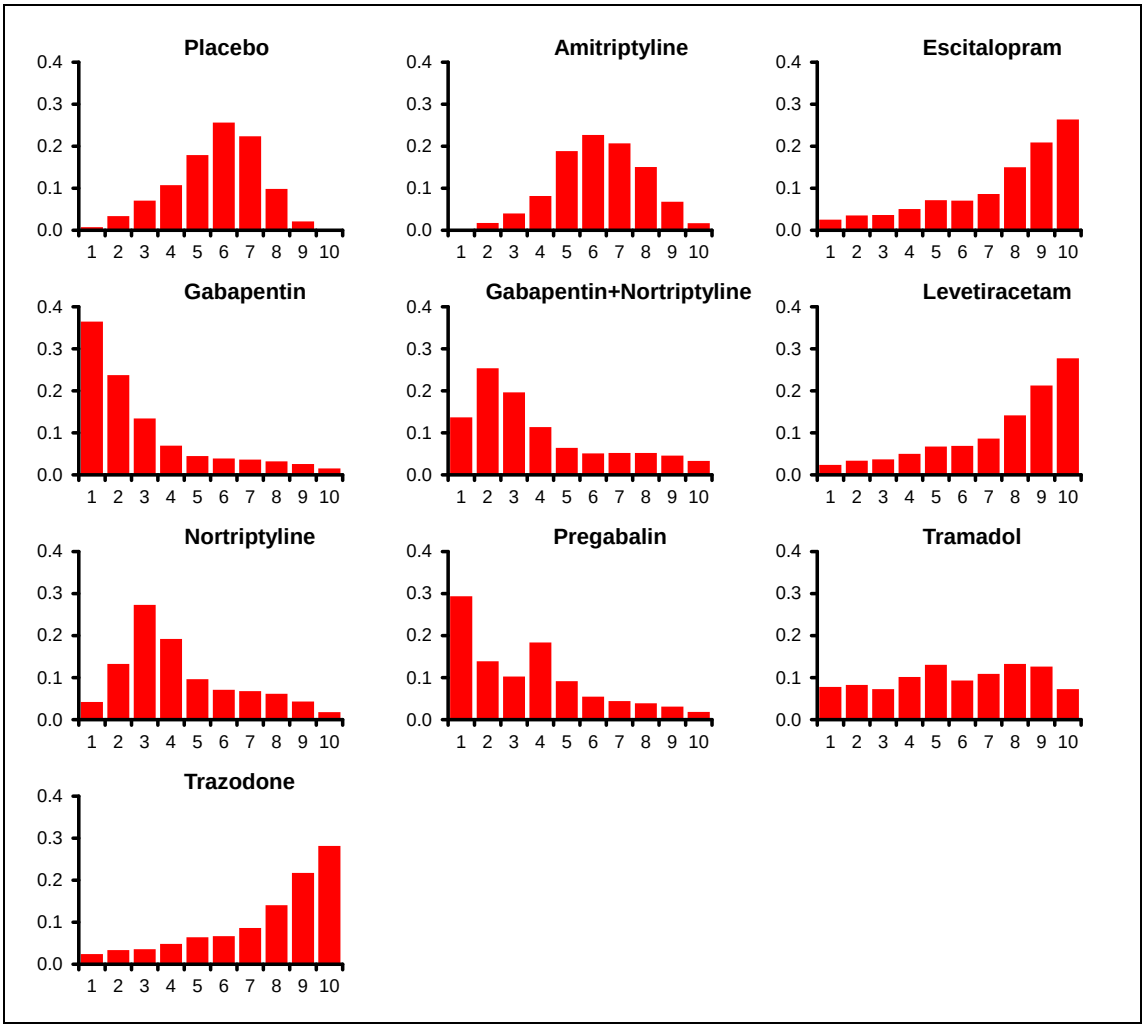

Figure 54 urine retention - rank probability histograms

Table 88 urine retention - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
22.87 (compared to 21 data-points)	67.756	49.941	17.815	85.571	0.000 (95%CI 0.002, 20.504)

Table 89 urine retention - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 20000 burn-ins and 50000 iterations.
- It was not possible to include the results from Huse (2001) in the synthesis because the study recorded the intensity of adverse events on a visual analogue scale (from 'not at all' to extremely) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- It was not possible to include results from Rintala (2007) in the synthesis

because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.

Summary GRADE profile 3s: Network meta-analysis for weight gain

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Weight gain	14 RCTs[a] n=3170	very serious[1]	not serious[2]	not serious[3]	very serious[4]	Very low	Important

[1] over half of studies were unclear about allocation concealment; there is uncertainty about comparability at baseline between groups in all but 2 studies (particularly for use of concomitant drugs); during 9 studies, it was unclear if the same care was received by each group, particularly with concomitant drug and rescue medication use; average baseline severity ranged from 4.5 to 7.7 on a 11-point scale across the network; concomitant drugs permitted varies across the studies in the network

[2] I^2 was 0% pregabalin vs placebo which may indicate that any inconsistency might not be important (heterogeneity not possibly for comparisons where there is only one trial); there appear to be some differences in direct and indirect estimates on visual inspection but comparison of a consistency and inconsistency models showed general consistency

[3] all aspects of PICO conform to review protocol

[4] all but one link has only one trial; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] Placebo-controlled trials:

Morphine, nortriptyline, nortriptyline+morphine (n=110): Khoromi et al. (2007)

Pregabalin (n=2625): Arezzo et al. (2008), Freynhagen et al. (2005), Guan et al. (2011), Kim et al. (2011), Richter et al. (2005), Satoh et al. (2011), Stacey et al. (2008), Tolle et al. (2008), van Seventer et al. (2006)

Valproate (n=41): Agrawal et al. (2009)

Head-to-head trials:

Amitriptyline vs Gabapentin (n=50): Morello et al. (1999)

Amitriptyline vs Nortriptyline (n=66): Watson et al. (1998)

Gabapentin vs Gabapentin+Nortriptyline, Gabapentin vs Nortriptyline, Gabapentin+Nortriptyline vs Nortriptyline (n=112): Gilron et al. (2012)

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

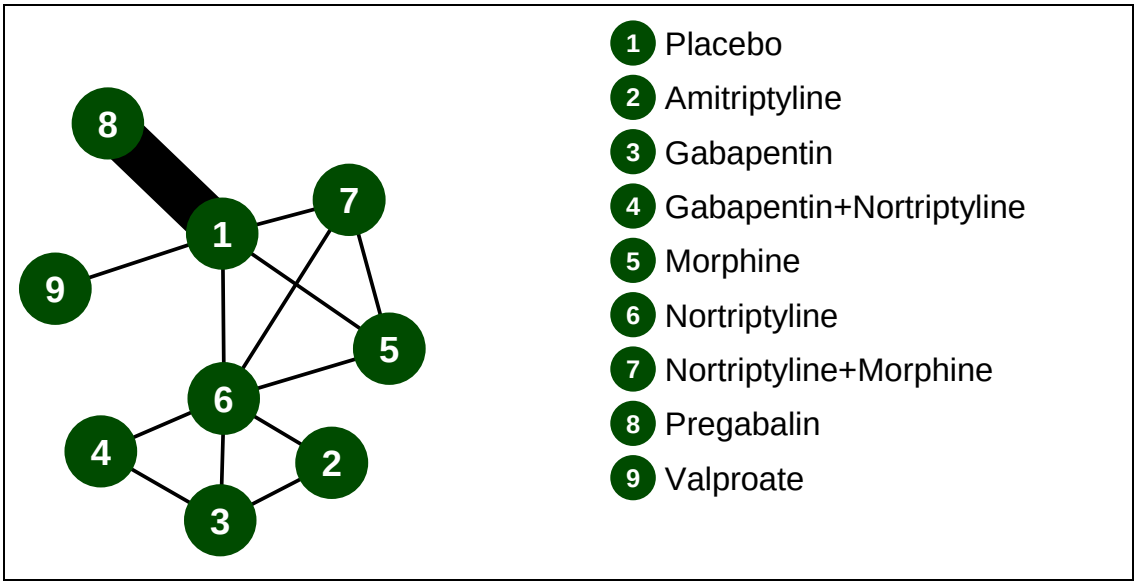

Figure 55 Weight gain - evidence network

Table 90 Weight gain - trials included in analysis

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Nortriptyline	Morphine	Nortriptyline	Nortriptyline +Morphine	Pregabalin
Amitriptyline	-							
Gabapentin	-	1 RCT[8] total n=50						
Gabapentin +Nortriptyline	-	-	1 RCT[4] total n=112					
Morphine	1 RCT[6] total n=110	-	-	-				
Nortriptyline	1 RCT[6] total n=110	1 RCT[14] total n=66	1 RCT[4] total n=112	1 RCT[4] total n=112	1 RCT[6] total n=110			
Nortriptyline +Morphine	1 RCT[6] total n=110	-	-	-	1 RCT[6] total n=110	1 RCT[6] total n=110		
Pregabalin	9 RCTs[2,3,5,7,9,10,11,12,13] total n=2625	-	-	-	-	-	-	
Valproate	1 RCT[1] total n=41	-	-	-	-	-	-	-

(1) Agrawal et al. (2009); (2) Arezzo et al. (2008); (3) Freynhagen et al. (2005); (4) Gilron et al. (2012); (5) Guan et al. (2011); (6) Khoromi et al. (2007); (7) Kim et al. (2011); (8) Morello et al. (1999); (9) Richter et al. (2005); (10) Satoh et al. (2011); (11) Stacey et al. (2008); (12) Tolle et al. (2008); (13) van Seventer et al. (2006); (14) Watson et al. (1998)

Table 91 Weight gain - relative effectiveness of all pairwise combinations

	Placebo	Amitriptyline	Gabapentin	Gabapentin +Nortriptyline	Morphine	Nortriptyline	Nortriptyline +Morphine	Pregabalin	Valproate
Placebo		-	-	-	1.00 (0.02, 51.29)	5.19 (0.24, 110.57)	1.00 (0.02, 51.29)	5.92 (3.13, 11.21)	1.05 (0.02, 55.37)
Amitriptyline	152.70 (2.27, 259700.00)		0.06 (0.00, 1.11)	-	-	0.19 (0.01, 4.07)	-	-	-
Gabapentin	7.02 (0.12, 6836.00)	0.05 (0.00, 0.45)		0.33 (0.01, 8.21)	-	1.00 (0.06, 16.39)	-	-	-
Gabapentin +Nortriptyline	1.40 (0.00, 1939.00)	0.01 (0.00, 0.52)	0.22 (0.00, 7.08)		-	3.05 (0.12, 76.59)	-	-	-
Morphine	0.78 (0.00, 785.10)	0.01 (0.00, 0.38)	0.11 (0.00, 6.54)	0.58 (0.00, 530.30)		5.19 (0.24, 110.57)	1.00 (0.02, 51.29)	-	-
Nortriptyline	8.52 (0.44, 6861.00)	0.07 (0.00, 0.85)	1.36 (0.13, 16.63)	6.16 (0.26, 3601.00)	10.98 (0.48, 7998.00)		0.19 (0.01, 4.11)	-	-
Nortriptyline +Morphine	0.81 (0.00, 903.20)	0.01 (0.00, 0.38)	0.11 (0.00, 7.23)	0.56 (0.00, 599.60)	1.03 (0.00, 840.70)	0.09 (0.00, 2.07)		-	-
Pregabalin	7.32 (3.91, 15.12)	0.05 (0.00, 3.33)	1.06 (0.00, 64.44)	5.26 (0.00, 7092.00)	9.36 (0.01, 7705.00)	0.84 (0.00, 18.65)	9.41 (0.01, 6615.00)		-
Valproate	0.91 (0.00, 614.90)	0.01 (0.00, 10.78)	0.12 (0.00, 178.20)	0.61 (0.00, 7268.00)	1.21 (0.00, 9786.00)	0.09 (0.00, 85.60)	1.12 (0.00, 8335.00)	0.12 (0.00, 86.42)	

Values given are odds ratios.

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

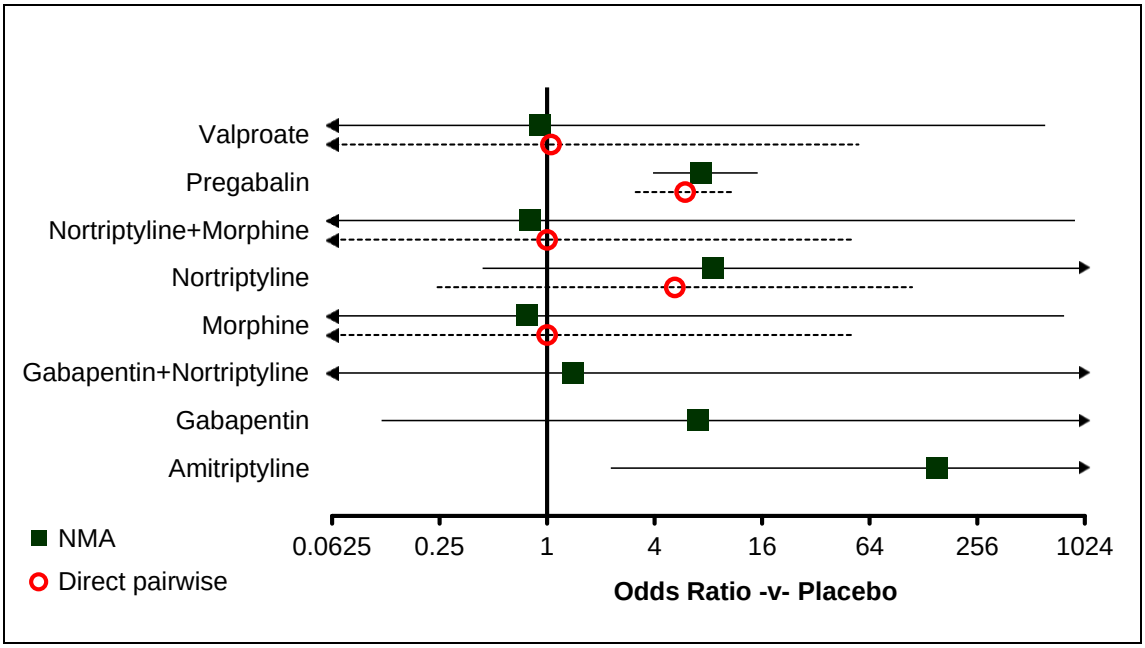

Figure 56 Weight gain - relative effect of all options compared with placebo

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

Table 92 Weight gain - rankings for each comparators

	Probability best	Median rank (95%CI)
Placebo	0.117	3 (1, 7)
Amitriptyline	0.000	9 (7, 9)
Gabapentin	0.009	6 (2, 8)
Gabapentin+Nortriptyline	0.184	4 (1, 8)
Morphine	0.222	3 (1, 7)
Nortriptyline	0.000	7 (4, 8)
Nortriptyline+Morphine	0.203	3 (1, 8)
Pregabalin	0.000	6 (3, 9)
Valproate	0.265	3 (1, 9)

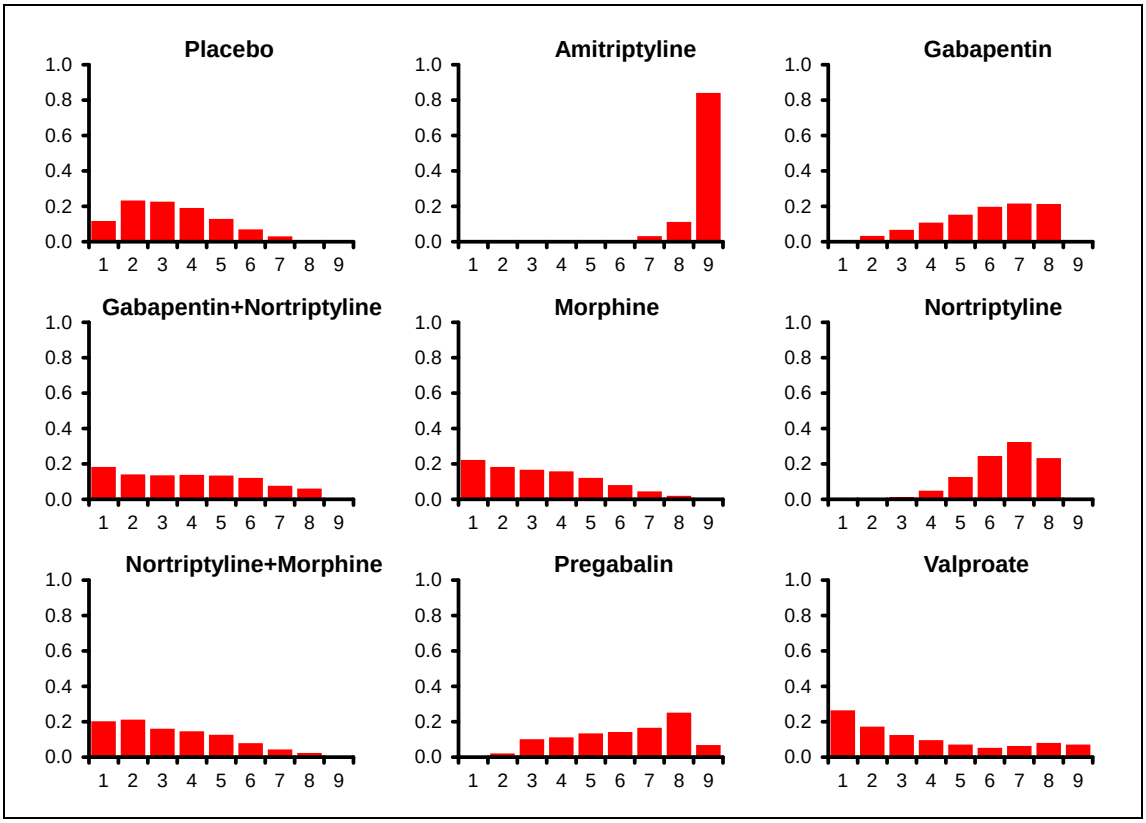

Figure 57 Weight gain - rank probability histograms

Table 93 weight gain - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
36.76 (compared to 39 data-points)	143.467	120.917	22.55	166.016	0.000 (95%CrI: 0.000, 0.628)

Table 94 weight gain - notes

- Random-effects model was used, with 0.5 added to cells of trials with 1 or more zero cell-count.
- 50000 burn-ins and 100000 iterations.
- It was not possible to include results from Rintala (2007) in the synthesis because the study reported the number of side effects reported in total (including patients more than once if they reported the event multiple times) rather than the proportion of patients who reported the event which the majority of the other studies reported.
- Model convergence: very poor for most of the interventions due to low event rates.

Summary GRADE profile 3t: Network meta-analysis for gait disturbance

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Gait disturbance	3 RCTs[a] n=567	very serious[1]	not serious[2]	not serious[3]	very serious[4]	very low	Important

[1] unclear about appropriate method of randomisation or allocation concealment in two studies; baseline pain severity slightly smaller in patients treated with gabapentin than patients treated with pregabalin; concomitant drugs permitted varies across the studies in the network; during the studies, there is unclear concomitant drug or rescue medication use between groups in two studies

[2] I^2 is 0% for pregabalin vs placebo so any inconsistency might not be important (heterogeneity not possible for gabapentin vs placebo since there is only one trial that forms this comparison); no loops in networks so no possibility of inconsistency between direct and indirect estimates

[3] all aspects of PICO conform to review protocol

[4] one link has only one trial; no head-to-head trial; wide confidence intervals for the effect estimates of most interventions compared to placebo and for overall rankings within the network

[a] Gabapentin (n=26): Hahn et al. (2004)
Pregabalin (n=541): Dworkin et al. (2003), van Seventer et al. (2006)
[all compared to placebo]

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

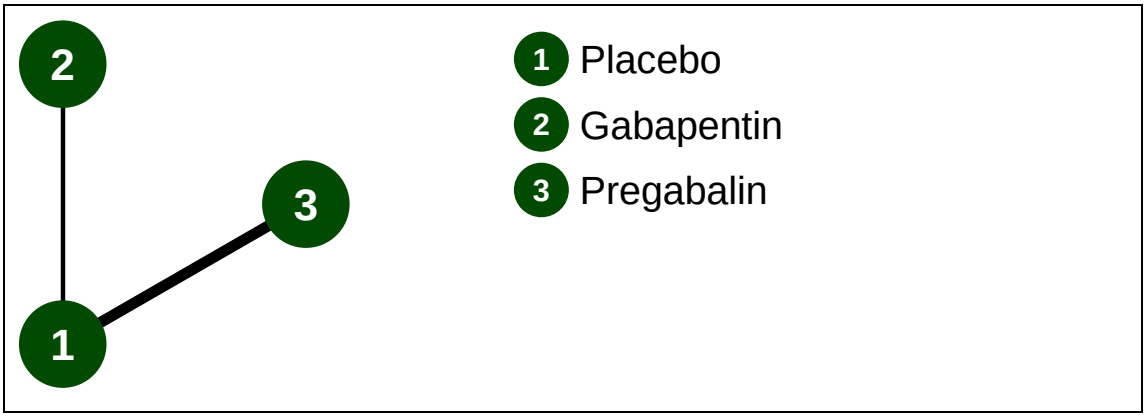

Figure 58 Gait disturbance - evidence network

Table 95 Gait disturbance - trials included in analysis

	Placebo	Gabapentin
Gabapentin	1 RCT[2] total n=26	
Pregabalin	2 RCTs[1,3] total n=541	-

(1) Dworkin et al. (2003); (2) Hahn et al. (2004); (3) van Seventer et al. (2006)

Table 96 Gait disturbance - relative effectiveness of all pairwise combinations

	Placebo	Gabapentin	Pregabalin
Placebo		2.33 (0.44, 12.40)	6.36 (1.16, 34.99)
Gabapentin	2.56 (0.07, 99.78)		-
Pregabalin	9.00 (0.73, 252.70)	3.65 (0.04, 488.00)	

Values given are odds ratios.

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

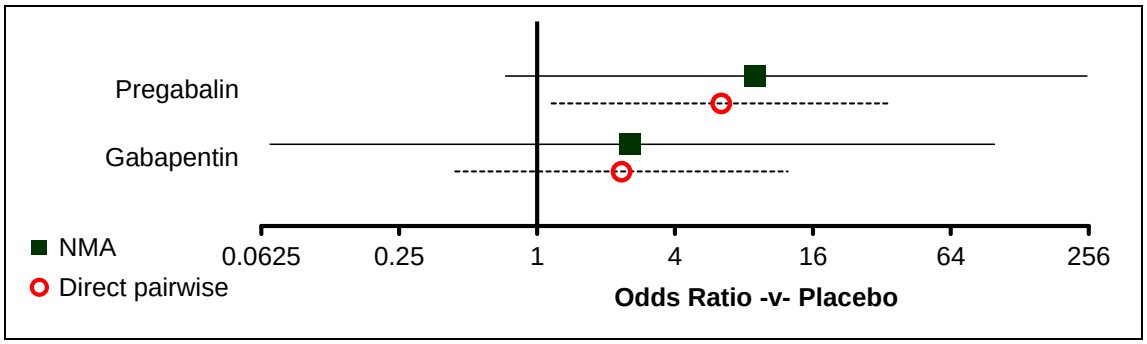

Figure 59 Gait disturbance - relative effect of all options compared with placebo

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

Table 97 Gait disturbance - rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.737	1 (1, 2)
Gabapentin	0.236	2 (1, 3)
Pregabalin	0.028	3 (1, 3)

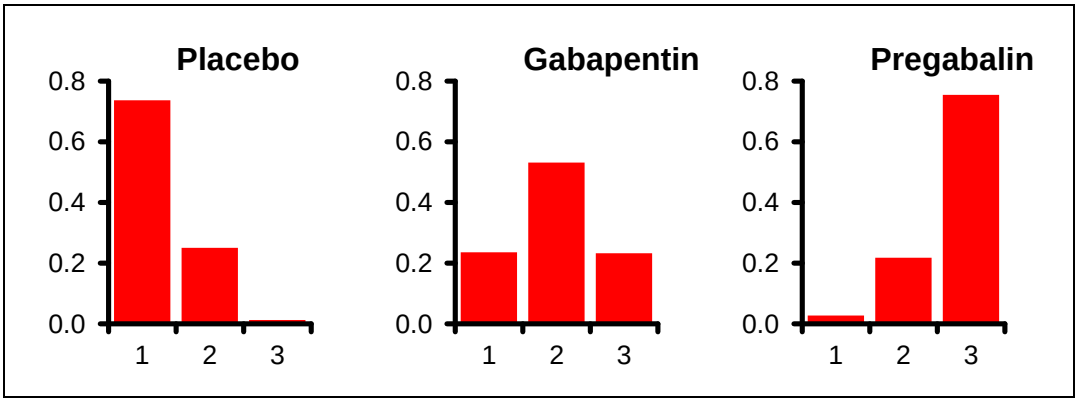

Figure 60 Gait disturbance - rank probability histograms

Table 98 Gait disturbance - model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau-squared
7.192 (compared to 8 data-points)	28.679	22.382	6.297	34.976	0.001 (95%CrI: 0.002, 15.711)

Table 99 Gait disturbance - notes

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